STUDIES ON THE TABLETING AND ANTIULCER PROPERTIES OF *FICUS SUR* FORSK LEAF EXTRACTS

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DECLARATION

I hereby declare that the work reported in this thesis was carried out solely by me under the supervision of **Prof. R.N. Nasipuri** of the National Institute for Pharmaceutical Research and Development, Idu-Abuja and **Dr. J.E. Ojile** of the Faculty of Pharmaceutical Sciences, A.B.U., Zaria. The work of other researchers are acknowledged and referred to accordingly. I also declare that no part of this work has been submitted elsewhere for a degree.

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CERTIFICATION

This thesis titled **STUDIES ON THE TABLETING AND ANTIULCER PROPERTIES OF *FICUS SUR* FORSK LEAF EXTRACTS** by **KUNLE, OLOBAYO OLUFUNSHO** meets the regulations governing the award of the degree of **DOCTOR OF PHILOSOPHY** (Pharmaceutics) of AHMADU BELLO UNIVERSITY, and is approved for its contribution to knowledge and literary presentation.

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This work is dedicated with love to my ladies - Tayo, Tope and Yemisi -
daily reminders of Jah's immense love for me.

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ABSTRACT

The justification for the use of *Ficus sur* (Forsk) leaves in the treatment of peptic ulcer was investigated. This was done by extracting the dried leaves with various solvents (polar and non polar) and determining their smooth muscle relaxant (polar extract) and ulcero-protective effects. Their antimicrobial activity was also investigated. The results indicated that the polar extracts had smooth muscle relaxant and ulcer protective effect, with the hot water extract (HWE) having the most effect.

The HWE was used for formulation studies using the wet granulation method. The effect of three diluents - Lactose, Aerosil and Heavy Magnesium Carbonate on the formulation was investigated. Four binders - maize starch paste, PVF, sodium alginate and gelatin, were used at three concentration levels each. The effect of magnesium stearate as lubricant was also studied in order to determine the optimal amount required. These effects were studied on granules and tablets. The Meckel equation was used to investigate the compaction characteristics of the granulates.

All the granulates had good flow properties. Tablets produced with lactose as diluent had the highest physical strength while those produced with heavy magnesium carbonate were unsatisfactory in this respect. Some of the lactose - containing tablets however failed the disintegration time test.

Both the binder type and concentration affected the granule and tablet properties investigated. For example in most cases granule size increased, while bulk and tapped densities increased with binder concentration, with the extent depending on the binder type.

The granules were generally found to have Type B behaviour suggesting that strong compacts will be produced from these granulates. There were however a few granulates,

such as that with 5%w/w starch mucilage as binder and lactose as diluent which gave Type- C-like plots.

The optimum magnesium stearate concentration was found to be in the range 0.1 0.2%w/w, with respect to granule and tablet properties.

In order to improve the disintegration time of the tablets, surfactants (Tween 80 and SLS) at two concentration levels were incorporated into the formulations. They reduced the physical strength of the tablets. The disintegration and dissolution times however improved in most cases, although with some others it increased. The extent of these effects depended on the surfactant type and concentration, diluent and binder types.

'Fingerprints' for assessing the effect of formulation process and additives on the HWE were developed. They were UV spectroscopy, TLC and biological. They showed that these factors did not affect the HWE.

It was concluded that the use of the leaves of *Ficus sur* in the treatment of peptic ulcer could be justified and that tablets of suitable properties could be formulated from the HWE with either lactose or aerosil as diluent. The binder type and concentration will need to be carefully selected.

TABLE OF CONTENTS

CHAPTER ONE 1

INTRODUCTION AND LITERATURE REVIEW 1

1.1 GENERAL INTRODUCTION 1

1.2 PEPTIC ULCER DISEASE 3

1.2.1 *Helicobacter pylori* and Peptic ulcer 6

1.2.2 Antiulcer Test Models 8

1.3 COMPACTION CHARACTERISTICS OF PHARMACEUTICAL POWDERS 8

1.3.1 Effect of Particle Characteristics on Compaction Behaviour of Powders 13

1.3.1.1 Particle size 13

1.3.1.2 Surface Area 15

1.4 EFFECT OF BINDER CONCENTRATION ON GRANULE AND TABLET PROPERTIES 18

1.5 SURFACTANTS 26

1.5.1 Surfactants and Pharmacy 27

1.5.1.1 Wetting 27

1.5.1.2 Solubilization: 28

1.5.1.3 Deaggregation: 29

1.5.2 Surfactants in Tableting 29

1.6 LUBRICANTS IN TABLETING 33

1.7 *FICUS* SPP. 38

1.7.1 Medicinal Uses of *Ficus sur* Forsk (formerly *Ficus capensis*) 39

1.8 STATEMENT OF OBJECTIVE 40

CHAPTER TWO 42

GENERAL METHODS 42

2.1.1 Plant material collection 42

2.1.2 Preparation of the extracts 42

2.1.3 Preparation of Granules 43

2.1.4 Characterisation of Granules 44

2.1.4.1 Size analysis: 44

2.1.4.2 Moisture content: 44

2.1.4.3 Flow time: 44

2.1.4.4 Bulk and Tapped densities: 45

2.1.4.5 Percent compressibility 45

2.1.4.6 Granule density: 45

2.1.4.7 Angle of repose: 46

2.1.5. Compression of Granules 46

2.1.6 Test of Tablet properties 46

2.1.6.1 Weight Variation 46

2.1.6.2 Hardness: 50

2.1.6.3 Friability 51

2.1.6.4 Diameter/Thickness: 51

2.1.6.5 Disintegration time 51

2.1.6.6 Dissolution time 51

CHAPTER THREE 53

STUDIES OF THE ANTIULCER ACTIVITY OF SOME FICUS LEAF EXTRACTS ON ASPIRIN-INDUCED ULCER 53

3.1 INTRODUCTION 53

3.2 MATERIALS AND METHOD 53
3.2.1 MATERIALS 53
3.2.2 METHODS 54
3.2.2.1 Acute toxicity 54
3.2.2.2 Studies on isolated rabbit jejunum 54
3.2.2.3 Studies on ASA-induced ulcer 54

Table 3.1: LD_{50} of the various extracts 55

3.3 RESULTS AND DISCUSSION 56
3.3.1 Effect on pendular movement of rabbit jejunum 56
3.3.2 Effect on ASA-induced Ulcer 60

3.4 CONCLUSION 61

3.5 COMPARATIVE ANTIULCER ACTIVITY OF THE HOT WATER EXTRACT 62
3.5.1 Introduction 62
3.5.2 Materials and methods 62
3.5.3 Results and discussion 62

3.6 ANTIMICROBIAL ACTIVITY OF *FICUS SUR* EXTRACTS 65
3.6.1 Introduction: 65
3.6.2 Materials and method 65
3.6.2.1 Preparation of the extracts: 65
3.6.2.2 Microorganisms 65
3.6.2.3 Antimicrobial activity 65
3.6.3 Results and discussion 66

Table 3.2: Antimicrobial activity of the leaf extracts 66

Table 3.3: Determination of MIC for the Methanol Extract 66
3.6.4 Conclusion: 67

CHAPTER FOUR 68
EFFECT OF BINDER TYPE AND CONCENTRATION ON GRANULE AND TABLET PROPERTIES 68

4.1 INTRODUCTION 68

4.2 MATERIALS AND METHOD 68

4.3 METHODS 69
4.3.1 Preparation of Granules 69

4.3.1:Tablet formula 69
4.3.2. Characterisation of Granules 70
4.3.3 Compression of granules 70
4.3.4. Test of Tablet Properties 70

4.4 RESULTS AND DISCUSSION 71
4.4.1 Effect on Granule Properties 71
4.4.1.1 Lactose as diluent 71
4.4.1.2 Heavy Magnesium Carbonate as diluent 75
4.4.1.3 Aerosil as diluent 77
4.4.2. Effect on Tablet Properties 79
4.4.2.1 Lactose as diluent 79
4.4.2.2 Heavy Magnesium Carbonate as diluent 84
4.4.2.3 Aerosil as diluent 87

4.5 EFFECT OF BINDER TYPE ON GRANULE AND TABLET PROPERTIES 89
4.5.1 Granule Properties 89
4.5.1.1 Lactose as diluent 89
4.5.1.2 Aerosil as diluent 91
4.5.1.3 Heavy Magnesium Carbonate as diluent 93
4.5.2. Tablet Properties 95
4.5.2.1 Lactose as diluent 95
4.5.2.2 Aerosil as diluent 98
4.5.2.3 Heavy Magnesium Carbonate as diluent 100
CHAPTER FIVE 104

COMPACTION CHARACTERISTICS OF HWE GRANULATES 104

5.1 INTRODUCTION 104

5.2 MATERIALS AND METHODS 105
5.2.1 Granulation 105
5.2.2 Preparation and analysis of compacts 105

5.3 RESULTS AND DISCUSSION 107
5.3.1 Effect of Binder Concentration on Heckel Plots 107
5.3.1.1 Lactose as diluent 107
5.3.1.2 Heavy Magnesium Carbonate as Diluent 118
5.3.1.3 Aerosil as Diluent 124

5.4 EFFECT OF DILUENT TYPE 128
5.4.1 Starch Paste as Binder 128
5.4.2 PVP as binder 132
5.4.3 Sodium Alginate as Binder 133
5.4.4 Gelatin as binder 136

5.5 EFFECT OF BINDER TYPE 138

5.6CONCLUSION 140

CHAPTER SIX 141

EFFECT OF SURFACTANT TREATMENT ON GRANULE AND TABLET PROPERTIES 141

6.1 INTRODUCTION 141

6.2 MATERIALS AND METHODS 145
6.2.1 Materials 145
6.2.2 Methods 145

6.3 RESULTS AND DISCUSSION 145
6.3.1 Granule Properties 145

6.3.1.1 Lactose as diluent 145
6.3.1.2 Magnesium Carbonate (heavy) as diluent 150
6.3.1.3 Aerosil as diluent 153
6.3.2 Tablet Properties 156
6.3.2.1 Lactose as diluent 156
6.3.2.2 Heavy Magnesium Carbonate as diluent 164
6.3.2.3 Aerosil as diluent 168
6.4 CONCULSION 171

CHAPTER SEVEN 173

EFFECT OF MAGNESIUM STEARATE AS LUBRICANT ON GRANULE AND TABLET PROPERTIES 173

7.1 INTRODUCTION 173

7.2 MATERIALS AND METHODS 174
7.2.1 Materials 174

7.2.2. Methods 175

7.3RESULTS AND DISCUSSION 176
7.3.1 Granule Properties 176
7.3.1.1 Lactose as diluent 176
7.3.1.2 Heavy Magnesium Carbonate as diluent 179
7.3.1.3 Aerosil as diluent 181
7.3.2 Tablet Properties 183
7.3.2.1. Lactose as diluent 183
7.3.2.2 Heavy magnesium carbonate as diluent 185

7.3.2.3 Aerosil as diluent 189

7.4 CONCLUSION 191

CHAPTER EIGHT 193

EFFECT OF FORMULATION ON HWE 193

8.1 INTRODUCTION 193

8.2 MATERIALS AND METHOD 194
8.2.1 Thin Layer Chromatography (TLC) 194
8.2.2 UV spectroscopy 194
8.2.3 Pharmacological Assessment 195
8.2.3.1 Sample preparation 195

8.3 RESULTS AND DISCUSSION 197
8.3.1 TLC 197
8.3.2 UV-Visible Spectroscopy 202
8.3.3 Pharmacological 202

8.4 CONCLUSION 204

8.5 INVESTIGATIONS INTO THE QUANTITATIVE REDUCTION OF HWE BY MAGNESIUM CARBONATE (HEAVY) RELATIVE TO UNFORMULATED EXTRACT 206
8.5.1 Introduction 206
8.5.2 Materials and method 208
8.5.2.1 Materials 208
8.5.2.2 Method 208

8.5.2.3 Results and discussion 210
8.5.2.4 Conclusion 212

CHAPTER NINE 213

CONCLUSION 213

REFERENCES 216

LIST OF TABLES

Table 3.1: LD_{50} of the various extracts 55

Table 3.2: Antimicrobial activity of the leaf extracts 66

Table 3.3: Determination of MIC for the Methanol Extract 66

Table 4.1:Tablet formula 69

Table 4.2.1: Effect of binder conc. on Granule Properties(Lactose as dilute) 73

Table 4.2.2: Effect of binder conc. on Granule Properties(Dilute: $MgCo_3$) 76

Table 4.2.3: Effect of binder conc. on Granule Properties(Dilute: Aerosil) 78

Table 4.3.1: Effect of binder conc. on Tablet Properties(Lactose as dilute) 80

Table 4.3.2: Effect of binder conc. on Tablet Properties(Dilute: $MgCo_3$) 85

Table 4.3.3: Effect of binder conc. on Tablet Properties(Dilute: Aerosil) 88

Table 4.4.1: Effect of binder type on Granule Properties(Lactose as dilute) 90

Table 4.4.2: Effect of binder type on Granule Properties(Dilute: Aerosil) 92

Table 4.4.3: Effect of binder type on Granule Properties(Dilute: $MgCo_3$) 94

Table 4.5.1: Effect of binder type on Tablet Properties(Dilute: Aerosil) 96

Table 4.5.2: Effect of binder type on Tablet Properties(Lactose as dilute) 99

Table 4.5.3: Effect of binder type on Tablet Properties(Dilute: $MgCo_3$) 101

Table 5.1.1: Heckel constants (Lactose as diluent) 108

Table 5.1.2: Heckel constants (Magnesium Carbonate diluent) 119

Table 5.1.3: Heckel Constants (Areosil as diluent) 125

Table 5.2.1: Effect of diluent type on Heckel constants (starch paste as binder) 129

Table 5.2.2: Effect of diluent type on Heckel constants (PVP as binder) 131

Table 5.2.3: Effect of diluent type on Heckel constants (Alginate as binder) 134

Table 5.2.2: Effect of diluent type on Heckel constants (Gelatin as binder) 137

Table 6.1.1:Tablet Composition (15% starch as disintegrant; 0.2% magnesium stearate as lubricant) 142

Table 6.1.2:7.5% Starch paste as binder, 15% starch as disintegrant; 0.2% magnesium stearate as lubricant 142

Table 6.1.3: 5% PVP as binder; 15% starch as disintegrant; 0.2% magnesium stearate as lubricant 143

Table 6.1.4: 5% alginate as binder; 15% starch as disintegrant; 0.2% magnesium stearate as lubricant 143

Table 6.1.5: 7.5% gelatin as binder; 15% starch as disintegrant; 0.2% magnesium stearate as lubricant 144

Table 6.2.1: Effect of Surfactant type and Conc. on Granule properties (binder: strach paste,diluent: lactose) 145

Table 6.2.2: Effect of Surfactant type and Conc. on Granule properties (binder: PVP,diluent: lactose) 145

Table 6.2.3: Effect of Surfactant type and Conc. on Granule properties (binder: Gelatin,diluent: lactose) 146

Table 6.2.4: Effect of Surfactant type and Conc. on Granule properties (binder: Alginate,diluent: lactose) 146

Table 6.3.1: Effect of Surfactant type and Conc. on Granule properties (binder: Strach paste,diluent: MgCo3) 151

Table 6.3.2: Effect of Surfactant type and Conc. on Granule properties (binder: PVP,diluent: MgCo3) 151

Table 6.3.3: Effect of Surfactant type and Conc. on Granule properties (binder: Gelatin,diluent: MgCo3) 152

Table 6.3.4: Effect of Surfactant type and Conc. on Granule properties (binder: Alginate,diluent: MgCo3) 152

Table 6.4.1: Effect of Surfactant type and Conc. on Granule properties (binder: Alginate,diluent: Aerosil) 154

Table 6.4.2: Effect of Surfactant type and Conc. on Granule properties (binder: PVP,diluent: Aerosil) 154

Table 6.4.3: Effect of Surfactant type and Conc. on Granule properties (binder: Gelatin,diluent: Aerosil) 155

Table 7.1.1: Tablet Composition (Lactose as diluent) 174

Table 7.1.2: Tablet composition (Heavy magnesium carbonate as diluent) 175

Table 7.1.3: Aerosil as diluent 175

Table 7.2.1:Effect of Mg stearate conc. on Granule properties with Lactose as Diluent 178

Table 7.2.2:Effect of Mg stearate conc. on Granule properties with heavy MgCo3 as Diluent 180

Table 7.2.3:Effect of Mg stearate conc. on Granule properties with Aerosil as Diluent 182

Table 7.3.1:Effect of Mg stearate conc. on Tablet properties Diluent:Lactose 184

Table 7.3.2:Effect of Mg stearate conc. on Tablet properties Diluent:Heavy MgCo3 186

Table 7.3.3:Effect of Mg stearate conc. on Tablet properties Diluent:Aersoil 190

Table 8.1.1: Effect of Formulation on the Rf values of the various formulations Lactose as diluent 196

Table 8.1.2: Effect of Formulation on the Rf values of the various formulations MgCo3 as diluent 196

Table 8.1.3: Effect of Formulation on the Rf values of the various formulations Areosil as diluent 196

Table 8.2: Composition of hot water extract (HWE) and heavy magnesium carbonate mixtures. 209

Table 8.3: Comparative concentrations of HWE and HWE/MgCo3 mixture. 210

Table 8.4: Values from the Plot of C/x/m against C 212

LIST OF APPENDICES

Appendix 1: Format for weight variation result

Appendix 2: Spectral charaeterises for weight variation studies

LIST OF FIGURES

Fig No.		Page No.
3.1	Effect of various extracts on pendular movement of rabbit jejunum	57
3.2	Comparative antiulcer activity of *Ficus* leaf extracts	59
3.3	Comparative antiulcer activity of some drugs	63
4.1	Granule size distribution (Na alginate as binder/Lactose as diluent)	72
4.2	Granule size distribution (Na alginate as binder/ Heavy Magnesium Carbonate as diluent	72
4.3	Granule size distribution (Na alginate as binder/Aerosil as diluent)	72
5.1.1	Heckel plots (Lactose /Starch)	106
5.1.2	Heckel plots (Lactose /PVP)	111
5.1.3	Heckel plots (Lactose /Alginate)	114
5.1.4	Heckel plots ($MgCo_3$ /Starch)	117
5.1.5	Heckel plots ($MgCo_3$ /PVP)	121
5.1.6	Heckel plots ($MgCo_3$ /Gelatin)	123
5.1.7	Heckel plots (Aerosil /Gelatin)	127
5.2.1	Effect of binder type (Low concentration) on Heckel plots	139
5.2.2	Effect of binder type (Medium concentration; Lactose as diluent)	139
5.2.3	Effect of binder type (high conc.; Lactose as diluent)	139
6.1.1	Effect of surfactant type & conc. on tablet hardness (Lactose as diluent)	157
6.1.2	Effect of surfactant type & conc. on tablet friability (Lactose as diluent)	157
6.1.3	Effect of surfactant type and conc. on disintegration lime (lactose as diluent)	159

6.1.4 Effect of surfactant type and conc. on dissolution time, T75% (Lactose as diluent) 159

6.2.1 Effect of surfactant type and conc. on tablet hardness ($MgCo_3$ as diluent) 165

6.2.2 Effect of surfactant type and conc. on tablet friability ($MgCo_3$ as diluent) 165

6.2.3 Effect of surfactant type and conc. on disintegration time ($MgCo_3$ as diluent) 167

6.2.4 Effect of surfactant type and conc. on dissolution time, T75% ($Mgco_3$ as diluent) 167

6.3.1 Effect of surfactant type and conc. on tablet hardness (Aerosil as diluent) 169

6.3.2 Effect of surfactant type and conc. on tablet friability (Aerosil as diluent) 169

6.3.3 Effect of surfactant type and conc. on tablet disintegration time (Aerosil as diluent) 170

6.3.4 Effect of surfactant type and conc. on dissolution time, T75% (Aerosil as diluent) 170

8.2.1 Effect of formulation on the spectra of the HWE (Lactose as diluent) 199

8.2.2 Effect of formulation on the spectra of the HWE ($Mgco_3$ as diluent) 200

8.2.3 Effect of formulation on the spectra of the HWE (Aerosil as diluent) 201

8.3.1 Effect of formulation on antiulcer activity (Lactose as diluent) 203

8.3.2 Effect of formulation on antiulcer activity ($MgCo_3$ as diluent) 203

8.3.3 Effect of formulation on antiulcer activity (Aerosil as diluent) 203

8.4 Plot of C /XM versus C 211

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1.1 GENERAL INTRODUCTION

Herbal medicines, as the major remedy in traditional medical systems, have been used in medical practice for thousands of years and have made a contribution to maintaining human health. A majority of the world's population in developing countries still relies on herbal medicines to meet its health needs. The use of these medicines has a particularly rich tradition among the peoples of the Southern hemisphere. The attention paid by health authorities to the use of herbal medicines has increased considerably, because they are often the only medicine available in less developed areas where for example over eighty percent of the African population which has no access to orthodox medicine depend on traditional medicine (Naomesi, 1996). They are also becoming a popular alternative medicine in more developed areas. The WHO has thus recognised herbal medicines as a valuable and readily available resource for primary health care and therefore endorsed its safe and effective use.

Phytomedicines may be defined as medicinal products containing as active ingredients parts of plants or plant materials, or combinations thereof, in whatever form, either crude or processed. This has probably led workers in the field of plant medicine research such as Ayafor (1996) to state that higher plants constitute living chemical factories that provide a vast array of unusual chemical structures that display a variety of biological

activities. It is also stated that of the estimated 250,000 -500,000 currently known higher plant species only a small percentage has been investigated phytochemically. The fraction subjected to biological or pharmacological screening is also very small. There is now an increased urgency in this direction because of the destruction of natural resources and the vastness of the field.

While the WHO supports the appropriate use of herbal medicines and encourages the use of remedies that have been proven to be safe and effective, it has also stated that most herbal medicines still need to be studied scientifically, although the experience obtained from their traditional use over the years should not be ignored. It has therefore published guidelines with the main purpose of defining the basic criteria for the evaluation of quality, safety and efficacy of herbal medicines and thus assist researchers and others to undertake an assessment of the documentation in respect of such products. This would result in standardisation of phytomedicines which Elujoba (1996), defines as the process of recommending a set of pharmacognostic, chemical, biological and pharmaceutical standards adequately controllable which could form an official monograph for a proposed plant drug preparation. The provision of a monograph for phytomedicine is evidence of standardization for that particular drug, ensuring its quality, safety, efficacy and reproducibility.

In practice, it is rare for a drug substance to be administered as the pure chemical compound itself. They are always administered as some kind of dosage form which may be as simple as solutions in water but more often they are complex mixtures containing the active drugs and other additives. This is even moreso with phytomedicines where in most cases, the traditional preparations might be unnecessarily bulky, unpalatable and prepared in generally unsanitary conditions that do not meet standards for substances produced for human consumption. One of the main ways by which the standard

characteristics (quality, safety, efficacy and reproducibility) can be guaranteed is by formulation of the products into appropriate dosage forms. It is also one of the major steps in the scientific evaluation and standardization of herbal medicines. While there are various dosage forms that could be used, the choice would depend on factors such as the physical nature of the medicine, the plant part, liability to deterioration. Naomesi (1996) has stressed that ethnomedical information on the mode of drug administration should form the basis for deciding the formulation method to be used for the phytomedicines, while complex chemical extraction processes should be avoided. In addition to this, Ngengwe (1996) has stated that the cost of production should also be considered in determining the dosage form to be used as the purpose of phytomedicine will be defeated if the cost of production is high.

1.2 PEPTIC ULCER DISEASE

An ulcer has been defined as an inflamed discontinuity in the skin or mucous membranes of the body, which may be due to injury, infection or the action of corrosive fluids.The Black's Medical dictionary defines it as a breach on the surface of the skin or on the surface of the membrane lining any cavity within the body, which does not heal quickly. An ulcer consists of a floor or surface, which in consequence of the loss of tissue, is usually depressed below the surrounding healthy surface, and an edge where the healthy tissues end.

When any degenerative change takes place in the mucous membrane of the stomach, that part is less able to resist the action of the gastric juice upon it and is apt to undergo disintegration all the more readily, hence forming an ulcer.

If the formation of the ulcer is as a result of the abnormal action of pepsin and other gastric juice constituents on the mucous membrane of the stomach or duodenum, it is referred to as peptic ulcer which can either be gastric or duodenal. Gastric ulcers (GUs) are those of the stomach while those found in the duodenum, which is the first part of the intestine after the stomach are referred to as duodenal ulcers (DUs). Duodenal ulcers are ten to fifteen times more common than gastric ulcers while both forms are more common in men than women. While gastric ulcers are frequently seen in patients above 40 years of age, duodenal ulcers occur from any age above 20.

Duodenal ulcers are usually found at sites with severe inflammation and gastric metaplasia, although it is unlikely that gastric mucosa *per se* is more susceptible to acid - peptic digestion than is duodenal mucosa, but the inflammation occuring at sites of gastric metaplasia may locally impair mucosal resistance to injury. Thus it can be speculated that DUs are simply GUs displaced to the duodenun. Acid is however quite important in the equation; patients with excess acid may experience more duodenal injury than those without.

Sanyal *et al* (1983) have stated that traditionally peptic ulcers have been described as an inbalance between the luminal acid peptic attack versus the mucosal defense. Acid and pepsin components forming the aggressive factors and the mucous layer of mucin - bicarbonate secretion, phospholipid layer, tight junctions, cell proliferations, prostaglandins and the urogastrone/epidermal healing factors (URO/EHF) forming the defensive factors. Graham (1995) also concluded that there is as yet no dispute among gastroentrologists that acid and pepsin are still prime aetiological factors in peptic ulcer disease. This has led to the axiom, no acid - no ulcer amongst researchers in the field. (Feldman, 1989; Freston, 1990; Graham, 1989)

Fry (1964) found that the natural history of peptic ulcer in an unselected patient population was marked by decreasing severity or burn-out occuring after a period of 7-15 years. This has been explained by Graham (1989) to probably be due to an increased extent of gastrins resulting in reduced ability to secrete acid thus reducing the rate of tissue destruction and allowing for healing of the ulcers.

However, not all patients with gastric or duodenal ulcers have increased acid secretion. It has been reported by some workers that acid secretion remains within the normal range in 40-70% of cases of duodenal ulcers and normal or even below normal in gastric ulcer patients (Gupta *et al*, 1980). It would therefore seem that decreased mucosal resistance could be the dominant factor. More recently, the role of mucosal factor in peptic ulceration has received much attention and the term cytoprotection has been introduced. It is now fairly well established that peptic ulcer disease can be prevented by strengthening the defensive mechanisms of gastric and duodenal mucosa rather than attenuating the factors of aggression causing ulceration. This has led to the introduction of agents such as carbenoxolone sodium, sucralfate and prostaglandins in the treatment of peptic ulcer disease (Barrowman, 1982).

Peptic ulcer is extremely common, affecting up to 2% of adults in the community. The natural history suggests that it is a chronic disease, characterised by frequent re-occurences, which in some patients may be complicated by life threatening bleeding or perforation. The many direct costs of the disease include medical consultation, endoscopic diagnosis, occasional hospitalisation, and the need for drug therapy, while indirect costs include time lost for work and a poor quality of life (Korman and Tytgat, 1995). Smoking, alcohol use, and male gender (Graham *et al*, 1992) and increased particule cell mass, increased basal secretary drive, increased post prandial gastrin release, increased sensitivity to secretagogues, decreased inhibition of acid and gastrin

secretion, rapid gastric emptying, increased duodenal acid load and decreased mucosal resistance (Graham, 1989) are some factors that are thought to be important in the pathogenesis of peptic ulcer disease. NSAIDs are also important causes of ulcer (Korman and Tytgat, 1995; Graham, 1989). They do this by inhibiting prostaglandins which are required to promote mucous protection of the stomach. They usually cause ulcer at the posterior wall towards the upper or lesser curvature of the stomach near to the pyloric orifice which is the point at which the mucus membrane is subjected to most friction by the food as it leaves the stomach. Geographical variations have also been seen in the incidence of peptic ulceration (Jayaraj *et al*, 1980; Holcombe, 1992).

From all of the foregoing, especially the high economic cost of the disease, any effort towards the treatment of peptic ulcer will be useful.

1.2.1 *Helicobacter pylori* and Peptic ulcer

Since the early eighties, the role of the bacteria, *H. pylori* in the pathogenesis of peptic ulcer has been studied very extensively. The dramatic experiment by Marshal (where he was the subject) where he drank a broth of *H. pylori* to demonstrate the contribution of the organism in the development of gastritis and subsequently ulcer (Graham, 1995) started off what has turned out to be an exciting area of research.

There is sufficient evidence now to be able to say that *H. pylori* is an important factor in the pathogenesis of peptic ulcer disease, which has led Graham(1985), to suggest an addition to the old diction "no acid-no ulcer", "no *H. pylori*-no ulcer". Although the

mechanism by which *H. pylori* exerts its effects is unknown (Holcombe, 1992), Graham (1985), has speculated that in patients with duodenal ulcer disease superimposed factors interact with *H. pylori* to break down normal defenses, thereby allowing an ulcer to form. He suggested that *H. pylori* infection has a number of possible adverse effects on gastric structure and function. For example, the mucosa is infiltrated with PMNs and lymphocytes and the normal surface mucous cells are altered. These structural changes may reduce mucosal resistance and promote the development of peptic ulcers in susceptible people. Wyatt and Dixon (1991) suggest that *H. pylori* infection leads to ulceration only in the presence of gastric metaplasia in the duodenun, which is increased in hyperacidity (Dixon, 1991).

There are still well articulated arguments challenging the role of *H. pylori* in the pathogenesis of peptic ulcer disease (Graham, 1995). The results of studies by Holcombe (1992) where he found that although 70-80% of Africans have *H. Pylori* infection, with only about 28% developing symptoms of ulcer, tend to show that *H. pylori* infection alone will not result in the development of the disease.

There are however many more studies showing a relationship between *H. pylori* and peptic ulcer disease such as an improved rate of healing with suppression of the bacteria (Bayerdorffer *et al* 1987; Evans, 1990) and markedly decreased recurrence rates for duodenal ulcer (Tytgat *et al*, 1993) and gastric ulcers (Graham *et al*, 1992) after eradication of *H. pylori*.

Almost every study in the past ten years has also substantiated the original observation that successful eradication of *H. pylori* cures duodenal ulcers (Coghlan *et al*, 1987).

The situation now is such that the National Institutes of Health consensus meeting in the

USA in 1994 pronounced *H. pylori* as a major factor in gastroduodenal pathology and strongly recommended that all patients with duodenal or gastric ulcer, infected with *H. pylori* should be prescribed treatment aimed at eradication of the infection.

1.2.2 Antiulcer Test Models

As has been earlier stated, peptic ulcer is injury caused either to the stomach (gastric ulcer) or duodenum (duodenal ulcer) by pepsin and other gastric juices. Most antiulcer models used in small animals especially rats attempt to induce the ulcer by wounding the stomach surface. Njar *et al* (1994) used indomethacin to induce ulcers, while Akah *et al* (1997) and Mitra *et al* (1996) used aspirin induction. Other agents used include reserpine (Tanaka *et al*, 1976) as well as alcohol, cysteamine and histamine (Mitra *et al*, 1996). Apart from drugs, processes which could induce stress such as cold restraint (Aguwa and Nwako, 1988) and a combination of drug and cold stress (Elegbe, 1978) can also be used. All of these processes would generally result in ulcers on the upper or lesser curvature of the stomach.

The choice of method would depend on the convenience and the nature of the action of the drug under test .

1.3 COMPACTION CHARACTERISTICS OF PHARMACEUTICAL POWDERS

The compaction behaviour of pharmaceutical powders has engaged the attention of investigators for a number of years. For example, Train, (1956), related applied pressure

to relative volume of powder. He suggested that elastic compression of the solid powder occurs at high compression force, where the compact is sufficiently strong to support the applied load with no further reduction in volume.

Various authors (Huffine and Bonilla, 1962; Heckel, 1961; Cooper and Eaton, 1962) have distinguished different stages during the compression of powders in dies. These include the filling and rearrangement of particles in the die, the elastic and plastic deformation of particles, their fracture and cold working. It is thought that in many cases, several of these processes occur simultaneously.

Kwakita and Ludde (1970) extensively reviewed a large number of equations that have been proposed to describe compressional behaviour of powders to differentiate the various stages in a compression process. They concluded that the Heckel's equation although deviating slightly from linearity at low compression pressures, was most informative because it provides information on mechanisims of powder consolidation. In addition to this, the Heckel's constants K and A were found to have valuable physical significance and could be used to draw conclusions concerning the effect of the characteristic of the material and the particle size on the densification process. York and Pilpel (1973) as well as Kurup and Pilpel (1978), have also concluded that the Heckel equation appears to be the most sensitive in distinguishing the various processes for certain soft pharmaceutical materials. Paronen and Juslin (1983), have also drawn the same conclusions from their work on the compressional characteristics of various starches.

The Heckel's equation is given as,

$$\ln \frac{1}{1-D} = KP + A$$

where D is the relative density at applied pressure P; K and A are constants. The reciprocal of K is the mean yield pressure P_y which is an important compressibility index that describes the tendency of a material to undergo total and plastic deformation. It also relates to the rate of deformation which is quite important because tabletting machines have short dwell times. A, is a function of the original compact volume and represents two stages of consolidation - one due to the initial relative density of the powder and the other due to densification by particle rearrangement. From the value of A, the relative density D_A, can be calculated using the following equation (Roberts and Rowe, 1986),

$$D_A = 1 - e^{-A}$$

D_a which is obtained from the ratio of loose density of powders to effective particle density, is the relative density of the powder bed when the applied pressure, P, is zero. It has been used to describe the initial rearrangement phase of densification as a result of die filling (Itiola, 1991).The relative density D_B, describes the phase of rearrangement of particles during the initial stages of compression. The extent of this phase depends on the theoretical point of densification at which deformation of particles begins. D_B is obtained from the equation,

$$D_B = D_A - D_a$$

Based on the Heckel equation, various workers have identified 3 types of powder compression behaviour (Hersey and Rees, 1971). Summers *et al* (1976) described powder compaction behaviour as type A and type B. With type A behaviour, a linear relationship is observed at all applied pressures indicating densification apparently only by plastic deformation. Sodium chloride is an example of a material with such a behaviour. For type B behaviour, there is an initial region, usually curved, followed by a linear region.

The initial region represents brittle fracture or particle fragmentation followed by plastic flow or deformation. This is usual with hard, brittle materials, such as lactose (Armstrong and Lowudes 1984) which require initial consolidation by fragmentation to form a consistent (denser) packing. Type A curves usually exhibit a steeper final slope than type B, indicating a lower mean yield pressure value. In practice, hard brittle materials are more difficult to compress than soft yielding ones because fragmentation with subsequent percolation of fragments is less efficient than void filling by plastic deformation.

York and Pilpel (1973) reported the effect of compression of fatty acids and lactose-fatty acids mixtures. They proposed a type C behaviour. Type C materials such as fatty acids exhibit initial steep linear regions, which become superimposed and flatten out as the applied pressure is increased. This is believed to be due to the absence of a rearrangement phase and densification is due to plastic deformation and asperity melting. It was noted that type C behaviour fits a typical type A curve except that the initial densification was observed to be slight due to the nature of the mixtures, the yield pressures were found to increase with the melting point of the fatty acids.

As earlier stated, the Heckel equation has been used in numerous compaction studies. However, the results of various workers tend to give different pictures. For example, Rue and Rees (1978) observed non-linear Heckel plots for a granular microcrystalline cellulose, and suggested the use of areas under the Heckel plots for different punch contact times. York (1979) demonstrated that the numerical values for yield pressures obtained by various workers, for crystalline lactose, were dependent on experimental conditions such as degree and type of lubrication of punches and die, punch diameter, compaction rate and method of determining relative density. Other workers have also found that compression time (Rue and Rees, 1978), and time of measurement i.e. whether density measurement is made during compression or after ejection (Fell and Newton, 1971)

affected the Heckel plot.

Paronen (1987) evaluated Heckel plots as indicators of elastic properties of pharmaceutical powders. Tablet-in-die and ejected tablet methods were used to determine values for Heckel functions. The total elastic recovery was obtained using the reciprocal of the difference of the Heckel upward slopes obtained from the two methods used in the study. The degree of densification obtained during the compression process at a compaction pressure of about 170 MPa was shown to decrease in the order; modified starch < microcrystalline cellulose < sodium chloride < dicalcium phosphate dihydrate. The tendency of the materials to deform both plastically and elastically was described by the reciprocal of the Heckel plot slope obtained using the tablet-in-die method. The tendency of the materials to deform plastically was shown to be the reciprocal of the slope of Heckel plot obtained by the ejected tablet method. The order of the materials according to this permanent densification tendency was sodium chloride < microcrystalline cellulose < modified starch < dicalcium phosphate dihydrate. The difference between the orders of materials obtained by the two methods was ascribed to the differences in the tendency of the materials to recover elastically.

The Heckel equation which is used to treat most powder compression data is only applicable at pressures above the yield strength. Carstensen *et al* (1990) proposed an equation based on the indication that powder void volume decreases exponentially with pressure and tends towards a value different from zero within the pharmaceutical pressure range, suggesting that the final compressed solid always possesses some level of porosity. The equation is of the form,

$$\ln \frac{1}{(1-e)-J} = -aP + \ln V_s D$$

where D is the true (non-porous) density and J is $V_s D$, where V_s is the actual specific solid volume towards which the solid tends during the low pressure region of compression.

1.3.1 Effect of Particle Characteristics on Compaction Behaviour of Powders

1.3.1.1 Particle size

Particle size may determine the deformation mechanism of a material and thus influence the consolidation and compaction characteristics of elastic and plastic components. For example, Gregory (1962) found that particle size and size distribution will have important effects on particle slippage which will affect compaction behaviour.

Although there are a number of equations describing powder compaction data of different particle sizes, the one proposed by Heckel (1961) considered the consolidation process to be analogous to a first order chemical reaction, where the pores are the reactants. This equation is the most widely used because it can provide information on the mechanism of consolidation of the powder and allows for the effect of particle size to be readily studied .

Consequently several workers have investigated the effects of varying particle size of a material on the constants derived from Heckel equation. Hersey and Rees (1971) reported the effect of particle size on the consolidation of powders, and noted that the Heckel treatment facilitated the determination of the influence of particle size on consolidation. It was possible, from the values of the true density, yield pressure and original packing

density to predict the consolidation mechanism and relative compact density at pressures above the material yield value.

Studies have also been carried out on changes in particle distribution of sulphathiazole powder during compaction (Carless and Sheak, 1976). It was shown that as the bigger sized particles are crushed, the fines are agglomerated, and the intermediate sizes are not significantly affected. They concluded that at a critical particle size of 76μm, the effects of crushing and agglomeration cancel each other, thence suggesting that the critical particle size at which bonding and fragmentation equalise may vary from solid to solid, with brittle materials found to have lower critical particle size values compared to ductile substances.

Mckenna and McCafferty (1981) found that the tensile strength of lactose and starch compacts respectively increased with decreasing particle size, while that of microcrystalline cellulose tablets were unaffected by particle size variation. With the Heckel plot at two different contact times, it was found that the principal compaction mechanism was independent of the size fractions used. They also found that the angle of repose and Hausner ratio data indicated an increase in interparticulate frictional and cohesive forces with decreasing particle size. This observation explained the increase in tablet strength with decreasing particle size of starch due to concomittant increase in density as a result of the increase in plastic flow and packing with decreasing particle size. For microcrystalline cellulose, the cohesion and interparticulate frictional forces appeared to be independent of particle size. The Heckel analyses also revealed the independence of deformation mechanism on particle size.

The effect of initial particle size on the binding properties of lactose was studied by Vromans *et al* (1985). They showed that a decrease in the initial particle size resulted in

an increase in tensile strength of the tablets. The compression of small particles produced tablets with increased thickness compared to those from large particles. This was found to be due to a change in porosity rather than an alteration of the density of the material.

Two materials - Avicel PH101 and magnesium carbonate with dissimilar compaction mechanisms were investigated for changes in particle size and size distribution (Armstrong and Cham, 1987). The particle size of the disintegrated compacts were found to be affected by both the initial particle size and the differences in the consolidation mechanisms of the two materials. However changes in particle size of the binary mixtures were dependent on the relative concentrations and the consolidation mechanism of the individual components. They concluded that the mechanical strength of a tablet is basically a function of the mechanism of interparticulate attraction and the area over which these attractions occur. These parameters are governed by a number of secondary factors which include particle size and shape, deformation and fragmentation of particulate solid, the rate of loading and die geometry.

Aldeborn *et al* (1988) found that a decrease in Starch 1500 particle size gave an increased tablet strength attributed to the high number of contact points and a possible increase in stress at each particle contact point, which facilitated plastic flow or the formation of solid bridges at the contact point.

1.3.1.2 **Surface Area**

The physical properties of a powder and interparticulate bonding where surface forces are involved depend significantly on the surface area of the constituent particles. A decrease in particle size of a powder that consolidates principally by fragmentation mechanism

increases the theoretical number of attraction points. It would therefore be reasonable to assume that the bonding surface area or the effective number of interaction points governs the strength to a high degree.

Armstrong and Haines-Nutt (1970) observed in a study on the compaction of magnesium carbonate that size reduction takes place at low compaction pressures up to about 140 MNm^{-2}, but that further increases in pressure caused a rise in geometric mean diameter. The estimation of particle fractions before and after compression indicated that at pressures up to $125MNm^{-2}$ the number of large particle showed a gradual reduction, whilst the number of small particles showed an increase; indicative of fragmentation. A higher compression pressure reversed the trend, supporting the evidence of dominant particle aggregation.

Paronen and Juslin (1983) studied the compressional characteristics of four starches - barley, corn, potato and wheat using constants obtained from the Heckel plots, they found that potato starch, with the greatest mean particle diameter, formed the densest column in the die filling stage because it had the least electrostatic forces that could prevent the packing of particles in the bulk state. Barley starch which had small and the most irregular particles had the loosest column because there were mechanical and electrostatic forces to prevent packing. They deduced that the values for the packing fraction in the bulk state are strongly dependent both on the particle size and shape. It was noted that there exists more resistance to particle movement where the contact area is large, which was seen from the D_A value. The phase of rearrangement of particles was found to be larger for materials with relatively less densification due to die filling. The rearrangement of particles occured more with smaller particle size (corn) and less with larger particle size (potato) and seemed to be particularly responsible for the densification of wheat and barley starches which have a relatively wide particle size distribution and

an irregular particle shape. Particle properties were also found to affect yield pressure values generally in an inverse manner. Fell and Newton (1971) have also made similar observations.

The shape of particles can affect the flow properties of a powder mixture. This is important because pharmaceutical powders could have different shapes due to their chemical identity or the different processes to which they are subjected. Ridgway and Rupp (1970) found that angle of repose increased whilst the bulk density and flowability decreased with increasing departure from spherical shape, due to the greater resistance to shear of flow of an assembly of irregular particles compared to one of spherical particles with the same size and density. In a related study, Ridgway and Shotton (1970) concluded that very small particles had inadequate kinetic energy to induce rearrangement of those particles already in the die. Increasing the average size correspondingly increased the average mass of powder filled into the die cavity, and enhanced particle rearrangement whilst further increases in particle size led to inefficient packing.

Alderborn *et al* (1988) studied the effect of particle size and shape on the mechanical strength of sodium bicarbonate tablets. The milled powder gave tablets with the highest strength probably due to the increased surface irregularity. This might have been because it increased the number of points with a close proximity between the particles, increase the total bonding surface area, enhance interparticulate friction and facilitate plastic flow at the contact points.

Starch 1500, a material which consolidates principally by plastic deformation, was investigated for effect of particle shape on its compression properties by Wong and Pilpel (1990). Large increases in compressibility, decrease in yield pressure values and elastic

recovery was observed from regular to irregular particles. For lactose and emcompress which consolidate primarily by fragmentation mechanisim, particle shape had no effect on the above properties. It was also observed that irregular particles fractured more than the regular ones.

From all of the foregoing, it should be noted that the use of identical experimental conditions will be of high importance when employing Heckel plots for the direct comparison of powders with different consolidation mechanisms.

1.4 EFFECT OF BINDER CONCENTRATION ON GRANULE AND TABLET PROPERTIES

Owing to their wide-ranging physicochemical and mechanical properties, pharmaceutical powders and their blends frequently exhibit poor flow and compaction behaviour (Krycer *et al* ,1983). Thus an intermediate step - granulation - is usually required in solid dosage manufacture to produce a free-flowing material with good compression characteristics. The process of wet granulation occurs by complex interactions of several parameters, each of which will affect the final product performance. A knowledge of the effect of each of these parameters is therefore necessary if the granulation process is to be adequately controlled (Kristensen and Schaefer, 1987).

Binders, which are substances that are added to tablet formulations to produce granules out of particulate powders, play a vital role in this process. They impart cohesiveness and structural strength to the powdered material and aid in the compression and bonding required to form tablets that can withstand handling. A substance used as a binder when

added in the right amount and concentration should impart just the degree of cohesiveness that will require minimum compression pressure to compact the granules to tablets.

There are various binders in use depending on the method of granulation to be used or whether manufacture is to be by direct compression or not. Those used in wet granulation include: acacia, which is used in solutions with concentration ranging from 10 to 20% or even higher depending on how much water the mixed powders can tolerate; gelatin, which must be used as solution while still warm since it gelatinizes on cooling and whose dissolution is enhanced if it is first suspended in cold water and then heated on a water bath; starch, which is most useful when the drug is insoluble and in high concentrations relative to the excipients, is used as a paste prepared by suspending it in one to one and a half parts of cold water with the addition of four times as much boiling water; sodium alginate, which should also be used when warm since it tends to gelatinise on cooling; and polymers, such as polyvinyl pyrollidone (PVP). Other binders are methyl cellulose, sodium carboxymethyl cellulose and sucrose.

These binders can also be added dry, blended with the diluents and drug and then activated by the addition of water or other solvents; but the same binder added as a slurry or paste is more efffective than when added dry to the formulation before activation. Dry binders are used in the direct compression of tablets whose aim is the production of elegant tablets with higher dissolution rate, minimum cost and processing time. Among the most important dry binders are microcrystalline cellulose (Avicel), amylose and polyethylene glycols (PEGs) with molecular weight higher than 6000.

The concentrations of liquid binders used vary depending on the nature of the binder and the powdered material to be granulated. In turn, the concentration of the binder along with its nature and mode of incorporation influences the compression characteristics of

the tablets to be prepared from the granules. It is therefore important to know the effects of these factors on tablet properties and take steps to eliminate those of them that are adverse.

The most pronounced and noticeable effect of binders in granules for tablet manufacture is on the disintegration and dissolution rate of tablets as has been shown by the result of investigations by various workers.

Jacob and Plein (1968) investigated the factors that affect the dissolution rate of medicaments from phenobarbital tablets. They found that increasing the binder concentration resulted in decreased dissolution rate of the drug. Shubair and Dingwall (1977) using three different drugs, showed that the *in vitro* release levels of the drugs were affected by the amount of binder (starch mucilage) used. Other workers have also reported that variation in starch mucilage concentration produced granules of different geometric surface area which will eventually affect dissolution rate, since surface area is an important factor in the determination of dissolution rate (Steiner *et al*, 1974).

Using cassava starch mucilage, Nasipuri and Akala (1986), studied the effect of binder concentration and quantity on lactose granule and tablet properties. It was found that the quantity of the mucilage employed appeared to have a greater effect than the concentration on the mean granule size and granule size distribution. The mean granule size increased with increasing concentration and the quantity of mucilage. The rate of packing down of the granules increased with increase in mucilage concentration or quantity and the higher the rate of this the better was the flowability of granules. Increasing the binder concentration or quantity increased the tablet hardness and disintergration times and reduced friability.

Kunle and Bangudu (1990) investigated the effect of cassava, cocoyam, yam and maize starches as binders and disintegrants on the properties of sulphadimidine tablets. It was found that both the type and concentration of starch paste used as binder affected the tablet properties. The relative effects varied with the tablet property tested and the concentration used as binder.

Stanley-Wood and Shubair (1979) evaluated the effect of binder concentration on the compressibility, friability, granule size and size distribution together with the variation of surface area of granules produced by wet mixing granulation. They found that increasing the concentration of the mucilages up to 10% resulted in variation in granule size distribution while at concentrations of 15 and 20% mucilage there was a decrease in mean granule size from the optimum size obtained at 10% . It was also noticed that at higher mucilage concentrations, the more viscous mucilages produced pasty masses which were not easily screened. This was explained as being due to a decrease in bond formation that also resulted in the production of a large amount of fines. Sakr *et al* (1972) reported that as the concentration of binder (gelatin) increased in lactose tablet formulations, the friability of the tablets decreased while the disintegration and dissolution rates decreased.

Davies and Gloor (1972) found that increasing the binder concentration in dicalcium phosphate formulations resulted in increase in granule size which might have been due to increased penetration, covering or wetting of the dicalcium phosphate particles by the mucilage. Carstensen *et al* (1976) explained a similar observation as being due to the increase in binder concentration resulting in increase in the number of bond formations until at a given maximum an equilibrium granular state is achieved. Rankel *et al* (1964) also found that increasing binder concentration resulted in increased mean size of granulations.

Examination of the literature reveals numerous other instances where final granule properties have been related to binder physical properties (Opakunle and Spring,1976; Jaiyeoba and Spring, 1979; Wells and Walker, 1983; Ritala *et al*, 1986; 1988).

Parker *et al* (1990) from their work on the effect of binder characteristics on binder-substrate interactions in wet granulation concluded that different polymers (binders) behave differently in the wet massing process and that there is a possible role of solid/liquid interactions in governing the rheological behaviour during wet massing and therefore predicting final product performance.

When considering the effect of binder viscosity, various authors have observed that increasing binder concentration, and thereby viscosity, results in stronger granules (Chalmers and Elworthy, 1976). Cutt *et al* (1986) suggest that this is due to the increased amount of binder per bond, increasing the bond strength.

Ritala *et al* (1986) on the other hand, found that binder concentration only had a minor effect on granule growth during the liquid addition phase, in a high shear mixer, and that densification of the material dictated the granule properties to a greater extent. They explained that the apparent decrease in power consumption with increasing binder concentration was attributable to a lubrication effect of the binder while Parker *et al* (1990) atrributed it to the resulting increased viscosity causing a poorer binder distribution and therefore reduced power consumption as compared to the more easily distributed, lower viscosity binder.

Ritala *et al* (1986, 1988) concluded that different binders alter granule strength by their influence on the intragranular porosity and suggested that the high surface tension of PVP solutions caused the moist agglomerates to have the lowest porosity values (by reducing

the wetting of the substrate surface) thus increasing the mean strength of the granules through the effect of liquid saturation.

Zayic and Buckton (1990) found that the formulation with the higher concentration of binder (PVP) had the highest friability and suggested that the presence of larger quantities of binder decreases granule strength. They found that the PVP concentration did not affect the size distribution. They also noted that the larger volume of solution is much more effective in terms of reducing the friability and increasing the size of the granules formed, which they explained as being due to increased distribution and hence availability of the fluid, rather than the fact that the lower quantities are inadequate to cover the surface and peform a binding function. It was concluded that amongst others, the type of binder used, the concentration and the volume of the binder solution all alter the properties of the granules that are produced.

Moisture is also known to contribute to the binding action of liquid binders (Rowe and Sodeghnejad, 1987). The pendular and funicular states are characterised by a progressively increasing network of liquid bridges. Both these stages will cause an increase in cohesiveness of the powder mass. The capillary state which is reached when all the air spaces in the granular material are filled with liquid will result in maximum number and strength of bridges. Any further addition of liquid will result in the destruction of bridges since a slurry of particles dispersed in liquid is formed (Newitt and Conway-Jones, 1958).

Leuenberger *et al* (1979) found that the quantity of granulating liquid is critical; when too small it forms agglomerates that are too soft and disintegrate on drying, while if too much, it forms a doughy mass which is too moist for further processing and in extreme cases there is a complete breakdown of the dough mass into a suspension. They also

noted that there is a build up of cohesive force due to the formation of liquid bridges throughout the entire powder mass. The formation of bridges is considerably retarded in solids that, at a high relative humidity, are capable of taking up a large quantity of liquid. Therefore with mixtures containing large amounts of moisture-binding corn starch, the agglomeration of solid particules is delayed. At a critical stage it was noted that only the volume of the liquid bridges increased, without any further changes in cohesive force. With the further addition of granulating liquid, the void spaces begin to fill up completely with liquid, resulting in the disappearance of the liquid bridges and subsequent collapse of the mass.

Niskanen *et al* (1990) have found that the mean granule size of KCl increased with increase in binder solution flow rate in a fluidized bed granulator as was also the case with granule flowability. It was also noticed that increasing the binder solution flow rate decreased the dissolution of potassium chloride.

Kurup and Pilpel (1979) found an increase in tablet tensile strength with an increase in the concentration of binding agent. On application of pressure, the binding agents being soft and plasto-elastic will undergo plastic and elastic deformation, forced into the interparticulate spaces, thereby increasing the area of contact between particles and forming more solid bonds. Increasing the binder concentration affected the magnitude of the various forces involved in bond formation between particles - frictional, electrostatic and van der Waal's forces decrease, while solid bonds increase with capillary forces unchanged. The overall effect of this is increased tensile strength.

Esezobo and Pilpel (1977) attributed the increase in tensile strength with increase in gelatin concentration to the increase in the amount of bonding that would take place as a result of the increased temperature, causing wetting of asperities. Therefore the strength

of the tablet would be expected in part to depend on the amount of gelatin (binding agent) available to be melted and solidify to form strong bonds between particles. Increased amount of gelatin also reduced the capping tendency of the tablets. They also found that the higher the gelatin (binder) content, the larger the granules and the wider their size distribution. It (binder concentration) was also found to affect the disintegration and dissolution times as well as the tensile strength which all increased with increase in concentration.

In investigating the factors affecting the disintegration and dissolution of chloroquine phosphate/starch tablets, Pilpel *et al* (1978) noted that the presence of a binder and its concentration affect the tablet dissolution rate. They concluded that the dissolution of chloroquine phosphate/starch tablets was very dependent both on the quantity and distribution of the starch in the formulation.

Kurup and Pilpel (1977), found that the tensile strengths and disintegration times of griseofulvin tablets depend on the binding agent concentration (PVP) and on the compression time and pressure.

It has also been found that the type of starch used as binder affects the disintegration/dissolution properties of sulphanilamide tablet formulation (Keshri *et al*, 1974). Esezobo and Pilpel (1977) also proposed that increased disintegration and dissolution time might, apart from increased bond formation, be due to the formation of a thin film of gelatin (binder) around the powder particles or granules; its thickness depending on the quantity of gelatin used. This film could be converted to a mucilagenous viscous barrier when the tablets contact the test media, thus decreasing fluid penetration and increasing dissolution and disintegration times.

1.5 SURFACTANTS

Surfactants or surface active agents are substances that are adsorbed at interfaces. They decrease the solid-liquid interfacial tension and are therefore widely used as wetting agents. This is because they displace most liquids or gases from solid surfaces. The surface activity property of each surfactant is largely due to the type which would depend on the nature of the geometry, chemical nature and the hydrophilic - lipophilic balance (HLB).

All surfactants have a molecular configuration which exhibit ampihilic behaviour, i.e. their molecules contain a hydrophilic head group, balanced with a lipophilic tail group. It is this duality of character within the molecule that gives them their surface properties.

The classification of surfactants is based on various properties, for example, contact angle, HLB value, or chemical nature:

(a) Contact angle: It expresses the interaction of the surfactant with the non-particles (Troster and Kreuter, 1988). It is a useful indicator of wetting, with a low value indicating effective adhesion that ensures wetting, while a high value occurs with poor wetting. Wetting occurs when the adhesive forces (solid-liquid) predominate over the cohesive forces within the solid. If the interaction between the solid and liquid is greater than the interaction between the solid and air, the angle will be less than 90^0 (Hem *et al*, 1986). Troster and Kreuter (1988) classified surfactants into 4 groups based on the contact angle: GP 1 - lowest affinity to solid surface e.g. polysorbate 60; GP 2- e.g. Polysorbate 80, Polysorbate 85; GP 3-e.g. Polysorbate 20; GP 4 - high affinity to solid surface, demonstrated by the low advancing and consistently zero receding contact angles indicating a strong interaction and adherence to the solid e.g. Polyoxamine 908.

(b) Hydrophilic - Lipophilic (HLB) value: On this scale, the higher the HLB, the more

hydrophilic is the substance. The Spans and Sorbitans, with low HLB values are more lipophilic.

(c) Chemical - The chemical nature is the most common method of classification. The nature of the charges on the effective moiety is used as the basis for classification.

(i) Anionic: These have negative charges,. The long alkyl chain sulfonates and alkyl amyl sulfonates such as sodium dodecyl benzene sulfonate are examples of materials in this group. Alkyl sulfates like sodium lauryl sulphate which are widely used as emulsifiers and solubilisers in pharmaceutical systems also belong to this group.

(ii) Cationic surfactants: To this group belong a number of long chain cations, like amine salts and quartenary ammonium salts which are useful as surfactants when dissolved in water. They are most commonly used as preservatives because they are adsorbed readily at the cell memberane and may thus be toxic.

(iii) Amphoteric agents: These contain both cations and anions. Those molecules that contain carboxylate or phosphate groups as the anion and amino or quarternary ammonium groups as the cation are in this category.

(iv) Non-ionic: They are the most commonly used surfactants since they are generally stable, compatible with various pharmaceuticals and safe. Examples are Polysorbates (Tween) e.g. Polyoxyethylene sorbitan monostearate, sorbitol esters (Spans) e.g. sorbitan mono oleate and Macrogol esters (Brijs), e.g. Polyoxyl 40 stearate.

1.5.1 Surfactants and Pharmacy

The effect of surfactants in various pharmaceutical systems is due to one or more of the following:

1.5.1.1 Wetting - This is the dsplacement of either a liquid or a gas by a second liquid (Hem *et al* 1986). Surfactant solutions displace the air phase at the solid-air interface by

lowering the advancing contact angle. They reduce tension by the adsorption of the two ends - the hydrocarbon chain and polar moiety by the hydrophobic surface and aqueous phase respectively. It is particularly useful in drug release from dosage forms as it speeds up the penetration of gastric fluid into the tablets and hence its disintegration. (Schott *et al*, 1982). Wesintraub and Gibaldi (1969) have demonstrated a good correlation between surface tension lowering property of non-ionic surfactants and the rate of release of drugs from tablets while the addition of surfactants to liposoluble excipients was found to increase the release of the active drug (Moes and Jaminent, 1976). Awe and Gelbrecht (1956) showed that the action of sodium salts of cetyl and myristyl sulphate in improving disintegration of phenacetin tablets was by enhancing the wettability of the tablets.

There is a critical concentration beyond which the addition of a surfactant could retard solid drug dissolution by dewetting. When hydrophilic solid surfaces of relatively high charge density come into contact with aqueous solution of ionic surfactant of the opposite charge, the surface active ions are chemisorbed by an ion-exchange mechanism which reduces the zeta potential on the solid surface to very low values or even zero (Schoot *et al*, 1982). The surface of the solid will also be covered by hydrocarbon chains, rendering it more hydrophobic and poorly wetted. Nogami *et al* (1963) observed that on addition of anionic surfactant, dioctyl sodium sulfosuccinate, to water, an increased rate of penetration into a powder bed of negatively charged aspirin particles but a lowered rate of penetration into a bed of positively charged magnesium oxide particles was observed.

1.5.1.2 Solubilization: This occurs when the dissolved surfactant is present at concentrations exceeding its critical micellar concentration which is the narrow concentration range at which there is a noticeable change in the properties of solutions containing surface active agents. Within this concentration range micelles (aggregates) which may contain 50 or more monomers may be formed. Substances that are normally

insoluble or slightly soluble in dispersion medium are solubilised by the formation of micelles.

1.5.1.3 Deaggregation: Some investigators (Fuchs *et al,* 1970) rejected surface tension lowering and micellar solubilisation as the only causes for the observed increase in dissolution rate, because they were not large enough to explain the magnitude of the observed increase. Wan and Heng (1986) reported that surfactants use promoted dissolution by producing a fine dispersion of disintegrated particles thereby increasing surface for drug dissolution. Samgligy and Szantuniklosi (1978) found that surfactants affected diffusion rather than drug dissolution. Schott *et al* (1982) investigated the effect of octoxynol 9 on the dissolution of prednisolone tablets and proposed that the surfactant increased the dissolution by deflocculation of prednisolone. Deflocculation, deaggregation or peptization is the breaking up or dispersing of aggregates or secondary particles into smaller aggregates or primary particles. Wan and Heng (1986) concluded that these processes increases the specific surface area of the solid drug particles from which dissolution can take place thus increasing the dissolution rate. It was postulated by Ganderton *et al* (1967) that the presence of sodium lauryl sulphate dissolved in the granulating liquid greatly increased the rate of dissolution by preventing the formation of agglomerates of hydrophobic drug particles in the tablets.

1.5.2 Surfactants in Tableting

Surfactants, as earlier stated, have been found to be quite useful in drug formulation especially in increasing drug release from dosage forms. They have, therefore, found wide use in tablet formulation where they increase disintegration of the tablet and drug dissolution. This is because drug release from tablet may be hindered by the largely

reduced surface area of the drug in the formulation which may make it more difficult to regenerate well dispersed primary drug particles after administration thus retarding drug absorption (Gibaldi, 1977). It is generally accepted that wettability of a solid material is important in pharmaceutical processes such as granulation, pelletization and tablet coating, and the properties of the end-product like disintegration and dissolution. To be used in compressed tablet formulations, surfactants must be safe and effective in low concentrations (Finholt, 1974).

Several investigations have been carried out to determine the effect of surfactant type and concentration on the properties of granules and tablets. Finholt (1974) found that polysorbates increase the dissolution rate of phenacetin tablets due to their solubilisation power and ability to decrease the interfacial tension between the substance and the dissolution medium.

Shah *et al* (1991) reported that sodium lauryl sulphate added to the dissolution medium markedly increased the dissolution rate of several water insoluble drugs such as griseofulvin clofribrate, medroxy progesterone, and cortisone acetate. Awe and Gelbrecht (1956) showed the action of sodium salts of cetyl and myristyl sulphate in improving disintegration of phenacetin tablets. They also included sodium dodecyl sulphate in isoamyl ethyl barbital tablets and found that this produced fast disintegration. Schott *et al* (1982) investigated the effects of octoxynol (a surfactant) on the dissolution of prednisolone tablets and found that the disintegration time of tablets without surfactant decreased with increase in the surfactant concentration in the disintegration medium. Adding the surfactant to the tablet formulation instead of the disintegration medium led to a larger decrease in disintegration time. They explained the results based on reduced tablet hardness, and temporarily high concentration of leached surfactant within the tablet.

Pandula and Kerezu (1969) from their examination of the effect of Polysorbates 20,40,60 and 80 on weight variation, hardness and disintegration of phenacetin and salicylamide tablets noted that the amount of surfactant required for optimal wetting effect produced tablets that were too soft. Borzuhov (1971) found that sodium lauryl sulphate increased the strength of phenacetin and ethocarbide tablets slightly and reduced disintegration time to less than 10% of those of tablets without surfactant.

The effect of surfactants on tablet formulations can differ depending on a number of factors, for example, the solubility of a drug is improved when the surfactant is present in excess of its critical micelle concentration, and at continually increased concentrations, the dissolution of the drug may be hindered by excessive increase in viscosity (Martins and Camarata 1983). Djuric *et al* (1989) have reported that it was only when the surfactant, dioctyl sodium surfosuccinate (DSS) was present in a high concentration of 1 % that a noticeable reduction in disintegration time of propylphenozone tablet was obtained. It was explained that the proportion of the hydrophobic drug affected surfactant action.

Possible drug-surfactant interactions have also been reported. Kurosaki *et al* (1989) observed a decrease in salicylic acid absorption with the addition of polysorbate 80 while there was increased absorption on addition of ionic surfactants like SLS and cetyl pyridinium chloride (CPC) which was due to the decrease in the free fraction of salicylic acid as a consequence of the action of polysorbate 80 in lowering pH conditions. They found that pretreatment with SLS or CPC resulted in increased salicylic acid absorption at all pH conditions. While Miyamoto *et al* (1983) explained interaction as being due to the formation of micellar complexes with surfactants by drug molecules, Kurosaki *et al* (1987) thought it to be due to inter-molecular electrostatic interactions which may reduce the thermodynamic activity of the administered drug.

Walters (1968) have shown that increasing the sorbitol content of paracetamol tablets caused a corresponding increase in their disintegration and dissolution rates and faster absorption rate of the drug. Wurster and Taylor (1965) showed that increase in the concentration of SLS substantially increased the dissolution of the drugs benzoic acid and predinisolone from their tablets. Esezobo (1985) in studying the effects of sorbitol and SLS (surfactants) separately on paracetamol tablet formulations found that the disintegration and dissolution rates increased with increase in the concentration of the surfactants

Nasipuri and Omotosho (1985) found that the addition of surfactants (SLS and polysorbate 80) produced sulphadiazine tablets with decreased disintegration time and better dissolution rates than those without. Polysorbate 80-treated starch as disintegrant gave better dissolution rate profiles than SLS-treated starch. Starch in which the surfactant was incorporated in the dry state proved to be a more effective disintegrant than the starch treated with a solution of surfactant. In studying the action of surfactants on disintegration and dissolution of tablets containing microcrystalline cellulose, Wan and Heng (1986) found that the inclusion of polysorbate 80 and SLS in sulphanilamide tablets helped improve disintegration and consequently dissolution significantly. Tablet hardness was however reduced. They found that the polysorbate 80 improved disintegration better than the SLS although SLS reduced hardness to a lesser extent. Fatmi *et al* (1988) found that even very low concentration of SLS (surfactant) significantly increased the dissolution of medroxyprogesterone acetate, a water insoluble drug, from its tablets.

Heng and Wan (1987) determined the effect of the presence of polysorbate 80 on granules of sulphanilamide. Increased surfactant content reduced granule strength, increased tablet triturate mean weight, bulk density and angle of repose. Low concentrations of the surfactant increased flow rate, up to 0.2%, while reducing it at higher concentrations.

Femi-Oyewo and Spring (1982) examined the effect of a number of surfactants on granule and compact properties when these were incorporated in the binder solution. They used two anionic, one cationic and one non-ionic surfactants in the granulations containing 5% sulphanilamide. The surfactant produced a reduction in granule size and compact hardness while the disintegration and dissolution profiles were improved. The effect of surfactants on granule properties was also given attention by Opakunle and Akinpelu (1990). They found that SLS and PEG generally increased the granule size of citric acid granules and decreased that of lactose and calcium carbonate granules. The porosity of the granules decreased in the presence of surfactant while friability increased in citric acid and lactose but decreased in calcium carbonate granules. While there was improved flow of citric acid granules in the presence of surfactant, the reverse was obtained for lactose granules.

Oyewumi (1995) more recently concluded that surfactant surface treatments at various stages of paracetamol tablet formulation affected the properties of the tablets. The effect was found to vary depending on the type and nature of surfactant interaction with the treated surface and the type of secondary bonding involved.

1.6 LUBRICANTS IN TABLETING

When granules are subjected to compression in a die there results a residual force, F, which acts against the die wall. It is perpendicular to the so-called ejection force, E, which is the force exerted by the lower punch to move the tablet out of the die during the ejection phase of the tableting cycle. The two forces are related by

$$E = MF$$

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where M is a frictional coefficient. The main reason for adding a lubricant to a tablet formulation is to reduce the magnitude of F. If a powder is not properly lubricated, then the resulting tablets may cap (i.e the crown will separate, or fall off, from the remainder of the tablet). In milder cases, hairline cracks will appear on the wall of the tablets. If very poorly lubricated the tablet may bind up in the die cavity, defying ejection, and the press will stop operating.

Lubricants are defined as those agents that act between surfaces in relative motion to prevent friction and wear (Gunsel et al,1970). True lubricant action is particularly required immediately after compression of the tablet within the die. It is needed to reduce the friction between the inner die wall and the tablet edge during the ejection cycle. The absence of a lubricant at this stage can lead to a characteristic screeching sound and the straining of the machine parts involved. Lubricants also help the granules to slip and slide to form the compact as well as facilitate the ejection of the tablet.

The most frequently employed materials are the metallic stearates - magnesium, calcium, or potassium (Gunsel et al,1970) which even in concentrations of less than 1 percent, are excellent lubricants. They are usually added at the very last step before compression since they must be present on the surfaces of the granules and in between them and the parts of the tablet press.

The addition of a lubricant into granules prior to their compression into tablets is a crucial step. The quantity of magnesium stearate added and/or the duration of its mixing with granules can significantly affect inter and intra-batch properties such as dissolution, hardness and friability (Mitrevej and Augsburger, 1982; Jarosz and Parrott, 1984; Bolhuis *et al*, 1987). As a result of overmixing, granules are coated with a hydrophobic film of lubricant (Bolhuis *et al*, 1975).

Desai *et al* (1993) found that increased mixing time resulted in decreased drug dissolution rate. They also found that among the three hydrophobic lubricants studied, magnesium stearate caused the maximum slow down in dissolution, followed by zinc and calcium stearate respectively. This was correlated with the surface area measurements of the three stearates which were 8,7 and 3.4 m^2/g for Mg, Zn and Ca stearate respectively. They obtained 0.25% w/w as the optimum concentration of magnesium stearate for lubrication that would not adversely affect dissolution. These workers employed the hypothesis of Poorest *et al* (1983), that the hydrophobic film of magnesium stearate does not envelope the granules completely, to explain their observation that the presence of 1% mg stearate did not affect dissolution when super disintegrants were used since their swelling is not inhibited once they come in contact with the dissolution medium.

Desai *et al* (1983) observed that the effects of overmixing of granules with hydrophobic lubricants could be overcome by compressing them into tablets. This is because the film is disrupted and the granules fragmented during compression, resulting in the formation of new, fresh, uncoated surfaces, with unimpeded dissolution.

Magnesium stearate, which can act as a lubricant or glidant when added to a powder mix, is the most frequently used additive to improve flow properties of powders. It has therefore attracted the most attention in terms of detailed study of its action and the mode by which it acts.

Gold *et al* (1968) have proposed that magnesium stearate reduces the adhesion due to long-range van der Waals forces between the particules of a powder bed. Jones (1968) on the other hand found that because of the hydrophobic nature of the material, this proposal might not be valid. However, other workers have reported the significant reduction of the forces of adhesion due to hydrophobization of materials (Zimon, 1982;

Deryaguin *et al*, 1978).

An optimal magnesium stearate concentration, i.e the concentration which would improve powder flow most, can be found when a complete film has been formed surrounding each individual particle as reported by Jones and Pilpel (1966), Gold *et al* (1968) as well as Irono and Pilpel (1982). It was found that above the optimal concentration, i.e when the film formed increases in thickness, or when an overshot of fine particles exists, there is a sharp drop in flowability which cannot be attributed only to a weakening of attractive forces betwen the host particles. It is known that during powder flow, particles are in frictional contact with each other. Tabor (1981) has identified the 3 basic elements of friction as (i) the area of true contact between the sliding particles (ii) the type and strength of the attractive forces between the contacting surfaces and (iii) the shearing and rupture of the materials at the contact points and the surrounding area during sliding. For lubricants such as magnesium stearate, which form a film around the particles, the last element is most important. Based on the analysis of equations relating the nature of particles and the resulting frictional forces proposed by Bowden and Tabor (1964) and Halling (1981), Podezeck and Miah (1996) concluded that the optimal magnesium stearate concentration is found at the minimum of any friction characteristics or the powder flowability plotted as a function of the magnesium stearate concentration. They also found that at an optimal lubricant concentration, the friction occuring is only partially due to shearing of the lubricant film, but mainly due to deformation of the surface with the more elastic, bouncing surfaces giving less friction. In addition they concluded that optimal magnesium stearate concentration (as glidant) appeared to depend on particle size with very large particles requiring no glidant.

Esezobo (1985) also found that increased concentration of aerosil, a material with lubricant properties, resulted in decreased hardness with corresponding increase in

friability. This was explained to be due to the weakening of the inter particulate bonds between the drug particles. Disintegration and dissolution rates were also observed to fall with the addition of aerosil which is similar to earlier observations by Pilpel (1970) and Bolhuis *et al* (1975). They ascribed this to the lubricant property of the material.

Sixsmith (1977) observed that the addition of magnesium stearate has a marked effect on the disintegration time of tablets which increase dramatically as the concentration of magnesium (mg) stearate increases. This was explained to be caused by the inability of the water to penetrate the tablet as a result of the hydrophobic nature of mg stearate. The dissolution rate from the tablets also decreases rapidly as the concentration of mg stearate increases, again because of the inability of the water to penetrate the tablet.

Shotton and Hersey (1970) have stated that during compression the lubricant is spread over the surface of the particles and therefore reduces the strength of the bond between the particles. They found that when methamite crystals were coated with a thin film of stearic acid and then compressed, particle size no longer affected the strength of the tablets and the tablets were weaker than when pure crystals were used. Treating sodium chloride similarly with stearic acid resulted in the reversal of the effect of particle size. They explained that it would appear that the presence of the film of lubricant on the hexamine crystals reduced the area of actual bonding and when the compressing force was removed elastic recovery took place with the partial separation of the surfaces in contact. With Nacl, which is a harder crystal than hexamine, the stress concentrations with the larger crystals was much greater than with the smaller ones, owing to the fewer contact points. Penetration of the lubricant film was therefore greater with the large crystals and a stronger tablet was formed. It was concluded that the addition of lubricants profoundly affect the compression characteristics of materials.

1.7 *Ficus* Spp.

The *Ficus* spp. is very widely distributed in many parts of Africa especially the Eastern, Western and Southern parts of the continent. It belongs to the family Moraceae. Watt and Gerdina (1962) have reported that there are twenty four species indigenous to South Africa and the fruit of most of them is edible, with monkeys and many species of birds feeding on them.

The West African species seems to be of little economic importance, although the latex of several species is used as bird lime (Burkill, 1985). It is also reported that some bear figs which are in diverse degrees regarded as edible by the people. They are the most familiar forms of shade trees in most towns and villages in the region, giving dense shade, usually wholly or in part evergreen.

They begin life as epiphytes, the seed being carried by birds. The aerial roots eventually embrace the stem of the host and in time replace it by their growth uniting and forming the compound trunk of an eventually independent tree, but the ficus may grow to maturity and bear fruit, ever before its aerial roots have established themselves in the ground. In most forests with still atmosphere, the pendulous roots from lateral branches may descend vertically to the soil, eventually establishing a typical banyan formation.

In Tangayika, the leaf of various species of wild fig is chewed and applied to a poison arrow wound which is then sucked. The latex of various species has long been used in folk medicine with the benefit being ascribed to its antihelmintic action. This effect is now known to be due to the presence of a proteolytic enzyme, ficin, which digests ascaris in a dilution of 0.1% in 1 - 2 hours (Watt and Gerdina, 1962). The proteolytic action varies from species to species. The interavenous injection of small doses of this enzyme

lowers the erythrocyte count and markedly prolongs the blood clotting time.

In West Africa, the bark of several species is chewed with kolanut either to relieve thirst or as a remedy for sore throat. There are several other uses which are specific for the different species.

1.7.1 Medicinal Uses of *Ficus sur* Forsk (formerly *Ficus capensis*)

In Eastern and Southern Africa, the plant is used both in human and veterinary medicine (Watt and Gerdina, 1962). The Zulu drink a decoction of the root and bark for suspected "ulceration of the lung" which could mean pulmonary tuberculosis. They also give an infusion of the root, leaf and bark to a cow yielding an insufficiency of milk. A decoction of the root is used to assist the expulsion of retained placenta in a cow. In Tangayika, a decoction of the bark is used as galactogogue in women and cows, while in some other parts it is used to prevent vomiting. In West Africa, the plant is one of those used by traditional eye doctors (Burkill, 1985), while the latex is used in Zaire for the treatment of burns. In virtually all parts of Africa, the abundant clustered fruits suggest the notion of fertility and are therefore used in various ways to promote conception and ensure an abundant crop. The Fulanis of West Africa give both leaves and fruits to bring about an increase in milk yield. The fresh young aerial root along with the inner bark is chewed with kolanut for the alleviation of thirst and the treatment of sore throat.There has been no published report of its use in the treatment of peptic ulcer.

1.8 STATEMENT OF OBJECTIVE

As has been earlier stated, there is renewed interest in the use of phytomedicines due to the realization that a significant proportion of the world's population especially in the developing countries depend on them for their health care needs. There has therefore been a lot of scientific work carried out to validate the claims of herbal medicine practitioners with respect to the pharmacological activities of their preparations, with quite a number of scientific journals such as Journal of Ethnopharmacology, Fitoterapia and Journal of Phytochemistry being completely devoted to the promotion of such studies (Femi Oyewo *et al*, 1993; Vennat *et al*, 1993). The studies on the formulation of such herbal medicines into suitable dosage forms have however not received the same attention, with published investigations being few and far between. The only folkloric use documented for *Ficus sur* leaf is as a galactogenic in combination with the root and the bark of the plant (Watt and Gerdina, 1962). However, some herbalists including one in Keffi, Nassarawa state of Nigeria, use the dried leaves in the treatment of clinically ascertained cases of peptic ulcer (personal communications). Discussions with some of his patients, who are all educated, indicated that they felt better after the use of the drug. The mode of administration was by chewing and swallowing the dried crushed leaves of the plant. The specific objectives of this investigation therefore are;

1. Since there has been no previous documentation of the antiulcer activity of this specie of Ficus, to determine if the claims of antiulcer activity of its leaves can be verified by the use of established animal models.

2. If found to possess antiulcer activity, to extract in different solvents and determine the most active extract in terms of antiulcer activity. In addition, because of the accepted role of *H. pylori* in the pathogenesis of peptic ulcer disease, determine the antimicrobial

activity of the extracts.

3. Considering the present inconvenient mode of administration of the drug, by the herbalist , formulate it into a suitable dosage form to improve patient compliance and specificity of dose. The tablet was chosen because of the convenience associated with it as well as the ethnomedical use of the drug. It is also one of the most suitable dosage forms for extracts because it maintains the drug in the dry state, thus reducing microbial activity to the minimum.

4. Since one of the most important stages in the development of a pharmaceutical product is the selection of the excipients to be used in the formulation, to conduct necessary tests that will result in the selection of the most suitable excipients.

5. Study the compactional characteristics of the various formulations.

6. Determine the effect of formulation on the drug by the development of the necessary (markers) 'finger prints'.

7. Suggest a suitable formula for the formulation of tablets of *Ficus sur* leaf extract

CHAPTER TWO

GENERAL METHODS

2.1.1 Plant material collection

The leaves of *Ficus sur* were collected from an area between Suleja and Abuja. The plant was identified by Prof. Z. O. Gbile (Plant Taxonomist) of the Department of Botany, Ogun State University, Ago- Iwoye, Nigeria. A voucher specimen is deposited at NIPRD herbarium.

2.1.2 Preparation of the extracts

The leaves were washed under a running tap several times and then with deionised water and finally with distilled water. The clean leaves were air dried until brittle to touch. They were then milled to a coarse (853μm mesh size) powder in a blender (Braun, Germany). A weighed amount of the powder was transfered into a flask, the relevant solvent (water, methanol or hexane) was then added, in a ratio of 1:10 (leaves: water); enough was added to completely cover the powder. In the case of methanol and hexane, exhaustive extraction was carried out by means of a soxhlet apparatus, while a water bath at 100°C for 48 hours in a covered container was used for the hot water extraction and the material simply macerated for 48 hours to obtain the cold water extract. The liquid extracts were filtered through a sieve of 150μm mesh size and again through a calico cloth. The filtrate was freeze dried with a Finn-Aqua, Lyovac GT3 freeze dryer in the case of the cold water extract, while it was concentrated on a hot water bath until a plastic mass was obtained in the case of the hot water extract. The organic extracts (hexane and methanol) were recovered on a rotary drier, from where the concentrated

extracts were transferred into porcelain evaporating dishes and further concentrated until a plastic mass was obtained. The hot water extract was then further dried in an oven at 65°C until completely dried and was powdered, while the organic extracts were concentrated to drieness on a water bath. The extracts were then stored in screw-capped bottles and kept in a refrigerator until required.

2.1.3 Preparation of Granules

The wet granulation method of massing and screening was used. The powders were dry-mixed for about 5 minutes in a mortar using a pestle before the addition of binder. The binder solutions were prepared as below :

Starch mucilage - The weighed amount of starch powder was suspended in a small amount of cold water (to prevent the formation of clumps) then boiling water was added to the suspension with continuous heating and stirring until a mucilage was formed. The mucilage was kept warm during use to avoid gelling.

Polyvinylpyrollidone (PVP) - The weighed amount was suspended in cold water and stirred until it went into solution.

Sodium alginate - The weighed amount of the powder was dispersed in cold water. The suspension was then heated on a water bath with continuous stirring (to avoid lump formation), until a clear translucent flowing material was obtained. The solution was kept warm throughout use.

Gelatin - The required amount of the powdered material was suspended in cold water and allowed to hydrate. It was then warmed on a water bath until a flowable material was obtained. The solution was also kept warm during use to avoid gelling.

The binders were added to the powder mix in small portions. Mixing was continued in the mortar while the binder was being added. This was continued until proper mixing had been achieved (the end of granulation was determined as the point at which the wet mass when pressed between the thumb and the forefinger formed a stable mass). The moistened mass was forced through a 599μm screen. The granules were dried at 60°C for one (1) hour. The dried granules were again passed through the 599μm screen to break up any agglomerates that might have formed.

2.1.4 Characterisation of Granules

2.1.4.1 Size analysis:

50g of the granules were used for the analysis. The sieve method of measurement, using five (5) sieves of sizes 75, 150, 250, 355 and 500μm, was adopted. They were arranged in a stack with the sieve with the largest aperture size at the top and the one with the smallest and a dust collector at the bottom. The stack was mounted on an Endecotts test sieve shaker. The weighed amount of granules was placed on the top sieve and shaken for 15 minutes. The weight of granules retained on each sieve and the fines collector was taken and calculated as a percentage. The percent cummulative oversize was plotted against the sieve size as illustrated in fig.4.1-4.3. The mean size of the granules was taken as the 50% cummulative oversize (Femi-Oyewo *et al*, 1993)

2.1.4.2 Moisture content:

10g of granules was used for this test. Moisture content was determined on an Ohaus (MB 200) moisture balance.

2.1.4.3 Flow time:

This was determined on an Erweka (GWF) flow tester.

2.1.4.4 Bulk and Tapped densities:

30g of each granulate was gently and slowly poured through a short-stemmed funnel into a 100ml graduated glass cylinder. The orifice of the funnel stem was aligned with the 100ml mark. The volume occupied by the granules was read to the nearest 0.5ml and the bulk density calculated in gm/ml

Tapped density: The graduated cylinder was tapped using a Stampfvolumeter (Stav 2003) until a constant volume was obtained. The tapped density was calculated in gm/ml.

2.1.4.5 Percent compressibility(Stanley-wood and Shubair, 1978) :

This was calculated from the difference between the tapped and the bulk densities, divided by the tapped density and the ratio expressed as a percentage.

2.1.4.6 Granule density:

The specific gravity bottle method was used. The bottle was filled with xylene (in which HWE had been found to be insoluble), wiped dry and then weighed. One gramme of the granule was weighed into a 20ml specific gravity bottle which was previously calibrated with distilled water. Xylene was carefully poured into the bottle and allowed 5 minutes to condition at room temperature. The granules were gently stirred to release entrapped air and again left for 5 minutes to condition. This was repeated until no further bubbles were released. The bottle was then filled up and the lid carefully replaced. The outside was wiped dry and the bottle weighed. The density was calculated by,

$$\frac{W \times S.G. \text{ of xylene}}{[(a+w)] - b}$$

where,

w= weight of powder; S.G. is specific gravity of xylene

a= weight of bottle + xylene and

b= weight of bottle + xylene + granules

2.1.4.7 Angle of repose:

30g of powder was allowed to flow through a funnel at a fixed height onto a flat surface. The radius(r) and the height(h) of the powder heap was then determined. The angle of respose was calculated by,

$$\text{Tan } \theta = \text{h/r}$$

$$\theta = \text{tan h/r}$$

2.1.5. Compression of Granules

This was done on a power-driven single punch tablet press (Shanghai Tianxiang and Chentai Pharmaceutical Machinery Co. Ltd, China) after the granules had been mixed with the lubricant and exo-disintegrant in a tumble mixer. It was fitted with 12mm concave punch and die set. The upper punch was set at 8 on the machine scale, which had earlier been determined to be suitable for the production of suitable tablets with most of the granulates used in the study. The speed was set at 15tablets per minute.

2.1.6 Test of Tablet properties

2.1.6.1 Weight Variation : This was done with an automatic tablet weight checker (Checkweigher CGS UCW4). It weighs 10 tablets and determines the statistics of the population including the standard deviation. Appendix I shows a sample of the result format.

2.1.6.2 Hardness:

A Monsanto hardness tester was used. It indicates in kg the force required to crush the tablet. The mean of six readings are reported.

2.1.6.3 Friability: Tablets were subjected to friabillation in an Erweka double drum friabilator (Copley TAR) at 25 rpm for 4 minutes. The weight of 10 tablets before and after friabilation was taken. The percent loss in weight was calculated to obtain the friability. The mean of two determinations was calculated.

2.1.6.4 Diameter/Thickness:
A digital micrometer (Mituoyo Corporation, Japan) was used to determine this in mm. Each reported value is the mean of six (6) readings.

2.1.6.5 Disintegration time: Six tablets were assessed at the same time in a BP (1993) 4-station disintegration test apparatus containing distilled water as medium at a temperature of 37.2°C. The mean of two such determinations was calculated.

2.1.6.6 Dissolution time: An eight station Erweka dissolution apparatus(DT 80) was used. The medium was 900ml of distilled water. The tablet was placed in the medium and the paddle rotated at a speed of 100 rpm. The temperature of the medium was maintained at 37^0 +/- 0.5. At appropriate time intervals samples of the dissolution medium were withdrawn through a luer needle lock syringe with a wire mesh for filtration. The samples were suitably diluted with water for spectrophotometric determination. Drug content determination was done at 274 nm wavelength. Lactose, magnesium carbonate and aerosil did not absorb at this wavelength. A Shimadzu UV-160A spectrophotometer was used. The determinations were carried out on two tablets from each formulation. Earlier scan of the hot water extract had shown the presence of a peak at 274nm (Appendix 2). Standard solutions of the extract were prepared and filtered through a 0.2μm filter. It was possible to prepare a standard curve (Appendix 2)) from these solutions.

CHAPTER THREE

STUDIES OF THE ANTIULCER ACTIVITY OF SOME FICUS LEAF EXTRACTS ON ASPIRIN-INDUCED ULCER

3.1 INTRODUCTION

The leaves of *Ficus sur* have been used by a number of traditional practitioners in the treatment of peptic ulcer with reported success by some of their patients. A search of the literature (NAPRALERT data base; Dalziel, 1985; Gerdina and Watt, 1962) did not indicate any study of the antiulcer activity of this plant. The aim of this section was therefore to determine the authenticity of the claims by studying the ulceroprotective activity of the leaf extracts and where found to be active to compare such to those of some established antiulcer drugs. In view of the confirmed involvement of the bacterium *H. pylori* in the pathogenesis of ulcer, the antimicrobial activity of the extracts was also investigated.

3.2 MATERIALS AND METHOD

3.2.1 MATERIALS

Ficus leaf extracts, Methanol and Hexane (May & Baker Ltd Dagenham, England), Acetylsalicylic acid (Sigma - Aldrich Company Ltd, St. Louis, U.S.A.)
Winster (10-25g) rats, New Zealand rabbits, (1.8-2.5kg) Swiss albino mice(20-25g) of either sex

3.2.2 METHODS

3.2.2.1 **Acute toxicity**

The intraperitoneal (i.p) acute toxicity (LD_{50}) of the dried hot water extract was evaluated in Swiss albino mice. Twenty five mice divided into five equal groups were used. Varying doses of the extract ranging from 50-2000μg/kg were given to the animals as a single dose intraperitonially. The control group received 0.9% saline solution. The LD_{50} was evaluated according to Lorke (1983). The animals were observed for mortality over a 24 hour period. This was repeated for each of the four extracts.

3.2.2.2 **Studies on isolated rabbit jejunum**

Segments of rabbit jejunum (2 cm long) removed from freshly killed animals were suspended in a 20 ml-organ bath containing aerated Tyrode solution maintained at 37°c. The Tyrode solution had the following composition (mmol/l), Nacl 137; KCl 2.7; $Cacl_2$ 1.0; $NaHCo_3$ 12; NaH_2PO_4 0.2 and glucose 5.6. The tension on the tissues was 1.0g. After 60min. equilibration, the effect of 10,20,40,50,100,200,400 and 800μg/ml of cold water extract, 50,100,200,400 μg/ml hot water and methanol extracts on the pendular movements of the preparation was investigated. The responses were recorded on Ugo Basile microdynamometer 7050, through isometric transducer 7004. The effect of 25ng/ml noradrenaline was also recorded for comparison. Only the water soluble extracts (cold and hot water) as well as methanol could be used for this experiment.

3.2.2.3 **Studies on ASA-induced ulcer**

Thirty rats were fasted for 48 hrs with water allowed. The animals were then randomly divided into six (6) groups of five each. One group served as control and was

administered with distilled water p.o. The extracts were administered p.o. to the other groups at a dose of 250mg/kg. This dose was determined based on the herbalist's prescribed dose, which was found to be well below the LD_{50} of the extracts. Each of the test groups received a different extract, with one of them receiving a mixture (1:1:1:1) of all four extracts. Thirty minutes later, an aqueous suspension of aspirin was administered to each rat at a dose of 250mg/kg. After six (6) hours the animals were sacrificed and the stomach removed and opened along the greater curvature. The stomach was rinsed under a stream of water and pinned flat on a cork board. The various specimens were coded to avoid observer bias and examined with a hand lens (x10). Erosions formed on the glandular portion of the stomach were counted and the ulcer index calculated as previously described (Akah *et al*, 1993). Ulcers were scored based on their sizes - Pinpont = 1, 1-2mm = 2 and 3mm = 3. The total score for each animal is then calculated and divided by the magnification of the viewing lens (in this case 10) to obtain the ulcer index for that animal.

Table 3.1: LD_{50} of the various extracts

Extract Type	LD_{50} ,mg/kg (SD)
Cold water	1204 (154)
Hot water	1162 (137)
Methanol	1053 (212)
Hexane	902 (163)

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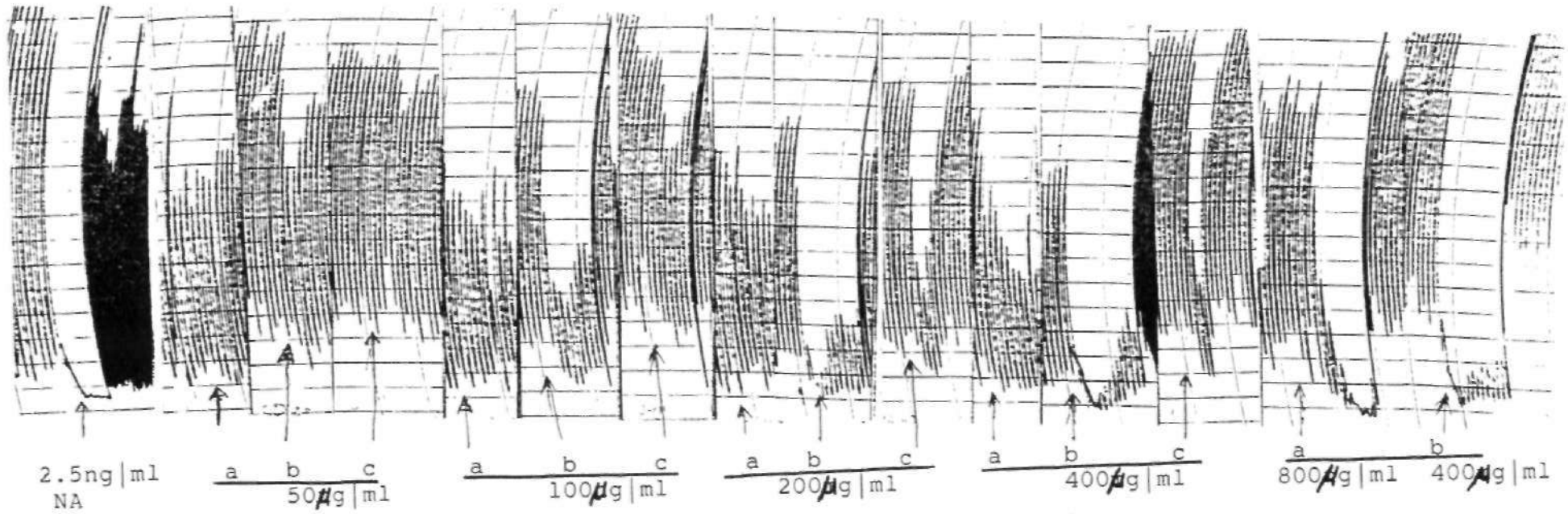
3.3 RESULTS AND DISCUSSION

This study was undertaken primarily to study the effectiveness of the various extracts of *F. sur* to protect against aspirin (ASA) induced gastric mucosal damage (anti-ulcerogenic effect) and also study its effect on gastric motility. An acute toxicity test was first conducted to determine the intraperitoneal (i.p) LD_{50} of the extracts in mice. The values of the LD_{50} are as indicated in Table 3.1. These values show that all of the extracts were well tolerated as there were no deaths and the animals showed no sign of toxic reactions such as diarrhoea or stereotypic behaviour.

3.3.1 Effect on pendular movement of rabbit jejunum

All of the extracts tested produced concentration - dependent relaxation of the intestine causing a sustained inhibition of the peristaltic movement of the rabbit jejunum (fig 3.1). The cold water extract did not produce significant relaxation at the lower concentrations of 10-100μg/ml. The first noticeable relaxation was seen at 200μg/ml although this was very slight. As the concentration increased to 400μg/ml the relaxation effect increased, doubling this concentration to 800μglml resulted in a substantial increase in relaxation with virtual complete inhibition of intestinal motility.

With the hot water extract, the first noticeable relaxation effect was seen at 50μg/ml and this continued increasing with increasing concentration to 100 and 200. Increasing the concentration to 400μg/ml did not seem to increase the extent of intestinal relaxation, implying that the maximum effect was obtained at 200μg/ml. Drug action is generally



key: a - Cold water extract
b - Hot water extract
c - Methanol extract

Fig. 3.1 Effect of various extracts on pendular movement of rabbit jejunnum

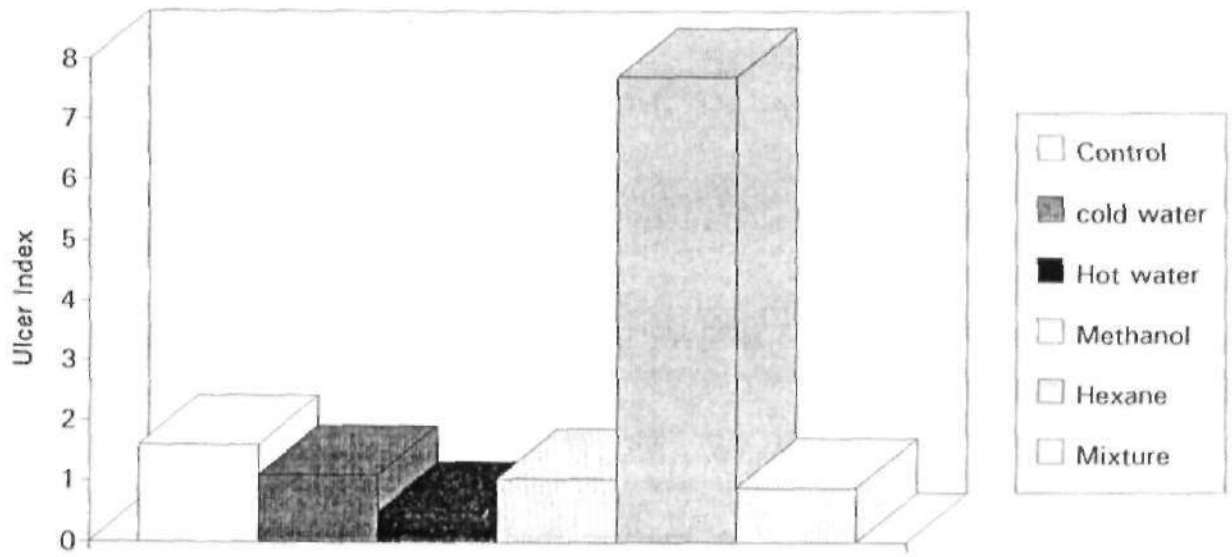
thought to be due to the activity of the drug on some receptor(s). It is assumed that this takes place in a lock and key fashion where the drug molecule fits into an endogenous receptor and thus elicits the observed pharmacological action either due to excitation or suppression of the receptor. As a result of this, a plot of drug action versus concentration would give an inital straight line, where the available receptor sites are greater than the drug molecules. However there is a plateau as the drug concentration is further increased when all available receptor sites have been saturated by the drug molecules. At this point any further increase in drug concentration would not change the drug effect that is observed, as seems to be the case beyond 200μg/ml of hot water extract.

Using the methanol extract, there was also a dose dependent relaxation of the preparation, with the first noticeable effect produced at 50μg/ml. The maximum effect (which was less than those of the water extracts) was obtained at 200μg/ml since increasing the concentration to 400mg/ml did not seem to have affected the extent of relaxation significantly. It was observed with this extract that its relaxation effect was very short, with intestinal motility recovering very quickly when compared to the two water extracts that produced sustained relaxation.

It was found that 400μg/ml of the hot water extract produced virtually the same quantitative effect as 800μg/ml of the cold water extract (fig. 2). The effect was similar to that of 25ng/ml of noradnenaline. In all cases the effect of the extracts were reversible as the tissues recovered soon after washout of the drug.

One of the ways in which antiulcer drugs may produce beneficial effects is the modulation of gut hypermotility (Akah *et al*, 1997) in ulcer patients. Reduction in intestinal motility helps to reduce ulcer pain with subsequent healing of ulcer wounds since there would be less irritation of the injured tissue. This spasmolytic action may thus play a major role

Fig. 3.2 Comparative Anti-ulcer Activity of Ficus leaf Extracts



in the antiulcer properties of the extracts.

3.3.2 Effect on ASA-induced Ulcer

Aspirin (250mg/kg) administered orally was effective in inducing ulcer (acute mucosal damage) in 100 per cent of the control rats with a mean ulcer index of 1.6 $\pm$0.13. Fig 3.2 shows that 4 of the 5 preparations reduced the aspirin-induced ulcer index. In the case of the cold water extract it decreased to1.1=/-0.12, and 0.5$\pm$0.15 for the hot water extract, while it was 1.04$\pm$0.17 and 0.9 $\pm$0.16 for the methanol and mixture of extracts respectively. On statistical analysis, only the hot water extract was found to significantly protect the animals from the ASA-induced ulcer at $P<0.05$. However all the others significantly protected at $P<0.5$.

On the other hand the hexane extract increased the ulcer index from 1.6$\pm$0.13 to 1.72$\pm$0.16. Although this was only significant at $P<0.9$, it shows that this extract has no activity against ASA-induced ulcers and might even have ulcerogenic effects.

From the results, it is clear that the water and methanol extracts have some cytoprotective (Mitra *et al,* 1996) action. The mechanism by which it does this is not clear. However since it has been reported by Robert (1975) and Whittle (1977) that prostaglandins cytoprotect gastric mucosa against injury caused by NSAID, it is probable that the cytoprotective effect of the extract of *F. sur* observed in this study is related to the prostaglandin type of cytoprotection. If this were correct, the extract could be acting by stimulating the production of endogenous prostaglandins which then protect the gut. Since Diatiang and Zamindost (1973) have suggested that NSAID-induced ulceration could involve the sympathetic nervous system, or both the sympathetic and parasympathetic

nervous systems (Elegbe, 1978), it is also possible that the extracts act by interfering with the sympathetic and/or parasympathetic systems. Further detailed studies using the active principle(s) of the extracts will be necessary to establish the mechanism by which the extract produces the antiulcer effect.

3.4 CONCLUSION

The extracts were found to be safe with high values of LD_{50}, which were much higher than the calculated quantities of extract that would have been consumed by patients using the herbalist's recommended dose of one tablespoonful of direct crushed leaves three times daily (personal communication).

The water soluble and methanol extracts produced dose dependent spasmolytic effect on the rabbit intestine. The cold and hot water extracts produced sustained effects while that obtained for the methanol extract was transient. The hot water extract was the most active in this respect with 400μg/ml producing the same effect as 800 μg/ml of the cold water extract.

The two water soluble extracts, the methanol extract and the mixture of all four extracts exhibited ulceroprotective activity by significantly reducing the ulcer index in the test animals. The hot water extract had the best activity, followed by the mixture, methanol and cold water extracts respectively. From the foregoing, the hot water extract was selected as the most suitable for formulation studies.

3.5 COMPARATIVE ANTIULCER ACTIVITY OF THE HOT WATER EXTRACT

3.5.1 **Introduction**

This study was carried out with the aim of finding out the relative antiulcer property of the extract when compared to two well established antiulcer drugs. The drugs selected each have different mechanisms of action - cimetidine which is an H_2-receptor antagonist and aluminium hydroxide, an antacid. Cimetidine is a potent H_2-receptor antagonist that is widely used in the treatment of peptic ulcer and acts by inhibiting secretion of gastric acid resulting in healing of ulcers (Domschke *et al*, 1979; 1980), while $AlOH_3$ is an antacid which is thought to act by covering the surface of the ulcer thus preventing the further action of acids and other irritants on the wounds and thereby promoting healing.

3.5.2 Materials and methods

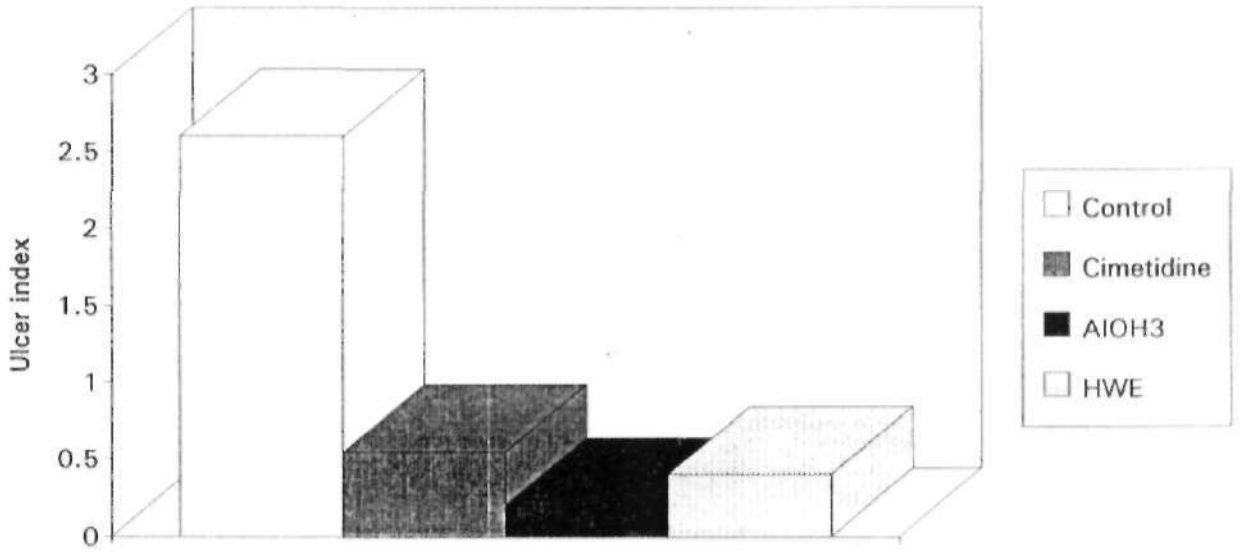
The extract was prepared as earlier described in Section 3.2.2.3
Cimetidine (Sigma) was used at a dose of 75mg/kg $AlOH_3$ at 15mg/kg while aspirin and HWE were used at 250mg/kg.

3.5.3 Results and discussion

The results show that ASA treatment was able to induce ulcer in all of the control animals with a mean ulcer index of 2.6 ± 0.88 (Fig 3.3).

All three drugs tested reduced the ulcer index significantly ($P < 0.05$) when compared to

Fig. 3.3. Comparative anti-ulcer activity of some drugs



the control group. The mean indices were 0.55 $\pm$ 0.15, 0.2 $\pm$ 0.09 and 0.4 $\pm$ 0.1 for cimetidine, aluminium hydroxide and HWE respectively. Aluminium hydroxide reduced the index the most followed by the extract. Cimetidine had the least activity.

Aguwa and Nwako (1988), while investigating the activity of the root bark of *Nauclea latifolia* on indomethacin-induced ulcers, found that cimetidine at a dose of 100mg/kg had less protective activity than the aqueous extract. It could be that the antiulcer models that induce ulcer by either chemical or physical methods would tend to favour locally acting drugs rather than systemic ones since these by their mere presence within the gut would exert their action as compared to those that would have to go into the circulation before exerting their effect. It should also be noted that this model measures the ulceroprotective action of agents rather than ulcer healing activity.This would explain the high reduction of the ulcer index by the antacid, aluminium hydroxide, compared to the other drugs, especially cimetidine, a potent antiulcer agent.

It is possible to say however that the HWE was more active than cimetidine in terms of ulceroprotective activity.

3.6 ANTIMICROBIAL ACTIVITY OF *FICUS SUR* EXTRACTS

3.6.1 Introduction:

In view of the earlier stated involvement of *Helicobacter pylori* in the pathogenesis of peptic ulcer disease, especially since it is well known that eradication of *H. pylori* results in the prevention of relapse of duodenal ulcer (Hentschel *et al*, 1993), it was considered necessary to investigate the potential of the extracts obtained from the leaves of *Ficus sur* as antibacterial agents.

Ideally, we would have used *H. pylori* but unfortunately we were unable to obtain the organism.

3.6.2 Materials and method

3.6.2.1 Preparation of the extracts:

The extracts were prepared as has been earlier outlined

3.6.2.2 Microorganisms

The following bacteria were used.

Staphylococcus aureus (Sa), *Pseudomonas aeruginosa* (Pa), *Bacillus subtilis* (Bs), *Dermatophilus congolensis* (Dc) and *Escherichia coli* (Dc). The yeast *Candida albicans* (Ca) was also used.

3.6.2.3 Antimicrobial activity.

20mg/ml concentrations of the extracts were prepared. One ml of this was added to 9mls of molten nutrient agar, poured into a plate and allowed to set, thus giving a concentration of 2000μg/ml of extract in the agar. The plates were then inoculated by the spot-inoculation method using 10ml of overnight cultures diluted to $1x10^6$ cfu/ml.

Three (3) controls were included for each extract - organism vialbility control (OVC), medium sterility control (MSC) and agent sterility control (ASC). All the plates were incubated at 37°C for 18-24 hours. Each experiment was carried out in triplicate.

3.6.3 Results and discussion

Table 3.2: Antimicrobial activity of the leaf extracts

	Dc	Sa	Bs	Ca	Pa	Ec
Cold Water	+	+	+	+	+	+
Hot Water	+	+	+	+	+	+
Methanol	-	-	+	+	+	-
Hexane	+	+	+	+	+	+
OVC	+	+	+	+	+	+
MSC	–	–	–	–	–	–
ASC	–	–	–	–	–	–

Table 3.3: Determination of MIC for the Methanol Extract

Conc (mg/ml)	Dc	Sa	Ec
2000	-	-	-
500	+	+	+
250	+	+	+
125	+	+	+
62.5	+	+	+
OVC	+	+	+
Methanol (1ml)	+	+	+

As can be seen from Table 3.2, the test organisms were selected to represent all classes of microorganisms with Gram positive cocci *Dermotophilus congolensis* as well as *Staphylococcus aureus* and a Gram positive bacilli, *Bacillus subtilis,* with two Gram negative bacilli, *Pseudomonas aeruginosa* and *Escherichia coli*. A yeast form of fungus *Candida albicans* was also included.

The results showed that the organisms used were viable since the OVC was positive, the media sterile (no growth for MSC) and that the extracts were not contaminated since the ESC was also negative (no growth).

Of the four extracts tested, only the methanol extract showed any activity at the 2000μg/ml concentration used.

The minimum inhibitory concentration (MIC) of the methanol extract was determined and the results are shown in Table 3.3. Five different concentrations of the extract were used as well as the solvent methanol. The results show that the antimicrobial activity of the methanol extract was not due to the presence of methanol since the negative control did not exhibit antimicrobial activity. None of the extract concentrations exhibited antimicrobial activity at below 2000μg/ml. It would therefore seem that 2000μg/ml. is the MIC for the methanol extract with the three test organisms.

3.6.4 Conclusion:

It was found that none of the extracts has antifungal activity. At 2000μg/ml concentration, only the methanol extract had antimicrobial activity. It was active against both Gram positive and Gram negative organisms. Because of its activity against *E. coli*, which is a Gram negative bacilli like *H. pylori*, this extract is worth investigating for anti-*H pylori* activity.

CHAPTER FOUR

EFFECT OF BINDER TYPE AND CONCENTRATION ON GRANULE AND TABLET PROPERTIES

4.1 INTRODUCTION

Several studies have shown the effect of both binder type and concentration on the properties of drug formulations (Shubair and Dingwall, 1976; Nasipuri and Akala, 1986; Kunle and Bangudu, 1990). All of these investigations were however carried out using synthetic drug substances.

The aim of this section was to investigate the effect of these variables (binder type and concentration) on the properties of the granules and tablets of the crude extract of *Ficus sur*.

Since different diluents were used for the formulations the effect of the diluents on the properties of the granules and tablets were also looked into.

4.2 MATERIALS AND METHOD

(a) **Materials**

Hot Water Extract; Lactose BP/USP, Aerosil, and Maize Starch BP, were all received as gifts from NIPCO Pharmaceuticals, Idu - Abuja.

Polyvinylpyrollidone,(PVP) 25000-30000 (Merck); Sodium alginate; Gelatin B.P.(Fisons Scientific,England), Heavy Magnesium Carbonate (BDH Chemicals, England).

4.3 METHODS

4.3.1 Preparation of Granules

As described in section 2.1.3 according to the formula shown in Table 4.1

TABLE 4.1: TABLET FORMULA

(a)	HWE	250mg
	Starch Powder (disintegrant)	45mg
	(Lactose Powder (diluent)	375mg
	Binder*	
	Starch Powder	45mg
	Mg stearate	0.2%w/w
(b)	HWE	150mg
	Starch Powder (disintegrant)	45mg
	Magnesium carbonate (diluent)	450mg
	Binder*	
	Starch powder	45mg
	Mg stearate	0.2%w/w

(c)	HWE	350mg
	Starch powder (disintegrant)	45mg
	Aerosil(diluent)	210mg
	Binder*	
	Starch powder	45mg
	Mg stearate	0.2%w/w
	**Starch paste*:	5,2.5 and 10%w/w;
	PVP, Alginate:	2.5, 5 and 7.5%w/w
	Gelatin :	7.5, 12.5 and 17.5%w/w

4.3.2. Characterisation of Granules

As earlier described in Section 2.1.4.

4.3.3 Compression of granules

As described in Section 2.1.5.

4.3.4. Test of Tablet Properties

As described in Section 2.1.6.

4.4 RESULTS AND DISCUSSION

4.4.1 Effect on Granule Properties

4.4.1.1 Lactose as Diluent

Fig 4.1. illustrates the particle size distribution of the granules with lactose as diluent. With all the binders used, except PVP, the average granule size was found to have increased with increasing concentration of the binder up to a certain level and then started decreasing (Table 4.2.1). The increase is because the higher concentrations of binder would result in stronger, solid bridges, due to its better penetration, covering and wetting ability. (Davies and Gloor, 1971; Carstensen *et al*, 1976). There would also be more binder available for the formation of stable bonds (Chalmers and Elworthy, 1976; Cutt *et al*, 1986). Viscosity of the binder solution normally increases with increasing concentration (Kunle, 1988), which was the case with the starch paste, sodium alginate and gelatin solutions. There was however no appreciable increase in the viscosity of the PVP soultion with increasing concentration.

Up to a certain level, even though the viscosity increases with binder concentration, the mucilages still retained sufficient flow, and when mixed with the powder generally disperses almost uniformly forming granules with increasing bonds and thereby increased granule size. With further increase in binder concentration, the viscosity of the mucilages became too high to allow for uniform dispersion within the powder mix resulting in the observed reduction in the average particle size. With PVP solution however, the slight increase in viscosity was insufficient to hamper the uniform dispersion of the solution within the powder resulting in increased contact with the powder particles and increased average granule size.

Fig. 4.1. Granule Size Distribution (Na alginate as binder/Lactose as diluent)

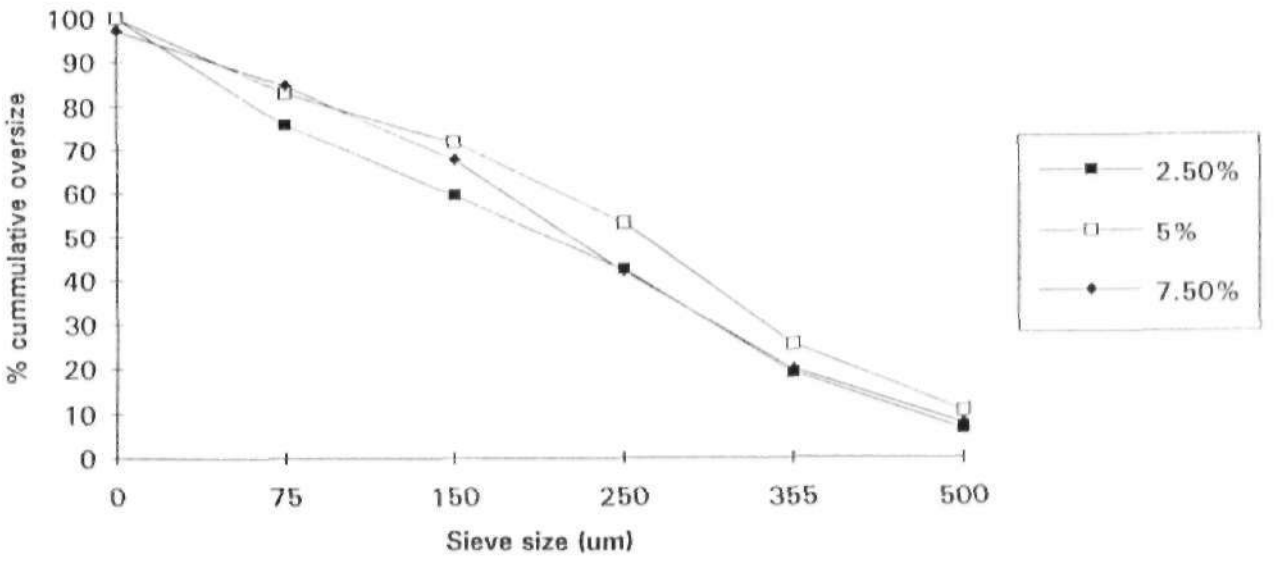


Fig. 4.2. Granule Size Distribution (Na alginate as binder/Heavy MgCo3 as diluent)

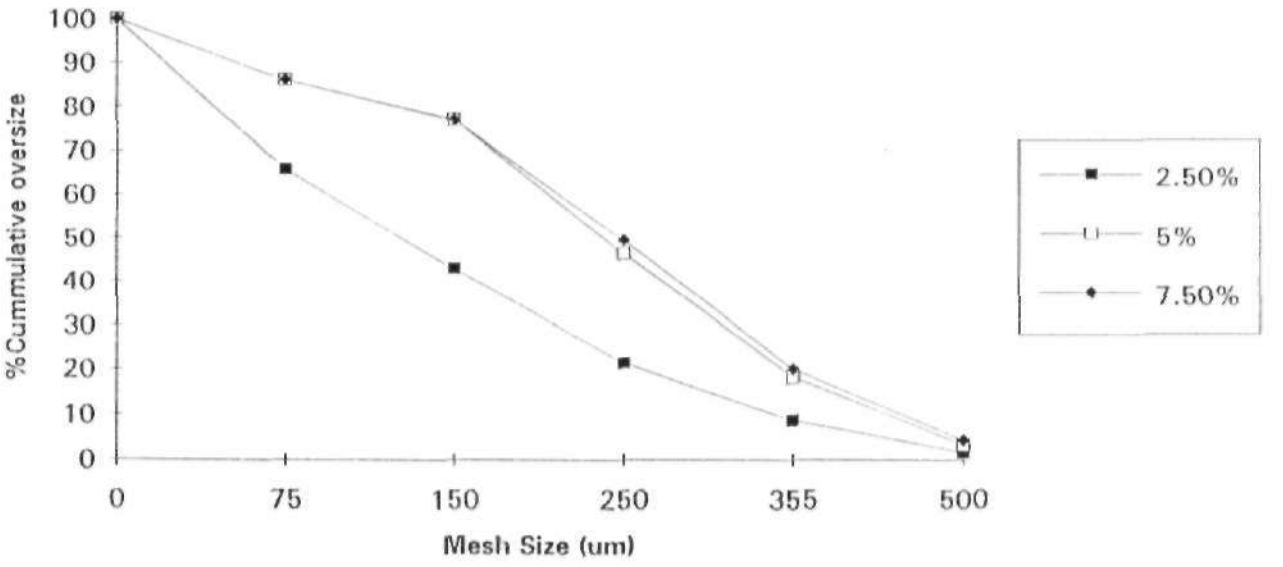


Fig. 4.3. Granule Size Disribution (Na alginate as binder/Aerosil as binder)

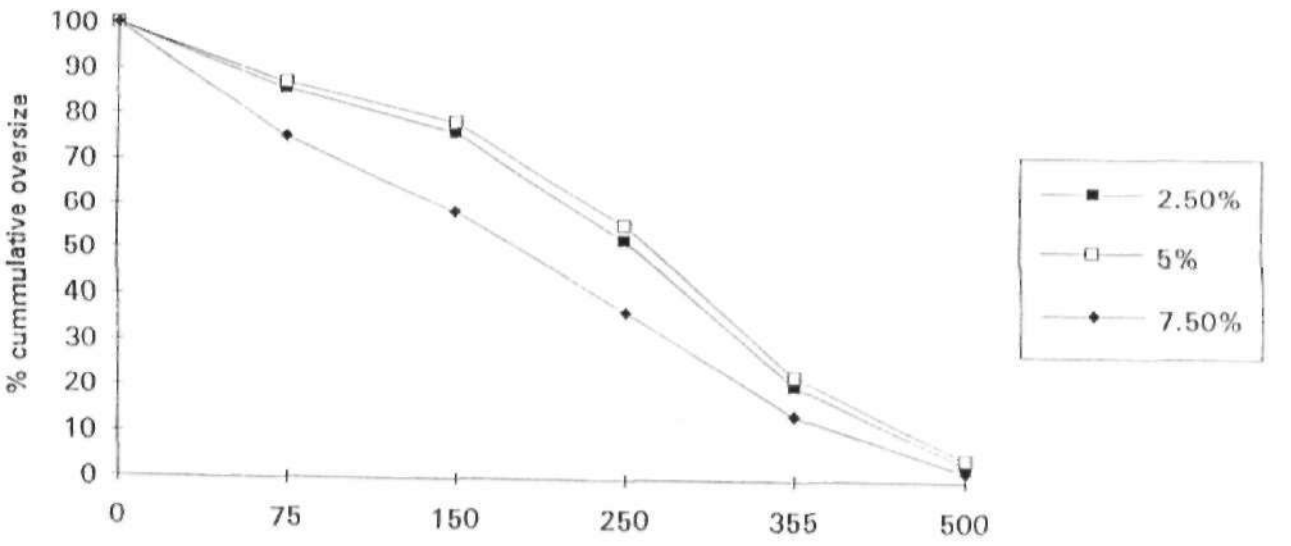


Table 4.2.1: Effect of Binder Conc. on Granule Properties (Lactose as diluent)

Binder Type	Binder Conc. %w/w	Av. Particle size(μm)	Moisture Content %	True Density	Bulk Density (g/ml)	Tapped Density (g/ml)	%Compressibility	Flow Rate (g/secs.)	Angle of Repose, θ
Starch paste	5.0	220	5.8	1.43	0.80	0.96	16.6	7.5	26.23
	7.5	230	5.5	1.45	1.04	1.25	16.8	10	25.41
	10	185	6.1	1.41	0.71	0.83	14.5	7.5	23.43
PVP	2.5	160	5.8	1.59	0.79	0.94	16.0	10	25.52
	5.0	180	6.1	1.45	0.65	0.75	13.3	7.5	25.41
	7.5	220	5.9	1.52	0.65	0.79	17.7	7.5	24.23
Na alginate	2.5	205	4.4	1.56	0.71	0.88	19.3	7.5	26.6
	5.0	265	4.5	1.54	0.65	0.81	19.8	6	26.6
	7.5	225	4.3	1.59	0.65	0.79	17.7	7.5	26.57
Gelatin	7.5	230	5.4	1.43	0.65	0.79	17.7	7.5	28.07
	12.5	277	4.7	2.09	0.63	0.75	16.0	7.5	29.25
	17.5	275	5.0	1.52	1.00	1.2	16.7	7.8	26.87

Table 4.2.1 shows the effect of the concentration of the four different binders used on the properties of granules of HWE. The results show that the binder concentration affected the different granule properties assessed but to different extents.

The moisture content of all the granulations, irrespective of starch paste concentration, were all below or equal to 6%. At this moisture level, the forces in operation within the granules due to moisture - pendular, funicular and capillary - will be expected to be similar (Pilpel, 1971). These forces result in liquid bridges where at the pendular stage attraction is by surface tension and hydrostatic suction pressure; while at the capillary stage it is by capillary suction at the liquid/air interface.

Binder concentration did not seem to affect the true density of the granulations in general. However the 12.5% gelatin granulate had an exceptionally high true density. Parker *et al* (1990) have proposed that the adsorption of binder molecules within the granule would lead to a reduction in the intra-granular viscosity, as the molecules are effectively removed from the solution. Such a reduction would result in reduced viscosity of the binder and possibly reduced granular volume which would increase granular density. It would seem that the 12.5% gelatin was the most affected by this adsorption. Okhamafe *et al* (1991) have stated that high values of true densities will suggest that the granules will exhbit good compressibility. The low (good) %compressibility obtained for this granulation tends to support this.

The effect of binder concentration on bulk and tapped densitites was inconsistent. While increased granule size would be expected to result in reduced densities due to increased inter granular voids, with starch paste and gelatin as binders the reverse was observed. It would therefore seem that apart from size, other factors such as particle rugosity, shape, the forces of attraction and repulsion, and the proportion of fines contribute to the

bulk and tapped densities of powder beds. Ridgway and Rupp (1969) for example, in investigating the effect of particle shape on powder properties, found that the angle of repose increased whilst the bulk density and flowability decreased with increasing departure from spherical shape, due to the greater resistance to shear of flow of an assembly of irregular particles compared to an assembly of spherical particles of the same size and density. A high value of these parameters is usually preferred because it ensures better particle packing within the die, which in combination with good flow would result in uniformity of tablet weight (Staniforth, 1985).

Based on the classification by Carr (1965), all of the granulations will be expected to have between very good to excellent flow because of their low percent compressibility values. Percent compressibility is a direct measure of the potential powder arch or bridge strength and stability (Staniforth, 1985). The binder concentration did not seem to affect this property significantly, as was also the case with flow rate which was generally good. All the granulates also had good angles of repose with values below 30^0 (Pilpel, 1964).

4.4.1.2 Heavy Magnesium Carbonate as diluent

All the size distribution were similar to that shown in fig 4.2. In all cases, average particle size increased with increase in binder concentration (Table 4.2.2). This is due to the formation of more and stronger bonds in the presence of more binder.

Increasing the PVP and gelatin concentrations from low to medium unexpectedly resulted in increase (although slight) in bulk and tapped densities in some formulations (Table 4.2.2). This is an indication of improved packing of the granules probably due to the

Table 4.2.2. Effect of Binder Conc. on Granule Properties (Diluent: $MgCo_3$)

Binder Type	Binder Conc. %w/w	Av. Particle size(μm)	Moisture Content %	True Density	Bulk Density (g/ml)	Tapped Density (g/ml)	%Compressibility	Flow Rate (g/sec.)	Angle of Repose,θ
Starch paste	5.0	95	3.1	2.15	0.61	0.77	20.78	5.00	21.67
	7.5	160	3.6	2.12	0.49	0.66	25.76	5.00	26.27
	10	170	3.7	1.84	0.52	0.68	23.53	5.00	25.55
PVP	2.5	80	3.7	1.89	0.54	0.69	21.74	5.50	22.41
	5.0	85	3.6	2.22	0.69	0.83	16.87	5.00	25.12
	7.5	90	3.7	1.96	0.56	0.69	18.84	5.00	24.74
Na alginate	2.5	130	3.1	1.87	0.50	0.66	24.24	5.00	24.78
	5.0	240	3.2	1.83	0.50	0.63	20.64	5.00	25.00
	7.5	250	3.2	1.85	0.48	0.57	15.79	5.00	26.57
Gelatin	7.5	90	3.8	1.80	0.63	0.78	19.23	6.25	23.55
	12.5	95	3.5	2.13	0.66	0.83	20.48	6.25	23.49
	17.5	140	3.9	1.69	0.63	0.78	19.23	6.25	24.30

medium concentration producing granules with a smoother surface than the lower one. It could also be that the particles of the latter formulations approached spherical shape more than the former. It was also noted that the low and medium concentrations in both cases produced granules with very low average particle sizes which were also quite close.

The least angle of repose was obtained at the lowest binder concentration with all the binders used except with gelatin where it was virtually unchanged between 7.5 and 12.5% concentrations. It shows that as the binder coat around the particles increased the interparticulate friction increased. This could have been due to increased surface rugosity, which might encourage some kind of meshing or mechanical interlocking between the granules. The absence of a similar effect on the flow rate of the granulates might be because the vibration involved in this test reversed the mechanical interaction between the particles.

4.4.1.3 **Aerosil as diluent**

Fig 4.3 is illustrative of the size distribution for this set of granulates. With the PVP granulate, the particle size increased with increase in binder concentration (Table 4.2.3). Ritala *et al* (1986) found that PVP has a high surface tension that could result in reduced wetting . This effect would increase with increased PVP concentration. It could therefore be that this reduced wetting effect, which could be very important with this insoluble diluent, aerosil, led to a reduction in bond formation between the particles. They also found that binder concentration had minor effect on granule growth when PVP was used as a binder.

The true density of the granulates was found to increase with increased binder concentration except with sodium alginate as binder (Table 4.2.3). This is because as the

Table 4.2.3. Effect of Binder Conc. on Granule Properties (Diluent: Aerosil)

Binder Type	Binder Conc. %w/w	Av. Particle size(μm)	Moisture Content %	True Density	Bulk Density (g/ml)	Tapped Density (g/ml)	%Compressibility	Flow Rate (g/secs.)	Angle of Repose, θ
PVP	2.5	200	5.3	1.81	0.71	0.93	23.66	6.17	21.43
	5	165	6.3	1.92	0.66	0.75	12.00	5.25	22.87
	7.5	90	6.4	1.97	0.70	0.88	20.46	6.17	21.66
Na alginate	2.5	260	5.1	2.16	0.73	0.91	19.78	6.67	20.60
	5.0	275	4.4	1.81	0.77	1.00	23.00	6.67	18.98
	7.5	195	6.0	1.82	0.81	1.05	22.86	6.67	24.87
Gelatin	7.5	180	6.3	1.97	0.61	0.73	16.4	5.75	25.23
	12.5	200	4.9	2.10	0.65	0.79	17.72	6.29	23.54
	17.5	220	6.3	2.76	0.68	0.82	17.07	5.75	23.29

binder concentration, and expectedly, binder efficiency increases, the packing of the particles in the granule will be expected to be better, resulting in higher density. While the average granule size increased with increased gelatin concentration, it increased to a maximum at 5% alginate concentration and subsequently decreased, probably because the optimum concentration for adequate binder distribution had been exceeded.

Bulk and tapped densities increased with increased binder concentration when gelatin was used (Table 4.2.3), which implied that larger sized granules formed powder beds with the highest density. This was unexpected and would indicate that other factors, apart from size, determine the nature of packing of particles in a bed.

The other parameters were relatively unaffected by binder concentration.

4.4.2. **Effect on Tablet Properties**

4.4.2.1 Lactose as diluent

As would be expected from the good flow properties of the granules, the tablet weight variation was minimal and conformed to the BP (1993) limits. All the tablets had good hardness properties, since a value of about 4kgf is considered to be the minimum permitted for a satisfactory tablet (Ansel, 1981). Increasing the binder concentrations from low to medium (Table 4.3.1) resulted in increased hardness. This is in agreement with the results of other investigators who have made similar observations (Esezobo and

Table 4.3.1. Effect of Binder Conc. on Tablet Properties (Lactose as diluent)

Binder Type	Binder conc. %w/w	Av.Weight, mg (SD)	Hardness (kgf)	Friability %	Disint. Time (min)	Dissolution Time (min.) T50	T75
Starch paste	5.0	759.50(6.88)	7.5	0.16	18.30	35	48
	7.5	753.22(3.81)	9.1	0.60	18.00	38	60
	10	754.55(7.07)	8.5	*	18.55	75	-
PVP	2.5	743.92(15.04)	8.9	1.35	9.33	25	40
	5.0	757.41(8.22)	14	0.10	25.13	55	90
	7.5	770.40(20.75)	9.6	0.23	9.30	12.5	19
Na alginate	2.5	755.98(20.74)	7.8	0.99	15.10	20	35
	5.0	740.94(15.06)	9.1	0.52	16.20	18	35
	7.5	738.17(20.79)	9.2	0.82	18.23	20	33
Gelatin	7.5	737.12(24.60)	8.7	0.52	11.50	18	29
	12.5	750.30(28.55)	8.6	1.59	19.05	63	119
	17.5	744.88(22.73)	9.5	7.07	23.17	-	-

* Tablets were badly damaged after the test.

Ambujam, 1982; Nasipuri and Akala, 1986 and Esezobo, 1986) and is as a result of the formation of more bonds in the presence of more binder. The amount of bonding that occurs between particles due to asperity melting and plastic deformation has been found to depend on the compressing force and the amount of binding agent present (York and Pilpel, 1973). Since the compressing force was the same for all the batches, the increase in hardness can be attributed to the amount of binding agent. With gelatin as binder, (Table 4.3.1), there was no change in hardness between the low and medium concentrations.

Further increase in binder concentration i.e from medium to high resulted in decreased hardness in the case of starch paste and PVP (Tables 4.3.1). The increased binder concentration would result in increased binder viscosity (Kunle,1988) which might have resulted in less efficient binder distribution within the powder mix in the case of starch paste. This could lead to the formation of fewer stable bonds and thus decreased hardness. It would therefore seem that in these cases, the optimal binder concentration for hardness had been exceeded at this stage.

The 5% PVP granulates produced tablets of exceptionally high hardness. This could be due to an interplay between its relatively small size and the availability of enough binder to ensure good solid bond formation, which would explain why the 2.5% granulate with the lower size did not produce tablets that were equally hard.

The higher concentrations of the starch paste and gelatin produced tablets with (Table 4.3.1) unacceptably high friability values since it is generally accepted that it should not exceed 1.2%. It was observed during the granulation process that mixing was quite difficult with these binders, which would result in poor binder distribution, that would be expected to result in reduced bond formation. These tablets however had good

hardness values. It would therefore seem that few very strong bonds were formed (over wet areas) resulting in high hardness, while the other bonds formed were fragile and easily broken by the tumbling action of the friability test. Because of the non-uniformity of density within a powder compact, hardness values are at best estimates of the strength and extent of bond formation within the tablet (Hiestand *et al,* 1977).

Only the formulations with PVP and gelatin were significantly affected by binder concentration with respect to disintegration time (Table 4.3.1). It was found to follow the same pattern as hardness with the hardest tablet having the longest disintegration time. This is because the harder tablets would have more bonds to be broken by the disintegration medium and this will expectedly take longer. In the case of gelatin however, the 7.5 and 12.5% concentration levels with similar hardness had different disintegration times. This is probably because other factors such as pore structure and size might influence fluid uptake by the tablet thus resulting in variation in disintegration time inspite of similarity in extent of bond formation.

Some of the tablets formulated had disintegration times slightly longer than the B.P. (1993) limit of 15 minutes for uncoated tablets.

The results of the dissolution test indicated that it was affected by binder concentration except with alginate as binder. The pattern was generally that of a fairly consistent but slow release, probably indicative that the drug was dissolving mainly from the intact tablet which could have been due to their long disintegration times. In most cases, dissolution rate decreased with increase in binder concentration. This is because of the formation of a binder film around the powder particles or granules, which will be expected to be converted into a mucilagenous viscous barrier when the tablets and break up fragments contact the dissolution medium, thus delaying dissolution (Esezobo and

Pilpel, 1977). The dissolution retarding effect of this film would depend on its thickness which would in turn depend on the binder concentration.

In other cases, however, this pattern was not followed, for example in the case of the 5% PVP tablets (Table 4.3.1), which had the poorest dissolution rate. This could have been because as Yen (1963) explained several factors such as particle size, capillary space size and disintegrant characteristics could interact to give unpredictable effects on tablet dissolution. In this case, the 7.5% PVP granulate had a relatively large particle size (Table 4.3.1) which might have resulted in larger interparticulate voids and consequently larger pores within the tablet, thus easing medium penetration into the tablet matrix. Levy *et al* (1963) and Yen (1964) have also found a relationship between granule size and tablet dissolution time.

In most of the batches, a direct relationship was not obtained between disintegration and dissolution times. For example while the tablets with starch paste as binder had similar disintegration times, they had diferent dissolution properties (Table 4.3.1). Adeyemi and Pilpel (1984) have found that particle and capillary or space sizes were some factors that could result in this. Finholt and Solvang (1968) have also proposed that the strong agglomeration between the particles which could reduce the contact surface area to much less than the external one of the primary particles could also contribute. It could also be because only a limited fraction of the surface area of the primary particles take part in the dissolution process (Nystrom and Westerberg, 1986) which could reduce or even nullify the effect of tablet disintegration. It is also possible that while the tablets disintegrated adequately enough to pass the disintegration test, the granules and fine particles resulting might have remained heavily coated with the binder, thus retarding media penetration and consequently drug dissolution.

4.4.2.2 Heavy Magnesium Carbonate as diluent

All of the tablets formulated were found to have low hardness values irrespective of binder concentration (Table 4.3.2) in all cases; increasing the binder concentration from low to medium had no significant effect on hardness, while further increase resulted in a slight increase in hardness. The only exception was with gelatin where the significant increase was between the low and the medium concentrations (Table 4.3.2), probably because of the high increase in viscosity between the 7.5 and 12.5% concentrations.

As expected from the hardness vaues, the tablets generally had high friabilities, with the 7.5% gelatin formulation having an exceptionally high value of 11.5%. In some cases, tablets which were harder than others, had higher friabilities. An example of this is the 2.5% PVP granulate tablets which had a friability of 5.8% inspite of being harder than the 5% granulate tablets (Table 4.3.2). This probably indicates that most of the bonds were weak and fragile although there were a few strong ones.

The disintegration time of all the tablets was very low because of the low physical strength of the tablets. Binder concentration did not significantly affect this parameter except for the alginate formulation (Table 4.3.2) between 2.5 and 5%, where the magnitude of the increase was quite high when compared with the slight difference in their hardness values. This could have been due to other factors that could influence disintegration time apart from number and strength of bonds. Such factors include particle shape, which will affect tablet porosity, compact characteristics and the nature of binder distribution in the powder bed and also after drying which might be uneven. The unexpected decrease in disintegration time between 7.5 and 12.5% gelatin concentrations (Table 4.3.2) could have been due to the very small size (90μm) of the

Table 4.3.2. Effect of Binder Conc. on Tablet Properties (Diluent: $MgCO_3$)

Binder Type	Binder conc. %ww	Av.Weight, mg (SD)	Hardness (kgf)	Friability %	Disint. Time (min)	Dissolution Time (min.) T50	T75
Starch paste	5.0	723.98(35.21)	2.5	2.2	0.48	2.5	5
	7.5	716.64(23.70)	2.5	1.7	0.50	3	9
	10	707.68(18.24)	2.9	1.4	0.56	22.5	46
PVP	2.5	715.85(20.08)	2.4	5.8	0.42	21	80
	5	712.32(28.27)	2.1	2.3	0.37	39	81
	7.5	711.50(20.38)	3.0	1.5	0.48	50	-
,Na alginate	2.5	706.90(19.51)	1.7	4.0	0.80	30	55
	5.0	714.43(14.14)	2.0	3.5	10.33	40	80
	7.5	722.25(36.89)	2.7	4.3	16.18	50	112
Gelatin	7.5	732.34(19.83)	2.0	11.9	0.42	30	80
	12.5	735.81(21.63)	3.7	1.1	0.37	48	120
	17.5	743.09(30.99)	3.8	0.9	0.48	52	120

7.5% granulate (Table 4.2.2). This might have resulted in a reduction of the number or size of the pores in the resulting tablets, thus reducing the rate of water penetration and hence tablet disintegration at the 7.5% concentration.

With all the binders used, dissolution rate was found to decrease with increase in binder concentration, with the extent depending on the stage of dissolution (T50 or 75%) being assessed. With PVP as binder, at 2.5 and 5% concenetration levels, the dissolution profiles were similar, with initial high release, followed by a portion of almost zero slope and then increased rate. The initial high rate is probably due to the disintegration of the tablet which would increase the surface area available for drug dissolution. The initial high release from all the three batches which had similar disintegration times (Table 4.3.2) would support this assumption. The second portion of hign rate could be due to the action of the endodisintegrant, resulting in further breakdown of the granules to expose a much larger surface area. The 7.5% concentration did not have this portion, probably indicating that further dissolution in this case was by some kind of leaching action.

It was noted that inspite of their low hardness and disintegration time some of the $MgCo_3$-based tablets had poor dissolution properties. It could be that when in water, rather than break apart, the granules become gel-like thus delaying disintegration and dissolution. It could also be because of poor water penetration. It might also be that there was adsorption between the HWE and the diluent, which delayed dissolution with subsequent desorption resulting in higher dissolution at longer times as was observed.

4.4.2.3 Aerosil as diluent

The effect of binder concentration on tablet hardness was dependent on the binder type and the concentration level. Hardness decreased with increased PVP concentration indicating that the lowest concentration used (2.5%) is the optimum with respect to this property (Table 4.3.3). Sodium alginate as binder produced the best tablets with respect to tablet physical strength (Table 4.3.3) since they had very good hardness and friability.

The friability results followed the same pattern with hardness. In the case of gelatin as binder, however, (Table 4.3.3) friability increased between 7.5 and 12.5% concentrations rather than decrease, as would have been expected from the hardness values indicating that more fragile bonds/bridges were formed in the latter.

Disintegration time generally increased with increased binder concentration. Based on the hardness and friability results, this was unexpected for PVP between 2.5 and 5% concentrations (Table 4.3.3) since tablet hardness decreased while friability increased. It could have been as a result of the presence of overwet areas, with exceptionally high concentration of binder and even some areas consisting purely of binder (with little or no disintegrant) which would take longer to disintegrate. It was also observed that the formulation with 5% alginate which produced tablets with similar hardness and friability with the 2.5% granulate (Table 4.3.3) took almost twice as long to disintegrate. This is because of increased thickness of the binder (mucilagenous) layer around the granules at the higher binder concentration, thus increasing the time required for penetration of the disintegration medium.

With PVP as binder, the 7.5% concentration level which would have been expected to have the lowest dissolution rate had the highest probably because it had the shortest

Table 4.3.3. Effect of Binder Conc. on Tablet Properties (Diluent: Aerosil)

Binder Type	Binder conc. %w/w	Av.Weight, mg (SD)	Hardness (kgf)	Friability %	Disint. Time (min)	Dissolution Time (min.) T50	T75
PVP	2.5	655.24(19.75)	4.2	1.2	1.57	21	37
	5.0	686.90(29.10)	3.7	1.9	4.57	22.5	51
	7.5	660.18(11.08)	2.6	3.0	0.52	16	23
Na alginate	2.5	657.17(25.28)	6.1	0.6	5.73	42	53
	5.0	673.51(38.75)	6.1	0.6	11.32	35	53
	7.5	704.62(23.35)	7.2	0.5	16.18	17.5	41
Gelatin	7.5	679.94(23.31)	2.0	1.6	0.58	75	14
	12.5	704.89(30.52)	3.5	5.5	0.73	12.5	23
	17.5	719.05(37.94)	3.4	2.1	0.80	35	72

disintegration time and low granule size (Table 4.2.3), which would result in increased surface area. The profiles for the formulations with alginate as binder were in two portions: an initial region with 7.5% having the highest rate and 2.5% having the lowest, a second region with the relationship reversed. It would seem that the effect of the binder mucilagenous barrier around the particle (Esezobo and Pilpel, 1976) increased with time, because moisture absorption would increase its thickness. Since this effect would increase with binder concentration, the reversal in the relationship, with the lower concentation resulting in better dissolution, would support this.

4.5 Effect of Binder Type on Granule and Tablet Properties

4.5.1 Granule Properties

4.5.1.1 Lactose as diluent

The sodium alginate granulates had the lowest moisture content at all the binder concentration levels used (Table 4.4.1), although the moisture content of all the granulates was within the 4-6% range, implying that the forces due to moisture were similar (Adeyemi and Pilpel, 1984).

The concentration level at which the various binders were used seem to determine their relationship in terms of bulk and tapped densities. While gelatin had relatively lower values at the low concentration, it had the highest at the high concentration. Its high densities at the high concentration was unexpected because it had the highest average particle size which might be an indication that its granules had a smooth surface which

Table 4.4.1. Effect of Binder Type on Granule Properties(Diluent: Lactose)

Binder Conc Level	Binder Type	Moisture Content %	True Density	Bulk Density (g/ml)	Tapped Density (g/ml)	%Compressibility	Flow Rate (g/sec.)	Angle of Repose, θ
LOW	Starch	5.8	1.43	0.80	0.96	16.6	7.5	26.23
	PVP	5.8	1.59	0.79	0.94	16.0	10.0	25.22
	Gelatin	5.4	1.43	0.65	0.79	17.7	7.5	28.07
	Alginate	4.4	1.56	0.71	0.88	19.3	7.5	26.60
MEDIUM	Starch	5.5	1.45	1.04	1.25	16.8	10	25.41
	PVP	6.1	1.45	0.65	0.75	13.3	7.5	25.41
	Gelatin	4.7	2.09	0.63	0.75	16.0	7.5	29.25
	Alginate	4.5	1.54	0.65	0.81	19.8	6.0	26.60
HIGH	Starch	6.1	1.41	0.71	0.83	14.5	7.5	26.03
	PVP	5.9	1.52	0.65	0.79	17.7	7.5	24.23
	Gelatin	5	1.52	1	1.2	16.7	7.9	26.87
	Alginate	4.3	1.59	0.65	0.79	17.7	7.5	26.57

encouraged close packing. This could be because at this high concentration (17.5%) there was enough of the binder available to completely cover the particles, thus reducing the rough surfaces to a minimum. Apart from the high values obtained with starch paste at the medium concentration, (Table 4.4.1), all the other binders (PVP, alginate and starch paste) seemed to be quite similar with respect to the densities of their granulates.

The alginate granulates had relatively high % compressibilities, while that of PVP was quite low at the medium concentration. However from Carr's (1965) classification, all of the granulates will be expected to have good flow properties.

Binder type only affected flow rate noticeably at the medium concentration where the starch paste granulate had a high flow rate and the alginate granulate, with a high percent compressibility, had a low rate. This could have resulted from the high interparticulate friction and cohesiveness of the alginate granulate particles as indicated by the high angles of repose (Zajic and Buckton, 1990).

4.5.1.2 Aerosil as diluent

The gelatin and PVP granulates had relatively high moisture contents at the low and medium concentrations respectively (Tables 4.4.2). While the result for gelatin can be explained as being due to its higher viscosity which would tend to reduce the rate of water loss, the high value for PVP was unexpected. Except at the low concentration, gelatin granulates had the highest true density, which Okhamafe *et al* (1991) suggest will result in good compressibility.

The gelatin granulate, inspite of having the smallest particle size, had the lowest bulk and tapped densities at the low binder concentration (Table 4.4.2). It also had the highest

Table 4.4.2. Effect of Binder Type on Granule Properties (Diluent : Aerosil)

Binder Conc. Level	Binder Type	Moisture Content %	True Density	Bulk Density (g/ml)	Tapped Density (g/ml)	%Compressibility	Flow Time (secs.)	Angle of Repose,θ
LOW	PVP	5.3	1.81	0.71	0.93	23.66	3.0	21.43
	Gelatin	6.3	1.97	0.61	0.73	16.40	4.0	25.23
	Alginate	5.1	2.16	0.73	0.91	19.78	3.0	20.60
MEDIUM	PVP	6.3	1.92	0.66	0.75	12.00	2.5	22.87
	Gelatin	4.9	2.10	0.65	0.79	17.72	3.5	23.54
	Alginate	4.4	1.81	0.77	1.00	23.00	3.0	18.98
HIGH	PVP	6.4	1.97	0.70	0.88	20.46	3.0	21.66
	Gelatin	6.3	2.76	0.68	0.82	17.07	4.0	23.29
	Alginate	6.0	1.82	0.81	1.05	22.86	3.0	24.86

angle of repose and the lowest flow rate. It would seem that the force of attraction between the particles which increases with decrease in particle size, was strong enough in this case to retard granule flow. The sodium alginate granulate at the medium concentrations had the highest densities and also the highest average granule size, a possible indication that it had a smooth surface as would seem to be suggested by its good flow rate and low angle of repose. The PVP granulate at the medium concentration (Table 4.4.2) had an exceptionally low compressibility predictive of excellent flow (Carr, 1965).

4.5.1.3 Heavy Magnesium Carbonate as diluent

Moisture content and true density were relatively unaffected by the binder type used except for the high density of the starch paste granulate at the low concentration (Table 4.4.3) and the low value for the alginate granulates at the medium concentration (Table 4.4.3). In all cases, gelatin granulates had the highest bulk and tapped densities, probably because there was sufficient binder to fill the rough surfaces and thus produce smooth particles that would pack more closely. The relationship between the other binders was inconsistent.

Apart from a few exceptions, the percent compressibilities were quite high indicating that flow might be poor or at best fair. This could be due to the generally low particle sizes of the granulates and resulting cohesiveness, in addition to their high interparticulate friction (high angles of repose). This might explain the relatively poor flow rate observed for these granulates.

Table 4.4.3. Effect of Binder Type on Granule Properties(Diluent : $MgCo_3$)

Binder Conc. Level	Binder Type	Moisture Content %	True Density	Bulk Density (g/ml)	Tapped Density (g/ml)	%Compressibility	Flow Rate (g/secs.)	Angle of Repose, θ
LOW	Starch	3.1	2.15	0.61	0.77	20.78	5.00	21.67
	PVP	3.7	1.89	0.54	0.69	21.74	5.52	22.41
	Gelatin	3.8	1.80	0.63	0.78	19.23	6.25	25.23
	Alginate	3.1	1.87	0.50	0.66	24.24	5.00	24.78
MEDIUM	Starch	3.6	2.12	0.49	0.66	25.76	5.00	160
	PVP	3.6	2.22	0.69	0.83	16.87	5.00	85
	Gelatin	3.5	2.13	0.66	0.83	20.48	6.25	95
	Alginate	3.2	1.83	0.5	0.63	20.64	5.00	240
	Starch	3.7	1.84	0.52	0.68	23.53	5.00	170
	PVP	3.7	1.96	0.56	0.69	18.84	5.00	90
	Gelatin	3.9	1.69	0.63	0.78	19.23	6.25	140
HIGH	Alginate	3.2	1.85	0.48	0.57	15.79	5.00	250

4.5.2. **Tablet Properties**

4.5.2.1 Lactose as diluent

All the tablets passed the B.P. (1993) weight variation test. They all had good hardness and friability values, although the type of binder used affected these (Table 4.5.1). The ranking order for hardness was alginate > PVP > gelatin > starch which closely resembled that obtained for the particle density (Table 4.4.1). This observation indicates that granules with high density will be expected to have good compressibility and as such produce tablets with good physical characteristics.

The PVP granulate produced exceptionally hard tablets followed by starch, gelatin and alginate granulates respectively at the medium concentration (Table 4.5.1). It seems that the combination of high moisture content which would provide more and stronger bonds as well as low particle size which would imply high surface area resulting in more surface available for solid bridges/bond formation would account for the very high hardness and low friability of the PVP granulate tablets. The order for tablet hardness was the same as for moisture content and particle size. This confirms the observation by Kurup and Pilpel (1984) that the moisture content is a very important contributor to granulate and tablet strength, and this would be expected to increase with increase in the amount of moisture up to a limit (Esezobo and Pilpel, 1976; Sebhatu *et al* 1997). It has also been established that the surface area available for bond formation due to asperity melting, binder solidification and other forces is a major determinant of the strength of compacts (York and Pilpel, 1972). Although having good hardness, the starch granulate tablets at the high concentration had very high friability, because the bonds were fragile.

The type of binder used affected the disintegration time. Starch granulate tablets at low

Table 4.5.1. Effect of Binder Type on Tablet Properties (Diluent: Lactose)

Binder Conc. Level	Binder Type	Av.Weight, mg (SD)	Hardness (kgf)	Friability %	Disint. Time (min)	Dissolution Time(min.) T50	T75
LOW	Starch	759.50(6.88)	7.5	0.16	18.05	74	-
	PVP	743.92(15.04)	8.9	1.35	9.33	25	40
	Gelatin	737.12(24.60)	8.7	0.52	11.50	18	30
	Alginate	755.98(20.47)	7.8	0.99	15.10	20	35
MEDIUM	Starch	753.22(3.81)	9.1	0.60	18.00	32.5	57.5
	PVP	757.41(8.22)	14	0.10	25.13	52.5	90
	Gelatin	750.30(28.55)	8.6	1.59	19.05	63	115
	Alginate	740.94(15.06)	9.1	0.52	16.22	18	35
HIGH	Starch	754.55(7.07)	8.5	21.7	18.55	31	46
	PVP	770.40(20.75)	9.6	0.23	9.50	11	20
	Gelatin	744.88(22.73)	9.5	7.07	23.17	-	-
	Alginate	738.17(20.79)	9.2	0.82	18.23	20	33

concentration failed the BP disintegration test. The disintegration time of the tablets increased with decrease in tablet friability. As expected from the hardness and friability values at the medium concentration, the PVP granulate had the longest disintegration time, followed by gelatin, starch and alginate granulates respectively (Table 4.5.1). Only the PVP granulate tablets passed the disintegration test at the high binder concentration (Table 4.5.1). Even the starch granulate with the highest friability (indicating fragile bonds) did not pass this test probably due to the formation of a mucilagenous layer which retarded water penetration into the tablet. A similar observation was made for gelatin granulate tablets which had a much longer disintegration time than the PVP granulate tablets inspite of being more friable.

The relationship between the four different binders used with respect to dissolution depended on the concentration level at which they were used. For example, while gelatin had the best (low) T75 value at the low binder concentration, it had the poorest at the medium binder concentration. Several workers, (Keshri *et al*, 1974; Nasipuri, 1979a and Nasipuri, 1979b), have also found that the type of binder used affects dissolution rate of tablets.

At the low concentration, the starch granulate whose tablets had the least hardness, had the longest disintegration and dissolution times (Table 4.5.1). This could have been because the mucilage formed by starch around the drug particles was thicker when compared to the other binders used, thus delaying the penetration of the disintegration and dissolution medium.

The tablets formulated with gelatin as binder were found to have the longest T75 values at the medium and high concentrations levels (Table 4.5.1), not even releasing up to 75% at the latter concentration. Since it also produced granules with the largest particles at

these concentrations, the specific surface area available for drug dissolution would be expected to be the least, which could explain its poor dissolution. This would also be in addition to the fact that it was used at concentrations much higher than the other binders which would probably have resulted in a substantially thick binder coat around the drug particles.

Conversely, the PVP granulates with the smallest particle sizes would have been expected to produce tablets with the fastest dissolution rate because of the relatively larger surface area. However, this was not the case at the low and medium concentrations, probably because of the high hardness of the tablets which, apart from increasing the number and strength of the bonds to be broken, could also result in reduced effective surface area. Nystrom and Westerberg (1986) obtained similar results and explained that this was because only a limited fraction of the surface area of the particles takes part in the dissolution process. They further stated that this could also be because of the definition of surface area, where the experimentally determined particle size (surface area) may not be necessarily equivalent to the surface area taking part in the dissolution process i.e the contact area between solid and liquid . Parker *et al*, (1990) have also found that PVP has a relatively high surface tension which might reduce drug penetration through the binder barrier and could result in reduced drug dissolution.

4.5.2.2 Aerosil as diluent

All the granulates passed the weight variation test (Table 4.5.2). The alginate granulates produced tablets with the best physical properties (hardness and friability) at all the binder concentrations used. This could be due to its relatively higher bulk and tapped densities

Table 4.5.2. Effect of Binder Type on Tablet Properties (Diluent : Aerosil)

Binder Conc. Level	Binder Type	Av.Weight, mg (SD)	Hardness (kgf)	Friability %	Disint. Time (min)	Dissolution Time(min.) T50	T75
LOW	PVP	655.24(19.75)	4.2	1.2	1.57	21	37
	Gelatin	679.94(23.31)	2.0	1.6	0.58	7.5	14
	Alginate	657.17(25.28)	6.1	0.6	5.73	42	53
MEDIUM	PVP	686.90(29.10)	3.7	1.9	4.57	22.5	51
	Gelatin	704.89(30.52)	3.5	5.5	0.73	12.5	23
	Alginate	673.51(38.75)	6.1	0.6	11.32	35	53
HIGH	PVP	660.18(11.08)	2.6	3.0	0.52	16	23
	Gelatin	719.05(37.94)	3.4	2.1	0.80	35	23
	Alginate	704.62(23.35)	7.2	0.5	16.18	17.5	41

which would encourage good compact formation. Gelatin granulates, on the other hand, produced the poorest tablets in terms of physical strength, probably because its higher viscosity did not allow for optimum bond formation.

Tablet disintegration followed the same trend as the hardness except at the medium concentration (Table 4.5.2) where the alginate granulate tablets with the highest hardness had the shortest disintegration time, probably because its larger particles allowed for the formation of a good pore structure.

The gelatin granulates produced tablets with the lowest dissolution times at the low and medium binder concentrations, while at the high concentration, the PVP granulate had the best dissolution time. The good results obtained with gelatin are similar to those obtained by Finholt (1968) who attributed it to the ability of gelatin to render insoluble drug substances or formulations containing insoluble fillers more hydrophilic. The different result obtained at the high binder concentration could be because the thickness of the mucilagenous layer nullified this effect. It was also observed that the orders at the low and high concentration levels corresponded to those for the average particle sizes with the smallest particles having the lowest T75 values. This is because reduced particle size will result in increased specific surface area and thus increased surface from which dissolution can occur.

4.5.2.3 Heavy Magnesium Carbonate as diluent

The weight variation of all the tablets formulated with granules containing low binder

162957

Table 4.5.3. Effect of Binder Type on Tablet Properties (Diluent : $MgCO_3$)

Binder Conc. Level	Binder Type	Av.Weight, mg (SD)	Hardness (kgf)	Friability %	Disint. Time (min)	Dissolution Time(min.) T50	T75
LOW	Starch	723.98(35.21)	2.5	2.2	0.48	2.5	5
	PVP	715.85(20.08)	2.4	5.8	0.42	21	80
	Gelatin	732.34(19.83)	2	11.9	0.42	30	80
	Alginate	706.90(19.51)	1.7	4.0	0.80	30	55
MEDIUM	Starch	716.64(23.70)	2.5	1.70	0.50	3	9
	PVP	712.32(28.27)	2.1	2.3	0.37	39	81
	Gelatin	735.81(21.63)	3.7	1.1	0.37	48	120
	Alginate	714.43(14.14)	2	3.5	10.33	40	80
HIGH	Starch	707.68(18.24)	2.9	1.48	0.56	22.5	46
	PVP	711.50(20.38)	3	1.5	0.48	50	-
	Gelatin	743.09(30.99)	3.8	0.9	0.48	52	120
	Alginate	722.25(36.89)	2.7	4.3	16.18	50	112

concentration levels conformed to the BP standards as shown by their standard deviation values (Table 4.5.3).

The binder type did not seem to have affected tablet hardness signifcantly except for the alginate granulate tablet which had a much lower hardness than the others. All of the tablets had poor hardness and friability properties. The low densities of the granulates (Table 4.4.3), along with their very low average particle sizes, might have resulted in the formation of 'soft' tablets since there will be fewer solid bonds/bridges formed. The tablets from the granulates with the lowest average particle sizes (PVP and gelatin) had the highest friability at the low and medium concentrations (Tables 4.5.3). Only the tablets produced from the gelatin granulates had suitable hardness and friability at the meduim and high concentrations (Tables 4.5.3). This is probably because of the much higher concentrations used and therefore higher viscosity which might result in the formation of stronger and more stable bonds (Kunle, 1988).

The tablet disintegration time was very good for all of the tablets and did not seem to have been significantly affected by the binder type. The alginate granulate tablets at the medium and high concentrations (Tables 4.5.3) were however an exception to this as they had unexpectedly (see hardness values) long disintegration times. This is a probable indication that this binder (Na alginate) forms a difficult to penetrate mucilage film around the granules. Since it also had the largest particles there would be fewer particles per given weight, which could result in a more complete coating of the particles thus retarding liquid penetration.

Drug dissolution time was affected by the binder type. The specific relationship depended on the binder concentration level used. Starch paste granulates produced tablets with the best T75 values at all 3 concentration levels.. Although, as expected from the

disintegration times, the alginate granulates did not have very good dissolution times at the medium and the high concentrations (Table 4.5.3), it was still better than the PVP granulate tablets, which had the longest times at all 3 concentration levels. Its granules also had the smallest particles (Tables 4.5.3), which might have resulted in the formation of a highly aggregated mass by the granules after disintegration (Finholt and Solvang 1968) and consequently reduced surface area from drug dissolution can occur. Finholt *et al* (1966) have also found that with a hydrophobic system, reduction in particle size could result in a smaller effective surface area and a slower dissolution rate. The use of water-insoluble magnesium carbonate as diluent coupled with the low particle size of the PVP granulate might have resulted in the increased dissolution times observed.

CHAPTER FIVE

COMPACTION CHARACTERISTICS OF HWE GRANULATES

5.1 INTRODUCTION

The study of the compaction characteristics of pharmaceutical powders provides an insight into the series of events that lead to the formation of strong compacts that will serve as useful dosage forms. As a result of this, a lot of investigations have been conducted into the compaction behaviour of most pharmaceutical powders. Equations have also been described to explain the results of such investigations. The equation by Heckel (1961) has been the most widely used in describing the various stages involved in compaction. All of these investigations have been conducted on pure synthetic drugs. Being a herbal product that has not been subjected to any formulation studies, the aim of this section is to investigate the compaction characteristics of the HWE when formulated with lactose, heavy magnesium carbonate and aerosil as diluents. Since various types of binders and diluents are being studied in developing a suitable formulation of the HWE, the effect of these additives on the compaction characteristics will also be investigated. Lactose and magnesium carbonate, which were used as diluents in the formulation of the HWE tablets are known to be Type B, indicating that they are hard brittle materials that fragment mainly when subjected to stress. (Armstrong and Lowudes, 1984, Armstrong and Hinnes-Nutt, 1970). The effect of the presence of the additives and the HWE in the formulation on the compaction characteristics of lactose and magnesium carbonate will also be considered.

5.2 MATERIALS AND METHODS

5.2.1 Granulation

The dried hot water extract of *Ficus sur* was thoroughly mixed with the diluent - lactose, magnesium carbonate or aerosil. This was carried out in a blender for 5mins. The disintegrant (starch powder) was added at this stage. The wet granulation method of massing and screening was used and the procedure was as earlier described in Section 2.1.3.

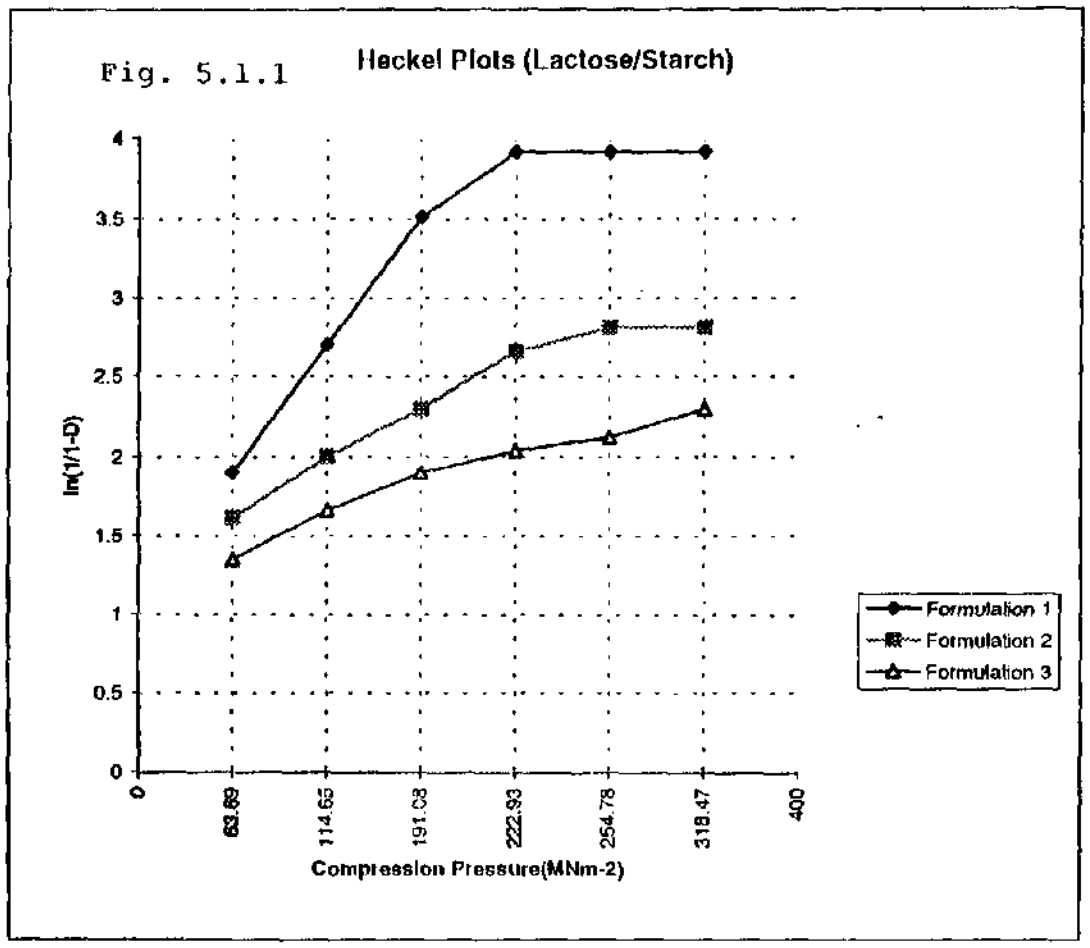
5.2.2 Preparation and analysis of compacts

The amount of granules that would give the required compact weight were determined for each group of granules prepared using lactose, $MgCo_3$ and aerosil as diluents. Compacts were produced from the granules by compressing them for 1 minute with predetermined loads (at various compaction pressures) using a Carver hydraulic hand press (Model C Carver Inc., Menomonee Falls, Wisconsin, USA).

Before each compression, the die (l0.5mm diameter) and the flat-faced punches were lubricated with a 1% w/v dispersion of magnesium stearate in ethanol. After ejection, the tablets were stored over silica gel in a desiccator for 24 hours to allow for elastic recovery and hardening. This was to prevent falsely low yield pressure values (Krycer *et al*, 1982).

Their weights and dimensions were then determined. Dimensions were determined with a Mitutoyo model IDC-1012EB (Mitutoyo Corporation, Japan) thickness guage to the nearest 0.0lmm.

Fig. 5.1.1



Key

Formulation 1 - 5% starch as binder
2 - 7.5% starch as binder
3 - 10% starch as binder

The graphs and regression equations were prepared with the Graphpad, a computer program designed for use in statistical analysis.

5.3 RESULTS AND DISCUSSION

5.3.1 Effect of Binder Concentration on Heckel Plots

5.3.1.1 Lactose as diluent

Fig 5.1.1 shows Heckel plots of ln (1/1-D) versus applied pressure for granules using starch paste as binder at three different concentration levels - 5, 7.5 and 10%. In general, all 3 plots have two discernible phases. There is an initial linear region followed by a portion of decreased slope at higher pressures. The initial linear portions are up to pressures of about 222.93MNm^{-2} for all the formulations. Based on the classification of powders with respect to their compaction behaviour by Hersey and Rees (1970) and York and Pilpel (1973) as well as Summers *et al* (1976), the behaviour observed in fig 5.1.1 tends to indicate a Type B behaviour, for the 7.5 and 10% binder concentration. The initial portion shows that there is initial fragmentation and rearrangement of the particles which is then followed by plastic deformation i.e the region of the plot with reduced slope. This result is not unexpected, as lactose, which was used as a diluent (60% of tablet weight), is known to be a hard and brittle substance, thus requiring initial fragmentation before plastic deformation which conforms to Type B compaction characteristic. The results also show that different concentrations of the binder (starch paste) produced differences in the plot. The plot for the lower starch paste concentration however most closely resemble a Type A material, since it flattened out at the last three pressure levels. This type of plot is obtained for soft and ductile materials. It could

Table 5.1.1 : Heckel Constants (Lactose as Diluent)

Binder Type	Conc(%)	P_y	A	D_A	D_O	D_B
Starch paste	5	66.67	1.1	0.67	0.51	0.16
	7.5	333.33	1.3	0.73	0.62	0.28
	10	166.67	1.1	0.67	0.39	0.10
PVP	2.5	250	1.17	0.69	0.42	0.27
	5	250	1.11	0.67	0.33	0.34
	7.5	333	1.22	0.71	0.34	0.37
Alginate	2.5	333	1.34	0.74	0.38	0.36
	5	166.67	0.77	0.54	0.52	0.02
	7.5	250	1.16	0.69	0.33	0.36
Gelatin	7.5	142.86	1.15	0.68	0.38	0.30
	12.5	333.33	0.86	0.58	0.30	0.28
	17.5	250	0.94	0.61	0.58	0.03

therefore be that with this formulation, the HWE affected the nature of lactose and a combination of both resulted in this observed behaviour.

Heckel constants were obtained from the plots in order to further explain the compaction characteristic of the granulations. The mean yield pressure (P_y) of the granulations were calculated from the initial linear portion of the plot (Kryer *et al*, 1982). The granulation with 7.5% w/w starch paste as binder had the highest yield pressure followed by 10 and 5% respectively (Table 5.1.1).

The mean yield pressure is an important indication of granule compressibility and describes the tendency of the material to deform either by plastic flow or fragmentation (Fell and Newton 1971; Paronen and Juslin, 1983). It is inversely related to the ability of the material to deform plastically under pressure. A low value indicates deformation plastically at relatively low pressure and that deformation occurs faster. The results (Table 5.1.1) therefore indicate that granulations with 5% w/w starch paste as binder deformed plastically most easily and rapidly followed by 10% and 7.5% respectively.

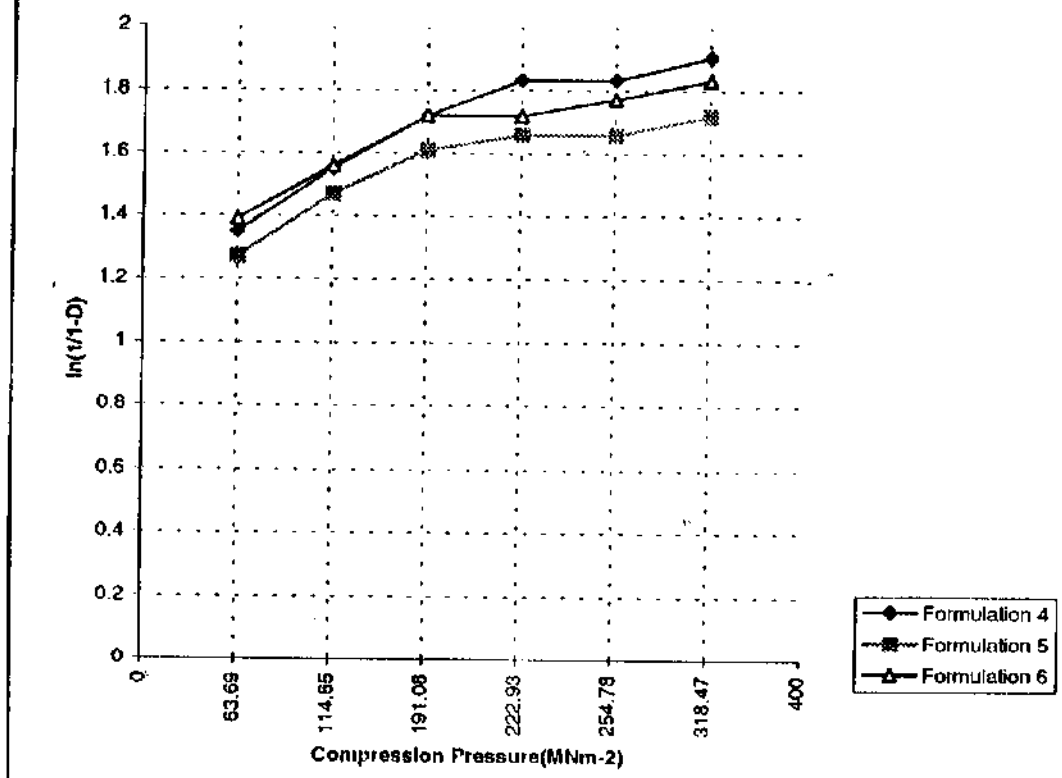
The value of A for each of the lines in the plot was also determined from the intercepts on the ln(1/1-D) axis by extrapolating the initial portion of the plots. A, is a function of the original volume of the compact and it can be said to relate to the movement of the particles during the initial stages of compression (Paronen and Juslin, 1983). The order for values of A was 7.5% > 10% = 5%.

From the value of A, the relative density D_A can be obtained (Roberts and Rowe, 1986). D_A describes the densification of the material due to die filling and rearrangement. The results (Table 5.1.1) indicate that the granulate with 5% w/w starch paste as binder became relatively more dense in the precompression phase especially during die filling

and also in the early stages of downwards movement of the upper punch into the die (low pressures) while the 7.5% granulate seemed to oppose the densification process most strongly with 10% being virtually the same as 5%. Itiola (1993) found a relationship between particle shape and size and densification behaviour of some starches. It was found that particles with similar mean diameters had similarities in D_A values. The results on Table 5.1.1 show that the 7.5% w/w starch paste granulate which had the largest average size (see Table 4.1.1) had the highest D_A value. The contribution of shape might have presented a direct relationship between the size and D_A values at the other concentrations.

D_o, which is the packing fraction of the granulate, was also determined. It describes the die filling or the density of the powder column in the die at zero pressure. A high value indicates a very dense packing while a low value shows that the packing is loose. The ranking order was 7.5% > 5 > 10. This order corresponds to that of particle size of the granulates with the largest particles having the highest packing fraction (see Table 4.1.1). Paronen and Juslin (1983) have established a relationship between packing fraction in the bulk state and particle size and shape. It would therefore seem that the 7.5% granulate with the lowest granule size was able to pack most densely. Based on size alone, the reverse of the observed situation would have been expected, since larger particles will allow for very large intergranular pores (Vroemens *et al*, 1985). The order obtained could have been due to surface characteristics (rougher edges will tend to pack more closely) or particle shape. The densification due to rearrangement of the particles during the initial stages of compression is described by D_{II} which was also determined for these granulates. The extent of this phase depends on the theoretical point of densification at which particle deformation begins. The results obtained (Table 5.1.1) show that the 10% w/w granulates had the lowest value followed by 5 and 10% granulates respectively. This relationship agrees with the findings of Huffine and Bonilla (1962) for sodium chloride, Fell and

Fig. 5.1.2 Heckel Plots(Lactose/PVP)



Key:
Formulation 4 - 2.5% PVP as binder
5 - 5% PVP as binder
6 - 7.5% PVP as binder

Newton (1971) for crystalline and spray dried lactose, and of York (1978) for four Pharmaceutical materials as well as Paronen and Juslin (1983). These workers found that the rearrangement of particles occurs more with smaller sized particles (10% granulate) and less with larger sized ones (7.5%) which seems to be because it allows for the almost complete filling of intergranulate voids.

Fig 5.1.2 shows the Heckel plot for HWE granules with lactose as diluent and PVP as binder. It can be seen that the concentration of PVP used as binder affected the plots since different lines were obtained for each of the granulates. All 3 lines generally had 2 portions. On closer examination, however, a third portion is discernible resulting from a slight rise between 254.78MNm^{-2} and 318.47MNm^{-2}. However, the presence of two regions in the curve tends to indicate that there was some fragmentation and rearrangement in the initial stage. The slight rise noticed between the last two readings indicates that the rate of plastic deformation increased at these high pressures or that there was a breakdown of some of the HWE particles structurally due to the pressure being too excessive for them. A reduction in volume could also have resulted from asperity melting. The slightness of the rise could be because very few particles were involved.

The ranking order for the yield point of the granulates (Table 5.1.1) was, 7.5% > 5% = 2.5%. The result follow the same pattern as binder concentration. It therefore means that the higher the concentration of PVP as binder the more the resistance to deformation by plastic flow or fragmentation. Davies and Gloor (1972) have proposed that binders form a coat around the drug particles and that the thickness of the coat will increase with increase in binder concentration. It has also been noted that soft and plastoelastic binders will increase the rate of deformation of the material and thus initiate deformation at relatively low yield points. It would be expected that the 'softness' and plastoelasticity will decrease with increase in concentration, thus making the granule stronger and

increasing the point at which the material yields. All these can strengthen the particles, thus increasing their resistance to the forces of deformation. In addition, increasing the binder concentration is thought to result in an increase in the number and strength of intergranular bonds (Davies and Gloor, 1972; Chalmers and Elworthy, 1976) which might also increase resistance to plastic flow.

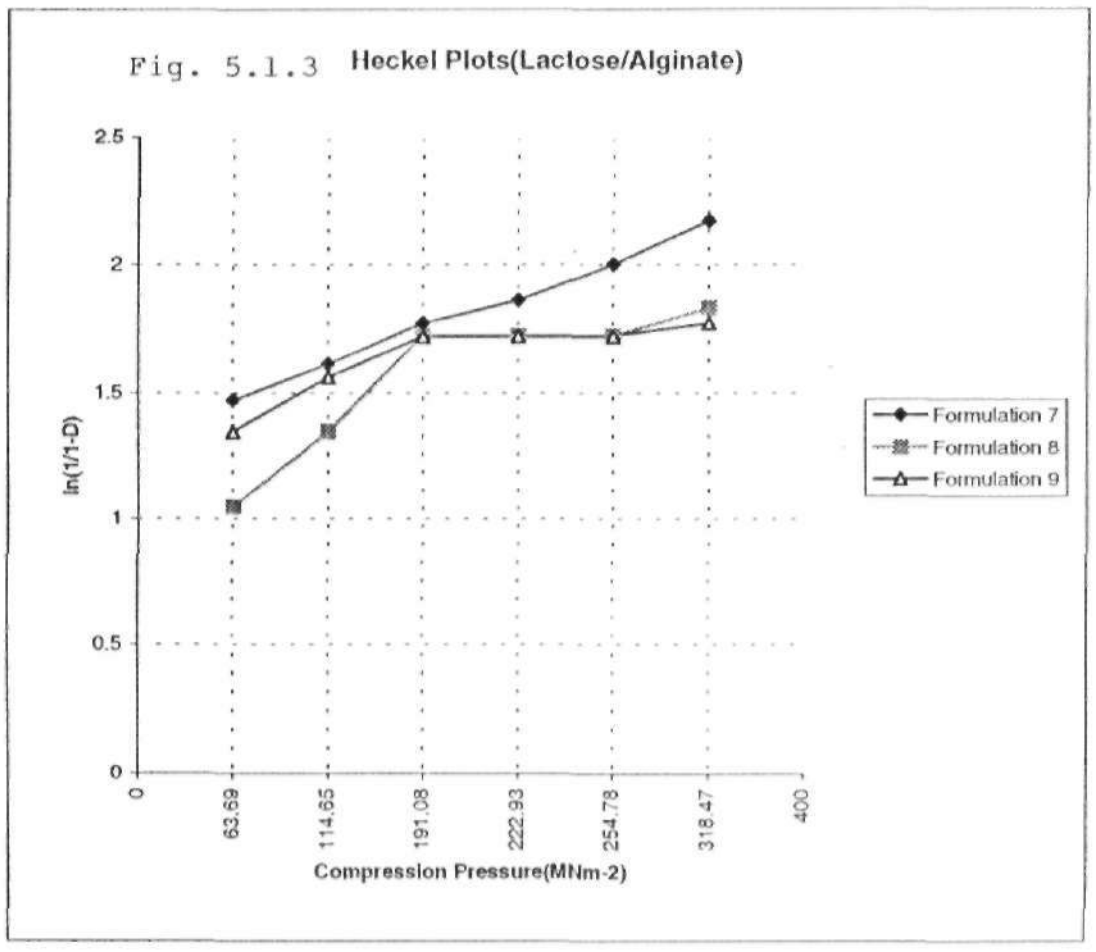
The granulate with 7.5% PVP as binder had the highest value of A (Table 5.1.1) followed by 2.5% while 5% had the least. Since A has been identified with the movement of particles during the initial stages of compression, the results indicate that the granulate with 7.5% binder had the most movement followed by 2.5% and 5%.

The stage of densification due to die filling and rearrangement is described by D_A, where the ranking order was 7.5 > 5 = 2.5. This is the same as that for yield point which tends to indicate that the more resistant particles have better overall packing at zero and low pressure.

D_o, describes the die filling stage and here the relationship was 2.5 > 7.5 > 5% implying that the 2.5% PVP granulate had the highest degree of initial packing while 5% had the least. This relationship bears some resemblance to that of average particle size with the smallest particles having the lowest density. A similar explanation as earlier given by Paronen and Juslin (1983) based on the elctrostatic forces of repulsion will also explain this observation.

The ranking order for D_B was 7.5 > 5 > 2.5 indicating that the phase of densification due to rearrangement decreased with increase in binder concentration. This order has close similarity to the particle size (see Table 4.1.1) of the granules with increase in particle size tending to decrease the extent of this phase.

Fig. 5.1.3 Heckel Plots(Lactose/Alginate)



Key:

Formulation 7 - 2.5% alginate as binder
8-5% alginate as binder
9-7.5% alginate as binder

Fig 5.1.3 shows the Heckel plot for HWE/Lactose mixture granulated with Na Alginate as binder. Three different concentration levels (2.5,5 and 7.5%w/v) were used. As with the other binders, the concentration of alginate used was found to affect the plot. All 3 lines were generally similar having 2 sections with different slopes. However there was a slight rise in the lines for the formulation with 5 and 7.5%w/v alginate as binder between compression pressures of 254.78 and 318.47MNm^{-2}. The formulation with 2.5%w/w alginate however continued to show a rise in value from 63.69MNm^{-2} right up to the highest pressure of 318.47MNm^{-2}. Before the rise noticed in the 5 and 7.5%w/w formulations, the lines were flat between 191.08 and 254.78MNm^{-2}, indicating that between those pressures there was no further plastic deformation of the granules; the increase at the end however tends to indicate that there were still particles that had not fully deformed which the higher pressure (318.47MNm^{-2}) was able to deform. This is probably due to the eventual breakdown of all of the binder coats around the particles which now allowed for full deformation. This is supported by the fact that the granulate with 2.5% alginate where a thin coat would be expected showed continuous deformation.

Values for P_y, A, D_o, D_A and D_B are presented in Table 5.1.1. The ranking for P_y is 2.5%>7.5>10, for A, 2.5%>7.5%>5%, for D_A, 2.5>7.5>5, for D_o 5>2.5>7.5 and for D_B 7.5=2.5>5. The P_y ranking is inversely related to the binder concentration. The earlier explanation with respect to thickness of binder coat around the particles resulting in harder particles would seem to explain this observation. The ranking orders for A and D_A were the same, this is probably because the movement of the particles during the initial stages of compression (A) will influence the densification due to die filling and rearrangement (D_A). The order was inversely related to that obtained for particle size of the different granulations (see Table 4.1.1). The results thus seem to indicate that the smaller particles moved and densified more easily thus bringing the particles closer together and resulting in better densification of the particles.

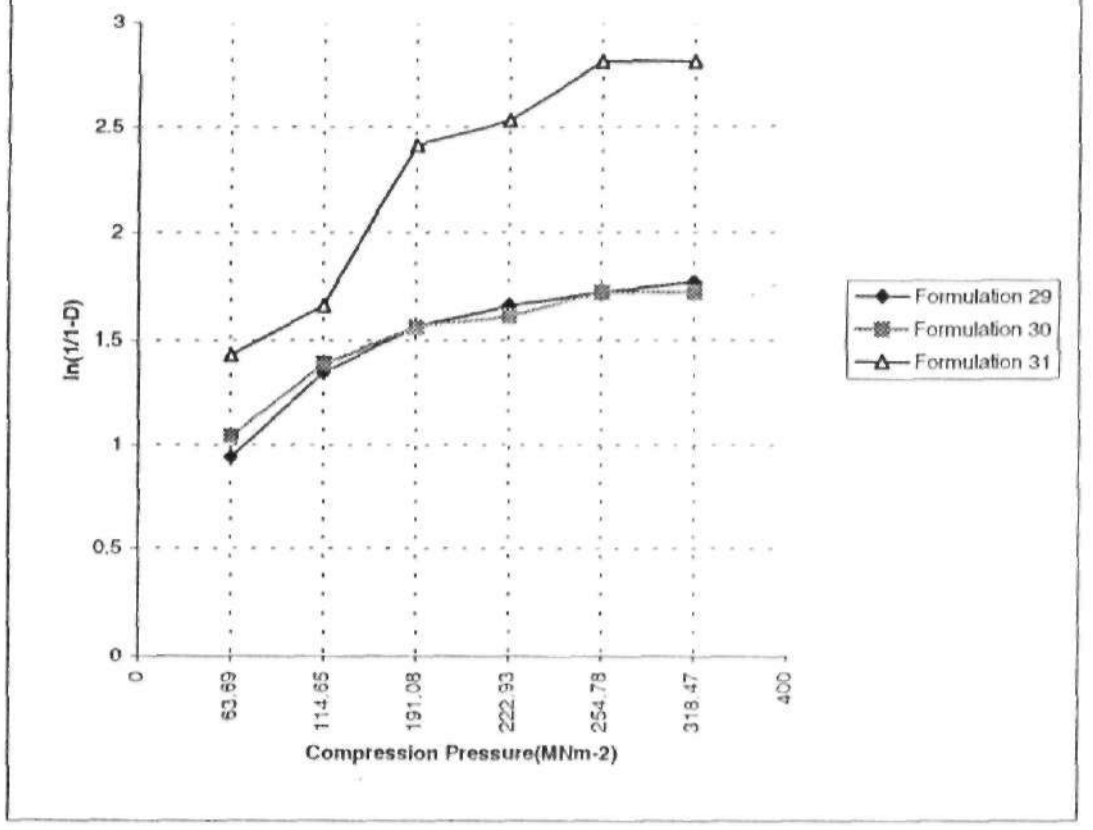
The plots for the formulations with 12.5 and 17.5% w/w gelatin closely resembled each other consisting of basically two portions, whose explanation is as earlier stated. There was however, a noticeable rise between the last 2 pressures for the 7.5% granulate. This indicates that there was still some reduction in volume. at this point, probably due to asperity melting at the high pressures which resulted in high temperatures (York and Pilpel, 1973). The fact that this occured only with the 7.5% granulate could indicate that these new bonds or melting was mostly between the drug particles which caused the thicker binder coat obtainable at the higher concentrations to prevent this from taking place.

The 7.5% granulate had the lowest yield point followed by 17.5% and then 12.5% (Table 5.1.1). Having the lowest binder concentration and subsequently the least number and probably the weakest bonds/bridges, it is understandable why the 7.5% granular had the lowest yield point. Based on this it would have been expected that it would be followed by the 12.5% granulate. This was however not the case. The ranking orders for A and D_A were the same and was the reverse of that obtained for the yield point. The similarity is understandable because the movement of the particles during the initial stages of compression (A) would be expected to affect the densification achieved due to rearrangement (D_A). The reverse relationship between yield point and D_A could be because high densification might improve the energy distribution within the die thus resulting in a low yield point.

The ranking order for D_0 (Table 5.1.1) was 17.5 > 7.5 > 12.5. A high value of D_0 indicates dense packing while a low value would indicate loose packing. It therefore means that the 17.5% granulate had the densest packing while 12.5% had the least.

For D_B, the ranking order was, 7.5 > 12.5 > 17.5 indicating that rearrangement was

Fig 5.1.4 Heckel Plots($MgCO_3$/Starch)



Key:

Formulation 29 - 5% starch as binder
30 - 7.5% starch as binder
31 - 10% starch as binder

most with 7.5% granulate and least with the 17.5% granulate.

5.3.1.2 Heavy Magnesium Carbonate as Diluent

Fig 5.1.4 shows the effect of starch paste (as binder) concentration on the Heckel plot. Two of the 3 lines had two (2) portions, with 2 different slopes, while the third (10% starch paste) had up to 4 different regions. The two similar plots (5 and 7.5%) most closely resembled a Type B plot. The 7.5% granulate however does not correspond to any of the three types of materials based on the Heckel plot. It is therefore obvious that the compaction characteristic of this granulate cannot be explained by the Heckel equation. Further statistical analysis showed that the slopes of the line were not significantly different from zero, indicating that a linear fit was not suitable for the data. It should however be mentioned that there was an initial portion, which was quite similar to what obtains with fragmentation.

With respect to yield point, the ranking order was 7.5% > 5, for A, D_A and D_B while for D_0 it was 5 > 7.5 (Table 5.1.2). The order for A and D_A was the reverse of that of binder concentration with the granulate with the highest starch paste concentration having the highest values. The order is the same as that for particle size (see Table 4.1.2). It is known that high D_A values indicate high resistance to particle movement, which would be expected to increase with increase in particle size if the volume or space available is fixed.

The particle sizes of the different formulations would also seem to explain the ranking order for D_B except for the fact that the values were virtually same for 7.5 and 10% granulates. D_B denotes the phase of densification due to rearrangement, which will again

Table 5.1.2 : Heckel Constants (Magnesium Carbonate as Diluent)

Binder Type	Conc(%)	P_y^*	A	D_A	D_O	D_B
Starch paste	5	125	0.55	0.42	0.28	0.14
	7.5	142.86	0.71	0.51	0.23	0.28
	10	-	-	-	0.28	-
PVP	2.5	166.67	1.03	0.64	0.29	0.35
	5	200	1	0.63	0.31	0.32
	7.5	111.11	1.12	0.67	0.29	0.38
Alginate	2.5	125	1.22	0.71	0.27	0.44
	5	166.67	1.14	0.68	0.27	0.41
	7.5	125	1.22	0.71	0.26	0.45
Gelatin	7.5	142.86	1.08	0.66	0.32	0.34
	12.5	200	0.97	0.62	0.31	0.31
	17.5	83.33	0.68	0.49	0.33	0.16

be expected to be inversely related to the particle size since this might affect the extent and ease of movement that results in rearrangement.

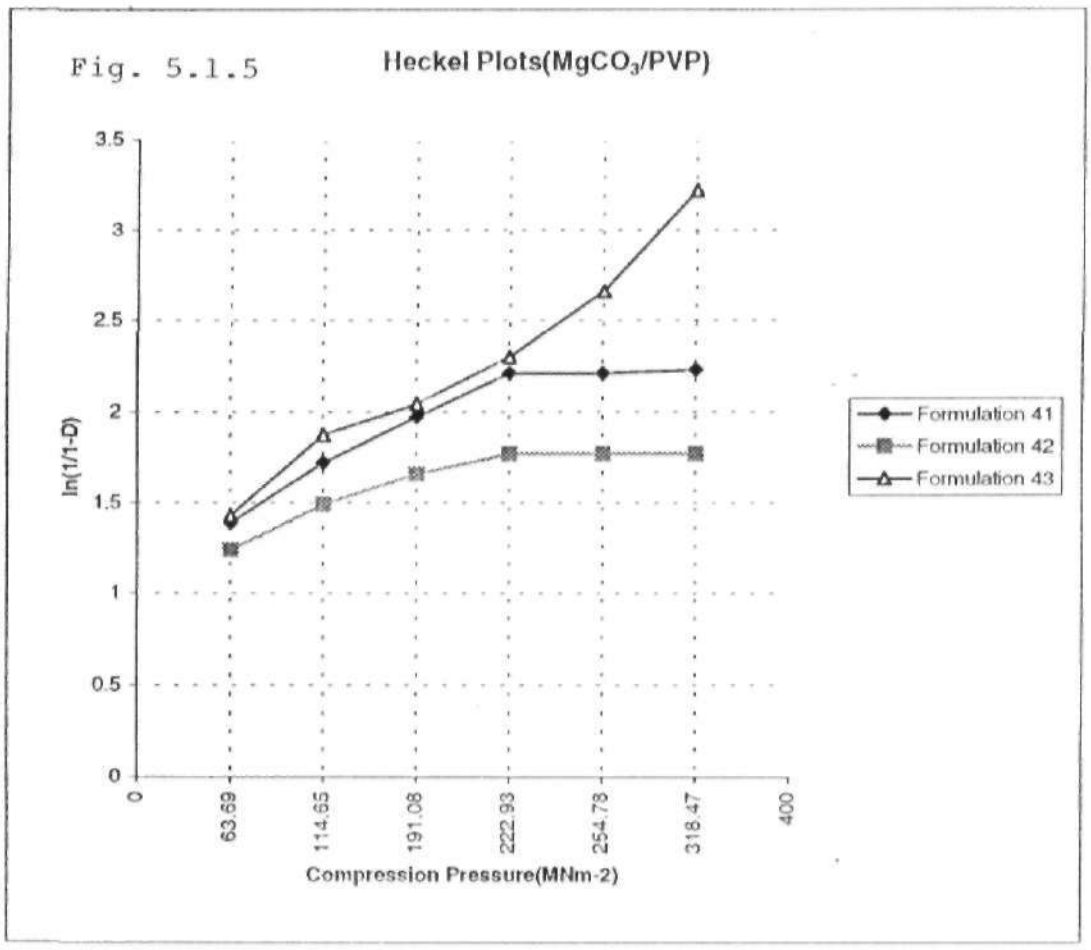
Fig.5.1.5 is the plot for granulations using PVP at 3 different concentration levels as binder. All the formulations had two distinct portions with two slopes. The lower concentrations (2.5% and 5% w/w), virually had a flat second portion. This is indicative of a tendency towards a type C behaviour which is most common for soft materials. It seems that the presence of the HWE has modified the type B behaviour of the diluent, $MgCo_3$ somewhat. The 7.5% formulation seems to have had the most plastic deformation.

The ranking order for yield point of the different formulations $5 > 2.5 > 7.5$ (Table 5.1.2) tends to support the earlier assertion that the 7.5% formulation with the lowest yield point resembled a Type A behaviour which is usually obtained from averagely hard, materials with low yield points which would allow for plastic deformation which is a more efficient compaction mechanism than fragmentation. The order was similar to that for particle size with the smallest particles having the highest yield point.

The ranking order for A and D_A, $2.5 > 5 > 7.5$ (Table 5.1.2) followed the same order as that for binder concentration and was quite similar to that obtained for average particle size with the largest particles having the least value (Table 4.1.2). The D_o ranking order was also related to the particle size, with the granulate having lower particle size forming the densest powder column. The ranking order for D_B was $7.5 > 2.5 = 5$.

The Heckel plots for formulations with different concentrations of sodium alginate as binder basically had 2 portions. The formulations containing 2.5 and 5% binder were identical and seem to have been compacted mainly by plastic deformation with very little

Fig. 5.1.5



Key

Formulation 41 - 2.5% PVP as binder
42 - 5% PVP as binder
43 - 7.5% PVP as binder

fragmentation of the particles. They both had a rise between the last two pressure settings.

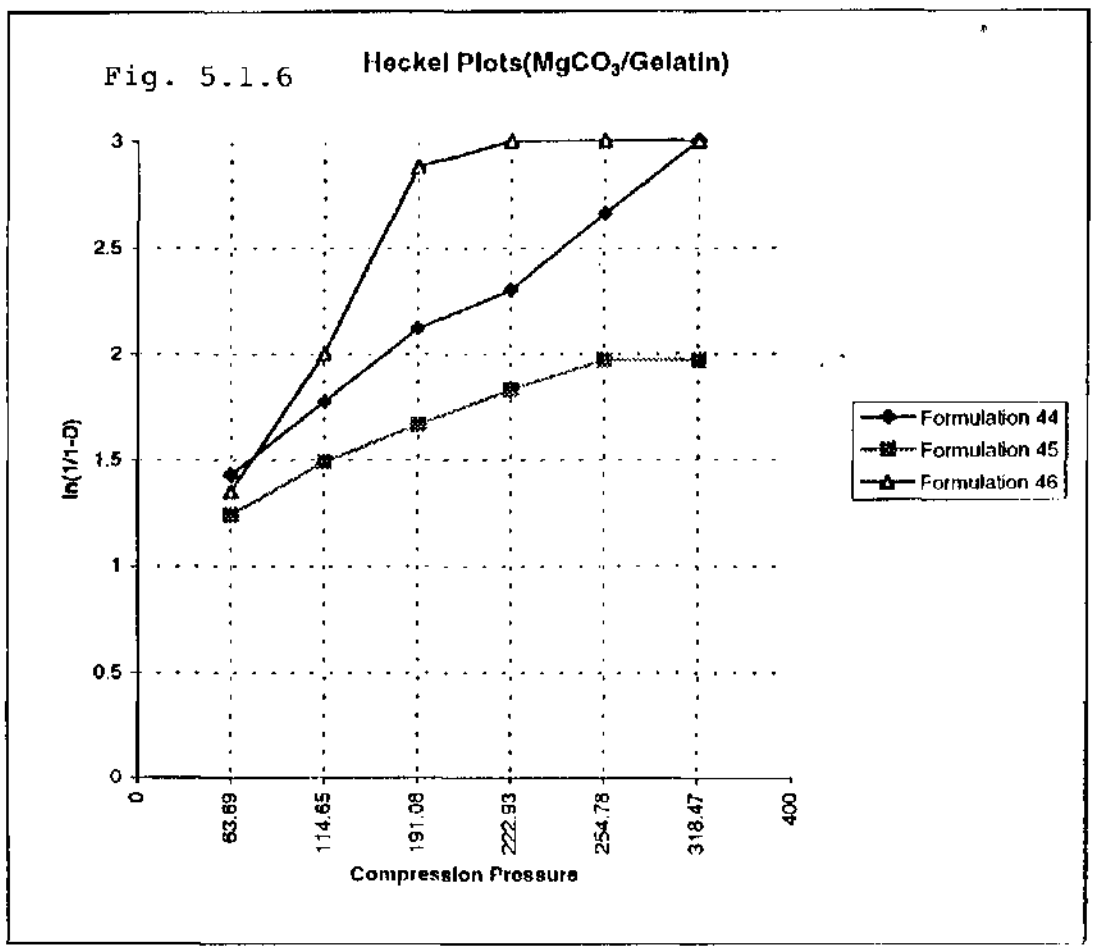
It seems that as the compression pressure was increased in the case of the 7.5% granulate, to 318.47 MNm^{-2}, it was sufficient to result in further plastic deformation, asperity melting or breakdown in particle structure of the material which the pressures between 191.08 and 254.78MNm^{-2} could not achieve.

A number of parameters which were determined for the various granulates, yield point Yp, A, D_A and D_B had the same ranking order (Table 5.1.2) (7.5>5>2.5) while for D_o it was 5=2.5>7.5. The yield point ranking showed that the larger particles had the highest resistance to yield.

A and D_A ranking order (Table 5.1.2) corresponds to that of average particle size, and can thus be explained as earlier done. The particle size could also explain the D_B ranking order since it follows the same order. It can be assumed that larger particles might tend to breakdown most easily during the rearrangement stage thus increasing the extent of densification.

Fig 5.1.6 shows the Heckel plot for formulations with different concentrations of gelatin as binder. The results indicate that the binder concentration affects the plot. Two of the formulations (12.5 and 17.5% granulates) had two portions, with the lines almost completely flattening out at the last 3 pressure settings which tends to indicate that plastic deformation had proceeded to the maximum extent possible and that further consolidation might have been due to asperity melting (Type C). The 7.5% granulate however, after being flat between 191.08 and 222.93 MNM^{2} pressures, rose sharply between 222.93 and 318.47MNm^{-2}. This could have been due to a breakdown of the binder coat around the

Fig. 5.1.6



Key:

Formulation 44 - 75% gelatin as binder
45 - 12.5% gelatin as binder
46 - 17.5% gelatin as binder

particles resulting in further fragmentation and the formation of fresh surfaces from which new bonds are formed and new particles undergoing further plastic deformation (Alderborn *et al*,1988).

The highest yield point was obtained with the 12.5% granulate while 17.5% had the lowest (Table 5.1.2). It seems that the best binder efficiency, resulting in the most number of stable bridge was obtained with the 12.5% concentration of gelatin followed by 7.5 and finally 17.5% which was particularly difficult to mix adequately during granulation.

The ranking order for A, D_A, D_o and D_B was the same - 7.5 > 12.5 > 17.5. In all cases the largest particles had the highest density (Table 5.1.2). This has been explained earlier.

5.3.1.3 Aerosil as Diluent

With PVP solution as binder, the plots had two regions except for the 7.5% granulate that had a slight rise between the last two pressures. Except for this rise, all the lines closely resembled that of Type B material.

The 5% granulate had the highest yield point while the 7.5% had the lowest (Table 5.1.3). The ranking order for A and D_A were virtually the same (2.5 > 7.5 > 5). This is understandable since they are all related as they all describe granulate (particle) movement before the commencement and the initial stages of compression. A high value of D_A points to increased resistance to particle movement. It is therefore not surprising that the 2.5% granulate with the largest average particle size had the highest value of D_A and the others followed in the same order as that for particle size. The 5% granulate had

Table 5.1.3 : Heckel Constants (Aerosil as Diluent)

	Conc(%)	P_y	A	D_A	D_O	D_B
PVP	2.5	100	0.94	0.61	0.39	0.22
	5	250	0.90	0.59	0.34	0.25
	7.5	83.33	0.78	0.54	0.39	0.15
Alginate	2.5	250	0.72	0.51	0.34	0.17
	5	200	1.07	0.66	0.43	0.23
	7.5	142.86	0.94	0.61	0.45	0.16
Gelatin	7.5	166.67	0.75	0.53	0.32	0.21
	12.5	333.33	0.75	0.53	0.31	0.22
	17.5	500	0.55	0.42	0.25	0.17

the lowest value of D_o while the others (2.5 and 7.5%) had the same values (Table 5.1.3).

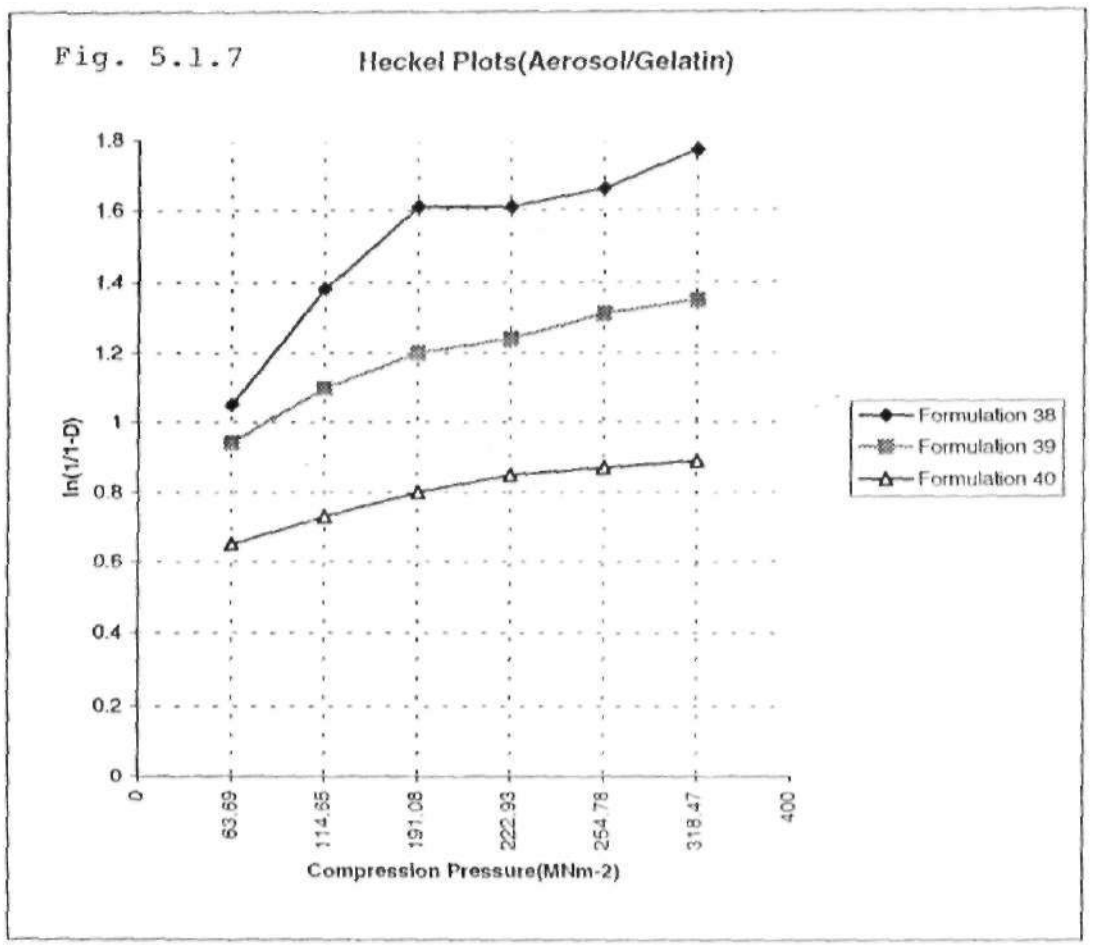
The 5% granulate as expected from its low D_o value had the highest extent of rearrangement (Table 5.1.3). It was also noted that the 5% granulate with an average granule size midway between the others had the highest D_B value, indicating that the larger sized granulate (2.5%) resisted rearrangement, probably because its large size, reduced the space available, while the excessively small size of the 7.5% granulate (90μm) resulted in cohesive forces resisting the forces of rearrangement.

The plots for formulations with different concentrations of sodium alginate as binder show that the binder concentration affects the plots with the effect being most pronounced between 2.5 and 5%. Two of the lines (2.5 and 7.5%) had two regions, with 2 slopes while the third, 5%, although having 2 regions had a sudden increase between the last 2 pressures. Similar explanations as had earlier been proferred would apply here. The lines most closely resembled Type B plots.

The ranking order for the P_y value was 2.5 > 5 > 7.5 (Table 5.1.3).

The results indicate that the 5% granulate had the highest resistance to granulate (particle) movement with the 2.5% granulate being the least. The 7.5% granulate also had a relatively dense column as shown by the D_o value. It would therefore seem that the higher the density of the packing (D_o) the lower would be the space available for movement due to rearrangement (A and D_A). The D_B values also had the same ranking order, indicating of course that the denser the packing during die filling, the more would be the extent of densification due to rearrangement, be as very little rearrangement would result in significant densification.

Fig. 5.1.7



Key:

Formulation 38 - 12.5% gelatin as binder
39-12.5% gelatin as binder
40-17.5% gelatin as binder

Fig 5.1.7 shows the Heckel plot for gelatin as binder at different concentration levels. All the lines had 2 regions with 2 slopes indicating a close resemblance to Type B behaviour. As in the other cases, the binder concentration affected the plot.

The relationship between the yield values of the various granulations was same as for their concentrations (Table 5.1.3), with the granulate with the highest binder concentration (17.5%) having the highest yield point. It therefore means that the higher the binder concentration, the higher was the number and strength of the solid bridges formed. It could be as a result of increased thickness of the binder coat.

All the other parameters determined, A, D_A, D_o and D_B, essentially had the same ranking order, 7.5>12.5=17.5 (Table 5.1.3). This is the reverse of the order for the binder concentration and average particle size. As has been earlier stated, it is logical that as the particle size increases the resistance to movement would also increase and thus justify the ranking order for A and D_A. For D_o, the larger the particle the less the density of the packing would be expected to be since larger particles will tend to have larger interparticulate voids. All these other factors taken together would explain the D_B ranking order.

5.4 Effect of Diluent Type

5.4.1 Starch Paste as Binder

Table 5.2.1 shows the comparative effect of the three different types of diluents - lactose, magnesium carbonate and aerosil - used. The results show that the diluent type affects the

Table 5.2.1: Effect of Diluent Type on Heckel Constants (Starch paste as binder)

Binder Conc.w/w	Diluent Type	P_y	A	D_A	D_O	D_B
5%	a	66.67	1.1	0.67	0.51	0.16
	b	125	0.55	0.42	0.28	0.14
	c	-	-	-	-	-
7.5%	a	333.33	1.3	0.73	0.62	0.28
	b	142.86	0.71	0.51	0.23	0.28
	c	-	-	-	-	-
10%	a	166.67	1.1	0.67	0.39	0.10
	b	-	-	-	-	-
	c	-	-	-	-	-

KEY (For Tables 5.2.1 to 5.2.3):
a - Lactose
b - Heavy Magnesium Carbonate
c - Aerosil

compaction behaviour of the granulates. The magnitude of the plots as indicated by their relative positions were affected in all cases but not the shape.

At the 7.5 and 10% w/w binder concentration, both diluents (lactose and $MgCo_3$) gave Type B plots with the lactose granulate having the higher yield point of the two. Armstrong and Haines-Nutt (1970) also found that magnesium carbonate also tends to consolidate by fragmentation thus indicating similarities in the deformation characteristics of lactose and $MgCo_3$. While lactose still gave Type B plot at 10% binder concentration, the $MgCo_3$ plot did not conform to the Heckel equation.

At 5% binder concentration the magnesium carbonate granulates had Type B plot, the lactose granulate had a plot which most closely resembled Type C which is commonly observed for soft materials. The higher yield point of the $MgCo_3$ granulate relative to the lactose granulate (Table 5.2.1) confirms that the latter was softer than the former. It would seem that the addition of HWE changed the characteristics of the lactose particles while the $MgCo_3$ particles were relatively unaffected.

At 5% starch paste concentration level, the lactose granulates had higher A and D_A values than the $MgCo_3$ granulates. This is an indication that this (lactose) granulation had a higher resistance to particle movement. The average particle size of the lactose granulate was higher than that of the $MgCo_3$ granulate (see Tables 4.1.1 and 4.1.2). It is therefore obvious that because of this large size, the lactose granulate particles would tend to resist movement to a larger extent than the $MgCo_3$ granulate particles. The relationship was the same at the 7.5% binder concentration level and a similar explanation would suffice.

At all the starch paste concentration levels used, the density of the powder column formed at the die filling stage as indicated by D_o was higher for the lactose granulate than for the

Table 5.2.2 :Effect of Diluent Type on Heckel Constants (PVP as binder)

Binder Conc.w/w	Diluent Type	P_y	A	D_A	D_B	D_B
2.5%	a	250	1.17	0.69	0.42	0.27
	b	166.67	1.03	0.64	0.29	0.35
	c	100	0.94	0.61	0.39	0.22
5.0%	a	250	1.11	0.67	0.33	0.34
	b	200	1	0.63	0.32	0.32
	c	250	0.90	0.59	0.34	0.25
7.5%	a	333	1.22	0.71	0.34	0.37
	b	111.11	1.12	0.67	0.29	0.38
	c	83.33	0.78	0.54	0.39	0.15

$MgCo_3$ granulate. This might also have caused the higher resistance of the lactose granulate to rearrangement since the high density of packing would tend to leave very little room for this.

The densification due to rearrangement (D_B) was highest with the $MgCO_3$ granulate than for the lactose granulate. This could have resulted from the availability of more room as a result of the low D_0 and D_A values, thus allowing for more rearrangement to occur at this stage.

5.4.2 PVP as binder

Table 5.2.2 shows the effect of diluent type at different (2.5, 5, 7.5%) concentration levels of PVP as binder. The diluent type quantitatively affected the compaction characteristics of the materials. At all three binder concentrations, the three diluents - lactose, aerosil and magnesium carbonate - gave plots similar to Type B behaviour although, at 7.5% concentration, the magnesium carbonate granulate tended towards Type A.

From the values of the yield points, it seems that all the three diluents produced hard brittle materials with relatively high yield points. Lactose consistently had the highest value (at all concentration levels) with the aerosil granulate having the lowest at 2.5 and 7.5% PVP concentrations, while the $MgCo_3$ granulation had the lowest at the 5% concentration level.

At 2.5, 5 and 7.5 % concentrations (Tables 5.2.2), the lactose granulate had the highest resistance to particle movement both at the die filling stage (D_A) and initial stages of

compression (A) while the aerosil granulate had the lowest. The $MgCo_3$ granulation, which had the lowest particle size, would have been expected to offer the least resistance to rearrangement, however, it seems that the particle size (85μm) is low enough to allow for some interparticulate forces to be strong enough to prevent easy movement of particles thus resulting in higher than expected A and D_A values.

At 2.5% concentrations, $MgCo_3$ granulates had the least dense column (low D_o). It would have been expected, based strictly on the particle sizes of the granulates, that the $MgCo_3$ with the smallest size would provide the most dense column. However, its extremely small size might have brought some other forces into play that would discourage the particles from easily rolling over each other and packing closely.

With respect to D_B values, $MgCo_3$ granulates had the lowest value. At the 2.5 and 5% concentration levels, the aerosil granulate , with the smallest average particle size had the least rearrangement as shown by the D_B values. This is understandable as smaller particles would be expected to rearrange to a larger extent than the larger ones.

5.4.3 Sodium Alginate as Binder

Table 5.2.3 shows that the diluent type affected the compaction characteristics of the HWE using these different concentration levels of alginate as binder. The plots also indicate that all the granulates with the different diluents had Type B behaviour at the binder concentration levels used.

For the 2.5% alginate concentrations (Table 5.2.3), the lactose granulate had the highest yield point while the magnesium carbonate granulate had the lowest with the aerosil

Table 5.2.3 :Effect of Diluent Type on Heckel Constants (Alginate as binder)

Binder Conc.w/w	Diluent Type	P_y	A	D_A	D_O	D_B
2.5%	a	333	1.34	0.74	0.38	0.36
	b	125	1.22	0.71	0.27	0.44
	c	250	0.72	0.51	0.34	0.17
5.0%	a	166.67	0.77	0.54	0.52	0.02
	b	166.67	1.14	0.68	0.27	0.41
	c	142.86	0.94	0.61	0.45	0.16
7.5%	a	250	1.16	0.69	0.33	0.36
	b	125	1.22	0.71	0.26	0.45
	c	142.86	0.94	0.61	0.45	0.16

granulate in-between. The lactose granulate had the highest values of A, followed by the magnesium carbonate and aerosil granulates respectively. The order was the same for D_A indicating that the lactose granulate offered the highest resistance to particle movement. For D_o, the lactose granulate had the most dense column due to die filling, with the $MgCo_3$ granulate having the least. The observation that lactose granulate had better packing than the aerosil granulate is consistent with the earlier relationship explained based on their particle sizes, since lactose had a smaller size than aerosil. $MgCo_3$ granulate with the smaller particles would have been expected to have the densest packing, but it does seem that the particles were so small (130μm) that the forces of cohesion might have interferred with this. The densification due to rearrangement (D_B) was highest with the magnesium carbonate granulate and lowest for the aerosil granulate.

With 10% alginate concentration as binder, the lactose granulate had the highest yield point while the $MgCo_3$ granulate had the lowest. It would therefore be expected that the lactose granulate will produce the hardest tablets at the same compression pressure. The ranking order for A and D_A was $MgCo_3$ > lactose > aerosil in both cases (5 and 7.5% binder conc.) indicating high resistance of the aerosil granulate to particle movement.

For D_o, the ranking order was $MgCO_3$ > aerosil > lactose and aerosil > $MgCO_3$ > lactose for 5 and 7.5% binder concentration granulates respectively. This was also same for D_B with respect to 5% granulate, which is logical as densification will be expected to be higher for the granulate with the most dense packing. However in the case of the 7.5% granulate the order for D_B ($MgCO_3$ > lactose > Aerosil) was same as for particle size with the largest particles having the highest amount of densification due to rearrangement.

5.4.4 Gelatin as binder

The compaction behaviour of the granules were affected by the diluent type (Table 5.2.4). The plots were similar and most closely resembled that of Type B materials. However, the 12.5 and 17.5% gelatin granulates ($MgCo_3$ as diluent) had plots that tended to indicate Type C behaviour, this was also the case with 12.5% gelatin (lactose as diluent).

It was found that $MgCo_3$ granulates had the lowest yield points at all the binder concentration levels.

The ranking order for A and D_A was same for the 7.5 and 17.5% gelatin concentrations, with the lactose granulate having the highest value and the aerosil granulate having the lowest.

In the case of the 12.5% preparations, however, the $MgCo_3$ granulate had the highest values of A and D_A, while the aerosil granulate had the lowest.The average particle size of the granulate which was the highest would explain its having the highest resistance to particle movement.At 7.5%, for D_0 and D_B, the ranking order was Aerosil > lactose > $MgCo_3$ and Aerosil > $MgCo_3$ > lactose respectively.

The D_0 ranking order for 12.5% binder concentration granulates, was $MgCo_3$ = aerosil > lactose and $MgCo_3$ > lactose > aerosil for D_B. The order was lactose > $MgCO_3$ > aerosil for D_0 and the reverse D_B at 17.5% binder concentration. As stated earlier, the better the die fill (D_0) the higher the densification due to rearrangement.

Table 5.2.4 :Effect of Diluent Type on Heckel Constants (Gelatin as binder)

Binder Conc.w/w	Diluent Type	P_y	A	D_A	D_0	D_B
7.5%	a	142.86	1.15	0.68	0.38	0.30
	b	142.86	1.08	0.66	0.32	0.34
	c	166.67	0.75	0.53	0.32	0.21
12.5%	a	333.33	0.86	0.58	0.30	0.28
	b	200	0.97	0.62	0.31	0.31
	c	333.33	0.75	0.53	0.31	0.22
17.5%	a	250	0.94	0.61	0.58	0.03
	b	83.33	0.68	0.49	0.33	0.16
	c	500	0.55	0.42	0.25	0.17

5.5 Effect of Binder Type

With the granulations using lactose as diluent, the plots all basically had two sections (Figs 5.2.1-5.2.3). At all three binder concentration levels used, the plot for granulation with starch paste as binder was higher than all the others while the other three were relatively the same. The difference between the starch plot and the others reduced with increase in binder concentration, which seems to be due to a decrease in the ln(1/1-D) values for the starch plots. This relationship is seen in the fact that starch granulates had the lowest yield point at all the concentration levels used indicating that it was the softest of the granulates. Apart from the high binder concentration levels where its A and D_A values were only less than that of the PVP granulate, the starch granulates had the highest resistance to densification due to rearrangement.

When magnesium carbonate was used as diluent, the starch plots were the lowest in magnitude at all 3 binder concentration levels. It also had the highest yield point, with the alginate formulation having the lowest at the low and medium concentrations while the PVP formulation had the least at the high concentration.

At the medium binder concentration, the PVP plot was clearly distinct from the others which were virtually the same. Their fragmentation behaviour(as seen from the initial part of the curve) was also virtually same with a complete overlap. At the low binder concentration levels, the PVP granulate had the highest resistance to particle movement, had the most dense packing and the highest value of D_B. In all of these, it was followed by the gelatin granulate, with the starch granulate having the lowest values. The interesting thing to note here was that all the parameters had the same ranking order. The results for the other binder concentration levels are as shown. The fragmentation behaviour of the different granulates seem to be quite similar especially PVP, gelatin and

Fig. 5.2.1. Effect of Binder Type (Low Conc.) on Heckel Plots

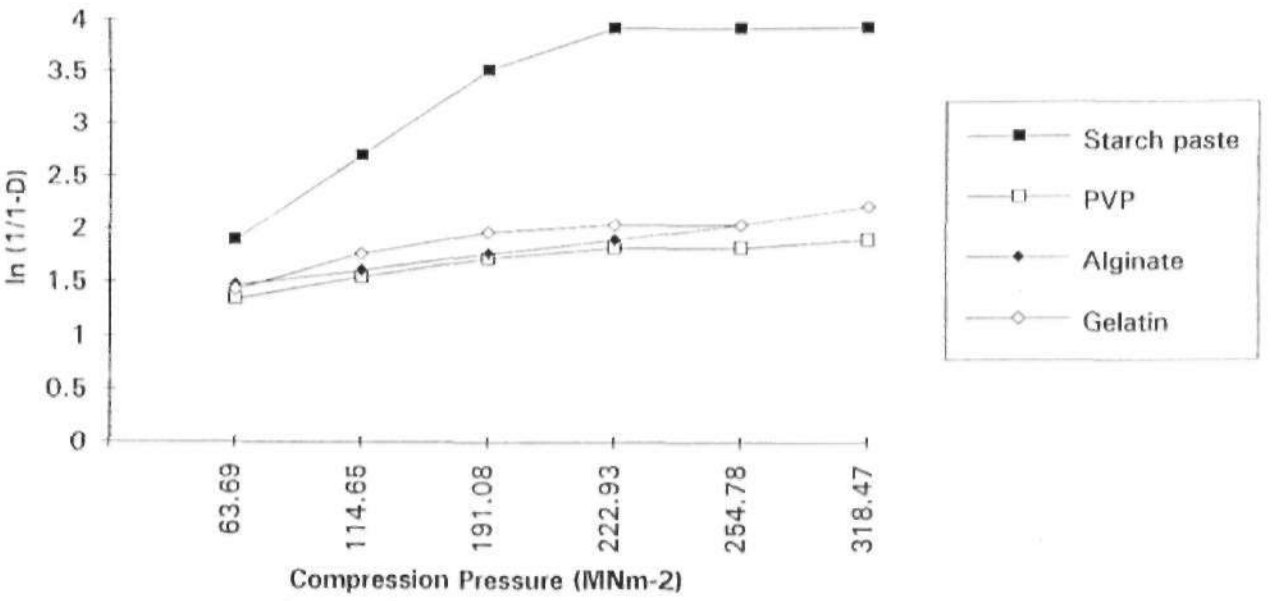


Fig. 5.2.2. Effect of Binder Type (Medium Conc.; Lactose as Diluent) on Heckel Plots

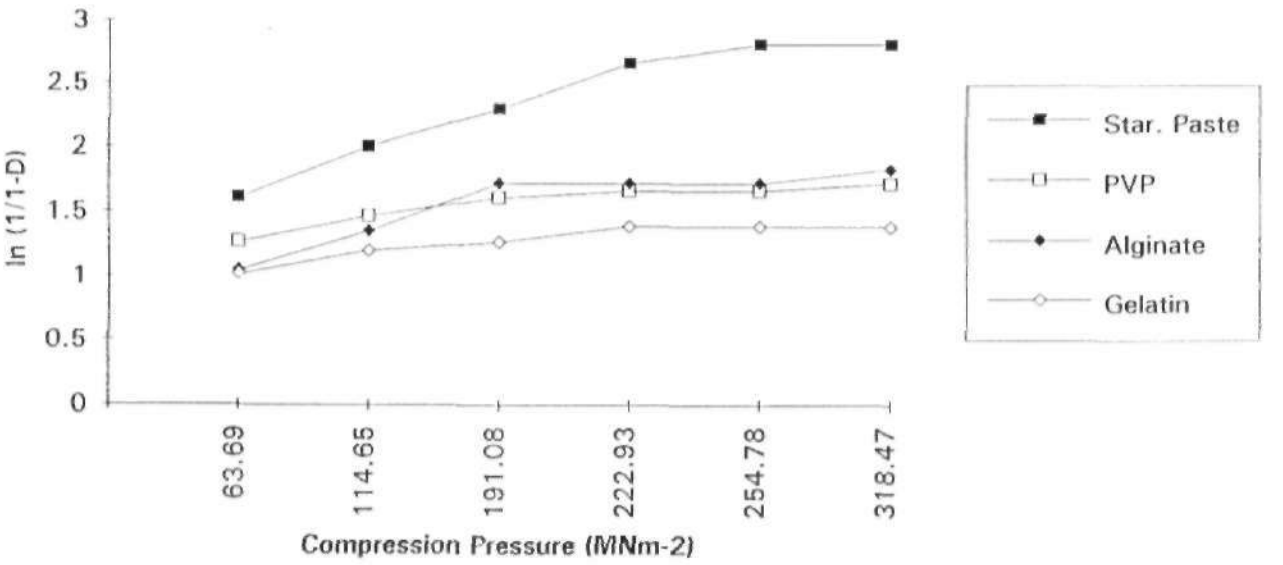
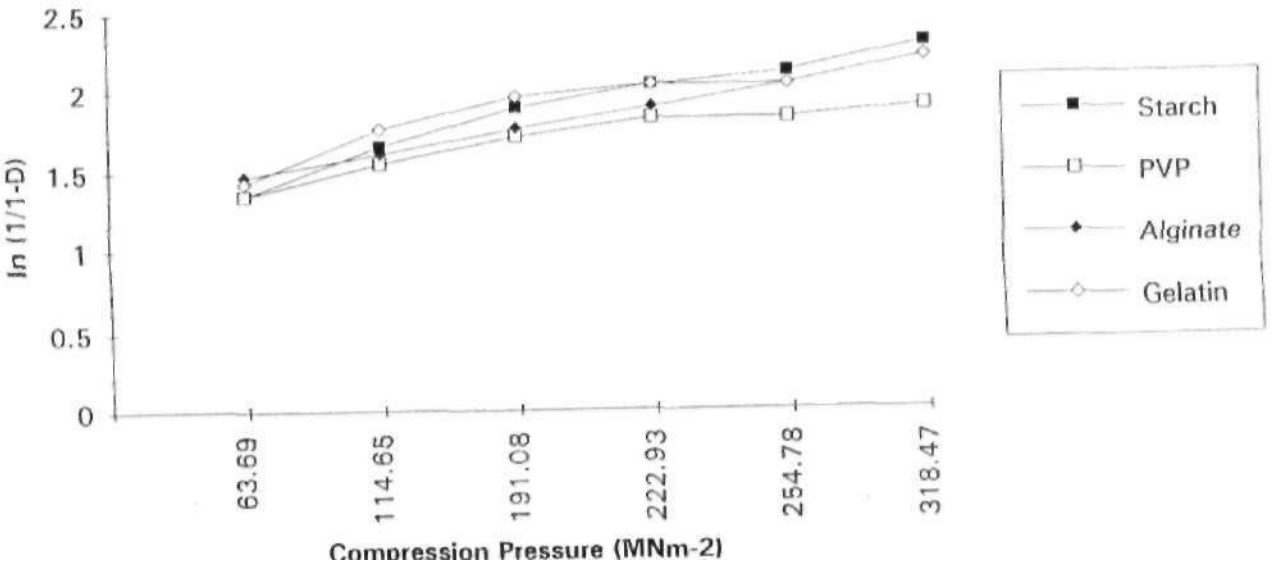


Fig. 5.2.3. Effect of Binder Type (High Conc.; Lactose as Diluent) on Heckel Plots



alginate.

With aerosil as diluent, the shape of the plots was not significantly affected by the binder type. However, at the low binder concentration level, the granulate with PVP as binder was distinctly different from the other, being higher. This is reflected in the fact that the other parameters, where PVP granulate had the lowest yield point, highest resistance to densification due to rearrangement, probably because it had the powder column with the highest density at the die filling stage resulting in less space for rearrangement.

At the high binder concentration, the plot for the gelatin granulate was found to be quite lower than the others which were similar to each other. This showed in its having the highest yield point, least resistance to rearrangement, probably due to the low density of its column.

5.6 CONCLUSION

All the formulations, except that with 10%w/w starch paste as binder and magnesium carbonate as diluent, produced granules with compaction characteristics that could be explained with the Heckel equation.

Most of the formulations exhibited Type B behaviour, i.e initial fragmentation and then rearrangement before plastic deformation. A few formulations (5% starch paste/lactose and 12.5% and 17.5% gelatin/magnesium carbonate) however changed the compaction behaviour of lactose and magnesium carbonate to Type C - like behaviour.
From the Heckel values determined from the plots - P_y, A, D_A, D_O and D_B - it was possible to determine that both the type and concentration of binder used affected the compaction behaviour. The type of diluent used also affected these values. It was possible to use the average granule size to explain some of the relationships that were observed.

CHAPTER SIX

EFFECT OF SURFACTANT TREATMENT ON GRANULE AND TABLET PROPERTIES

6.1 INTRODUCTION

Because of their wetting effect and consequent ability to improve water penetration into solid particles, surfactants have been widely studied as pharmaceutical additives in solid dosage forms to improve the disintegration and dissolution characteristics of such formulations.

In the study of the effect of binder concentration and type on tablet properties, some of the tablets formulated with lactose as diluent had disintegration time slightly longer than the BP (1993) limit of 15 minutes. The aim of this section was to consider the suitabilty of two surfactants - sodium lauryl sulphate, SLS (anionic surfactant) and Tween 80 (non ionic surfactant) at two concentration levels with respect to reducing the tablet disintegration time. Its effect on other tablet properties were also considered.

Since some studies such as those by Heng and Wan (1987), have shown that the inclusion of surfactants in tablet formulations would affect granule properties, the effect of these surfactants on HWE granule properties were also investigated.

Table 6.1.1: Tablet Composition (15% starch as disintegrant; 0.2% magnesium stearate as lubricant)

IIWE	250	250	250	250	150	150	150	150	350	350	350
Lactose	375	375	375	375	-	-	-	-	-	-	-
$MgCo_3$	-	-	-	-	450	450	450	450	-	-	-
Aerosil	-	-	-	-	-	-	-	-	210	210	210
Binder	(i)	(ii)	(iii)	(iv)	(i)	(ii)	(iii)	(iv)	(ii)	(iii)	(iv)

Key:

(i) 7.5% starch paste *(iii) 5% Na alginate*

(ii) 5% PVP *(iv) 7.5% gelatin*

Table 6.1.2 7.5% Starch paste as binder, 15% starch as disintegrant; 0.2% magnesium stearate as lubricant

	I	II	II	II	V	VI	VII	VIII
IIWE	250mg	250	250	250	150	150	150	150
Lactose	375mg	375	375	375				
$MgCo_3$	-	-	-	-	450	450	450	450
SLS	0.2%	0.4%	-	-	0.2%	0.4%	-	-
T80	-	-	0.2%	0.4%	-	-	0.2%	0.4%

Table 6.1.3: 5% PVP as binder; 15% starch as disintegrant; 0.2% magnesium stearate as lubricant

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
HWE	250	250	250	250	150	150	150	150	350	350	350	350
Lactose	375	375	375	375	-	-	-	-	-	-	-	-
$MgCo_3$	-	-	-	-	450	450	450	450	-	-	-	-
Aerosil	-	-	-	-	-	-	-	-	210	210	210	210
SLS	0.2%	0.4%	-	-	0.2%	0.4%	-	-	0.2%	0.4%	-	-
T80	-	-	0.2%	0.4%	-	-	0.2%	0.4%	-	-	0.2%	0.4%

Table 6.1.4: 5% alginate as binder; 15% starch as disintegrant; 0.2% magnesium stearate as lubricant

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
HWE	250	250	250	250	150	150	150	150	350	350	350	350
Lactose	375	375	375	375	-	-	-	-	-	-	-	-
$MgCo_3$	-	-	-	-	450	450	450	450	-	-	-	-
Aerosil	-	-	-	-	-	-	-	-	210	210	210	210
SLS	0.2%	0.4%	-	-	0.2%	0.4%	-	-	0.2%	0.4%	-	-
T80	-	-	0.2%	0.4%	-	-	0.2%	0.4%	-	-	0.2%	0.4%

Table 6.1.5: 7.5% gelatin as binder; 15% starch as disintegrant; 0.2% magnesium stearate as lubricant

HWE	250	250	250	250	150	150	150	150	350	350	350	350
Lactose	375	375	-	-	-	-	-	-	-	-	-	-
$MgCo_3$	-	-	-	-	450	450	450	450	-	-	-	-
Aerosil	-	-	-	-	-	-	-	-	210	210	210	210
SLS	0.2%	0.4%	-	-	0.2%	0.4%	-	-	0.2%	0.4%	-	-
T80	-	-	0.2%	0.4%	-	-	0.2%	0.4%	-	-	0.2%	0.4%

6.2 **MATERIALS AND METHODS**

6.2.1 **Materials**

Hot water extract (HWE) was prepared as earlier outlined in Section 2.1.2.

Lactose B.P., Aerosil , Maize Starch B.P. (received as donations from NIPCO Pharmaceuticals, Idu Abuja), Heavy Magnesium carbonate (BDH Chemicals, England), Gelatin B.P.(Fisons Scientific Ltd. England), Sodium alginate, Tween 80 (Koch-Light laboratories, Bucks, England) , Sodium lauryl sulphate, PVP (Merck).

6.2.2 **Methods**

Granulation and Compression of Granules:

This was same as earlier described except that, the amounts of each surfactant required to achieve a final concentration in the granulation specified in the formula was added to disintegrant.They were then mixed thoroughly in a tumble mixer.

6.3 **RESULTS AND DISCUSSION**

6.3.1 **Granule Properties**

6.3.1.1 Lactose as diluent

Moisture content was generally increased by surfactant treatment (Tables 6.1.1 - 6.1.4) with the extent depending on the surfacant type and the concentration used. The lower concentrations of surfactant had very little effect in most cases, while the higher ones to

Table 6.2.1. Effect of Surfactant Type and Conc. on Granule Properties (binder:starch paste; diluent:Lactose)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow Rate (g/sec.)	Angle of Repose, θ
None	5.5	1.45	1.04	1.25	16.80	6.25	28.23
SLS 0.2%w/w	5.6	1.47	0.66	0.78	15.38	7.50	24.68
0.4%w/w	6.2	1.49	0.57	0.69	17.39	5.00	24.86
T80 0.2%w/w	5.7	1.46	0.63	0.78	19.23	6.25	22.86
0.4%w/w	6.2	1.48	0.78	0.89	12.36	6.25	27.62

Table 6.2.2. Effect of Surfactant Type and Conc. on Granule Properties (binder:PVP; diluent:Lactose)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow Rate (g/sec.)	Angle of Repose, θ
None	6.1	1.45	0.65	0.75	13.30	7.50	25.52
SLS 0.2%w/w	6.9	1.43	0.68	0.81	16.05	6.25	27.32
0.4%w/w	7.0	1.48	0.57	0.69	17.39	5.00	28.56
T80 0.2%w/w	6.6	1.45	0.63	0.78	19.23	6.25	29.01
0.4%w/w	7.2	1.49	0.59	0.72	19.86	6.15	31.77

Table 6.2.3. Effect of Surfactant Type and Conc. on Granule Properties (binder:Gelatin; diluent:Lactose)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow Rate (g/sec.)	Angle of Repose, θ
None	5.4	1.43	0.65	0.79	17.72	7.50	28.07
SLS 0.2%w/w	6.3	1.48	0.64	0.75	17.60	5.60	28.96
0.4%w/w	6.7	1.47	0.60	0.69	13.04	5.00	29.36
Tween 0.2%w/w	7.9	1.49	0.64	0.78	17.95	6.25	29.68
80 0.4%w/w	8.1	1.41	0.63	0.74	14.87	6.25	30.35

Table 6.2.4. Effect of Surfactant Type and Conc. on Granule Properties (binder:Alginate; diluent:Lactose)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow Rate (g/sec.)	Angle of Repose, θ
None	5.5	1.54	0.65	0.81	19.80	6.00	29.51
SLS 0.2%w/w	5.9	1.60	0.83	1.04	20.19	6.08	27.02
0.4%w/w	6.5	1.61	0.81	0.93	12.90	6.17	23.91
Tween 0.2%w/w	5.6	1.57	0.72	0.88	18.18	6.16	24.77
80 0.4%w/w	5.4	1.53	0.83	0.96	13.54	6.25	23.66

some extent increased the moisture content. This increase is probably as a result of the wetting action of the surfactants which would increase both the rate and extent of water penetration into the powder mix. This effect would be expected to increase with increased surfactant concentration. The particle density was unaffected by the addition of surfactant.

The addition of surfactants reduced both the bulk and tapped densities of the granules with all the binders except sodium alginate and the lower concentrations of SLS with PVP as well as the lower cocentration of T80 where the tapped density was increased (Table 6.1.2). These results are similar to the findings of Duchene *et al* (1968) who found that the nonionic surfactants including T80 generally reduced bulk densities of sulphanilamide granules containing starch. Opakunle and Akinpelu (1990) also found general increased porosity (reduced densities) with the addition of surfactant to citric acid granules. Heng and Wan (1987), at very low T80 concentration observed, a decrease in bulk density, which they explained to be due to the likelihood of the surfactant being inadequate to promote significantly particle slippage during the wet massing process although it had eased screening, thus producing granules with lower bulk density. It could also be that the increased moisture content, reduced the ease with which the particles could roll or slip over each other to fill the interparticulate voids. The extent of the reduction depended on the surfactant used and its concentration. For example with starch paste as binder, the extent of reduction increased with increased SLS concentration while with T80 the densities increased (Table 6.1.1).

With sodium alginate as binder (Table 6.1.4), the bulk and tapped densities were increased. Increasing the SLS concentration did not affect the densities, but increased T80 concentration resulted in further increase. Heng and Wan (1987) also observed an increase in density with the presence of T80 which increased with increased concentration as was also obtained in this study. They postulated that it was due to the lubricating effect

of the surfactant on the wet mass which allowed for greater slippage of particles thus forming denser granules due to tighter packing. It was noted that the increase levelled off with higher surfactant content. It could therefore be that the concentrations of SLS used were at that critical level where the effect on bulk density had levelled off, explaining the absence of any effect due to increased SLS concentration.

Percent compressibility was either reduced or unaffected by surfactant treatment in most cases. There were, however, cases where it was increased, as in the case of the formulation with PVP as binder (Table 6.1.2). In the case of starch paste as binder, the effect was inconsistent (Table 6.1.1), it decreased with the addition of 0.2% SLS, increased at 0.4%, while the reverse was the case with T80, with increased concentration resulting in decreased compressibility.

When starch paste and sodium alginate were used as binders (Tables 6.1.1 and 6.1.4), the angle of repose decreased. This would indicate that the addition of surfactants reduced the cohesive and frictional forces between the particles of these granulates. This could have resulted from the formation of a coat around the particles, which would smoothen their surface thus reducing friction. It has been established that decreased angle of repose would occur with the addition of surfactants up to a limit with further increases resulting in increased values because the higher concentrations would impart a degree of tackiness to the granules (Heng and Wan,1987). This would explain the increase observed between 0.2 and 0.4% T80 with starch paste as binder (Table 6.1.1). It would also seem that this effect resulted in the increased angles of repose obtained with PVP and gelatin probably because the amount of moisture present might have exceeded the optimal limit. The increase in the values with increased surfactant concentration with these binders (Tables 6.1.2 and 6.1.3) would tend to support this.

Surfactant treatment in virtually all cases resulted in reduced granule flow rate. Opakunle and Akinpelu (1990) also found that some surfactants resulted in poorer flow rates of lactose granules. Heng and Wan (1987) similarly observed decreased flow rate with the addition of surfactant. This is because increased moisture content resulted in tackiness of the granules thus reducing their ability to roll and slip over each other .

As would be expected from its increased density, the surfactant-treated alginate granulates (Table 6.1.4), had slightly better flow rates than the untreated granulates. Increased surfactant concentration resulted in further, though slight, increases in flow.

6.3.1.2 Magnesium Carbonate (heavy) as diluent

Unlike the observation with lactose granulates, true density was affected by the inclusion of surfactants. While it was increased with gelatin and alginate as binders (Table 6.2.3 and 6.2.4), it decreased with starch paste and PVP (Tables 6.2.1 and 6.2.2).

The effect of surfactants on bulk and tapped densities depended on the binder type used. With starch paste (Table 6.2.1) it increased and increasing the surfactant concentrations resulted in decreased values, probably an indication that lower concentrations are optimal for these parameters while it was relatively unaffected by SLS with PVP as binder (Table 6.2.2). T80 addition resulted in a decrease in bulk and tapped densities with the lower concentration having the most effect in this respect. When gelatin was used as binder, there was a concentration - dependent decrease in the densities with the addition of surfactants, with the SLS granulates being slightly better than the ones with T80. The % compressibility of the granulates were reduced by the addition of surfactants and the extent depended on the surfactant type, indicating that their differences - anionic and

Table 6.3.1. Effect of Surfactant Type and Conc. on Granule Properties (binder:starch paste; diluent:$MgCO_3$)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow rate (g/secs.)	Angle of Repose,θ
None	3.6	2.12	0.49	0.66	25.76	6.00	26.27
SLS 0.2%w/w	5.9	1.83	0.59	0.74	20.27	6.00	28.19
0.4%w/w	5.8	1.84	0.54	0.66	18.18	5.00	31.46
Tween 0.2%w/w	5.7	1.86	0.59	0.70	15.71	5.00	27.81
80 0.4%w/w	5.9	1.87	0.50	0.58	13.79	3.75	29.79

Table 6.3.2 Effect of Surfactant Type and Conc. on Granule Properties (binder:PVP; diluent:$MgCO_3$)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow time (secs.)	Angle of Repose,θ
None	3.6	2.22	0.69	0.83	16.87	4.50	22.41
SLS 0.2%w/w	6.0	1.92	0.63	0.81	22.22	6.00	25.10
0.4%w/w	6.1	1.92	0.69	0.85	18.82	6.00	24.55
Tween 0.2%w/w	5.8	1.83	0.54	0.68	20.59	5.23	25.82
80 0.4%w/w	6.0	1.94	0.64	0.76	16.79	5.00	23.87

Table 6.3.3. Effect of Surfactant Type and Conc. on Granule Properties (binder:Gelatin; diluent:$MgCO_3$)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow rate (g/secs.)	Angle of Repose,θ
None	3.8	1.80	0.63	0.78	19.23	4.00	23.55
SLS 0.2%w/w	5.8	1.86	0.59	0.73	19.18	5.13	28.47
0.4%w/w	5.6	1.85	0.53	0.66	19.70	5.28	24.92
Tween 0.2%w/w	5.3	1.92	0.56	0.69	19.29	6.16	26.88
80 0.4%w/w	5.3	1.87	0.48	0.60	20.00	4.82	25.88

Table 6.3.4. Effect of Surfactant Type and Conc. on Granule Properties (binder:Alginate; diluent:$MgCO_3$)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow rate (g/secs.)	Angle of Repose,θ
None	3.2	1.83	0.50	0.63	20.64	5.00	25.00
SLS 0.2%w/w	6.1	1.92	0.54	0.64	15.63	5.00	26.56
0.4%w/w	6.0	1.91	0.70	0.86	18.61	7.35	24.56
Tween 0.2%w/w	5.9	1.98	0.54	0.66	18.18	5.33	25.32
80 0.4%w/w	6.3	1.96	0.53	0.67	20.60	5.33	19.29

nonionic - would result in differences on their effect on formulations. Where the compressibility was increased (Table 6.2.2), the SLS-treated granulates had higher values than T80.

Except with the formulation containing sodium alginate as binder, the angle of repose increased with surfactant treatment at all concentrations and could have contributed to the decreased flow rate that was observed in most cases (Tables 6.2.1 - 6.2.3). While this effect increased with increase in surfactant concentration with starch paste as binder, the reverse was true for the other binders used. In the case of alginate as binder (Table 6.2.4), the lower surfactant concentrations increased the angle of repose while the higher ones reduced it. It would seem that the lower concentrations were insufficient to completely cover the particles thus they were unable to reduce interparticulate friction.

6.3.1.3 Aerosil as diluent

Mositure content was relatively unaffected by the addition of surfactant except with alginate (Table 6.3.1) where it was increased. While SLS reduced the particle density, T80 increased it (Tables 6.3.1 - 6.3.3) indicating that the nonionic T80 was able to bring the particles within the granule closer than the anionic SLS. This effect was virtually unaffected by surfactant concentration.

The addition of T80 had a greater effect on increasing the bulk and tapped densities when compared to SLS (Tables 6.3.1 and 6.3.3). Coupled with the particle density, it would seem that the electrostatic properties of the powder mix is such as encourages the better penetration of the nonionic surfactant preferentially to the anionic one when aerosil is present as the diluent.

Table 6.4.1. Effect of Surfactant Type and Conc. on Granule Properties (binder:Alginate; diluent:Aerosil)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow time (secs.)	Angle of Repose, θ
None	4.4	1.81	0.77	1.00	23	3	18.98
SLS 0.2%w/w	5.1	1.75	0.66	0.78	15.39	4	22.3
0.4%w/w	5.2	1.72	0.68	0.86	20.93	4	26.56
Tween 0.2%w/w	5.7	2.38	0.8	0.93	13.98	4	22.06
80 0.4%w/w	5.4	2.36	0.82	0.91	9.89	4	21.52

Table 6.4.2. Effect of Surfactant Type and Conc. on Granule Properties (binder:PVP;diluent:Aerosil)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density g/ml	Tapped density g/ml	%Compressibility	Flow time (secs.)	Angle of Repose, θ
None	6.3	1.92	0.66	0.75	12.00	4	22.87
SLS 0.2%w/w	6.7	1.68	0.63	0.73	13.70	4	25.52
0.4%w/w	6.4	1.80	0.63	0.78	19.23	4	26.86
Tween 0.2%w/w	6.1	1.93	0.61	0.76	19.74	4	25.69
80 0.4%w/w	6.3	1.96	0.65	0.78	16.67	4	26.56

Table 6.4.3. Effect of Surfactant Type and Conc. on Granule Properties (binder:Gelatin;diluent:Aerosil)

Surfactant Type & Conc.	Moisture Content %	True density	Bulk density (g/ml)	Tapped density (g/ml)	%Compressibility	Flow time (secs.)	Angle of Repose, θ
None	6.3	1.97	0.61	0.73	16.4	4	25.23
SLS 0.2%w/w	6.7	1.85	0.70	0.83	15.66	4	26.56
0.4%w/w	6.7	1.82	0.67	0.83	19.28	4	25.06
Tween 0.2%w/w	6.9	1.91	0.73	0.87	16.09	4	25.06
80 0.4%w/w	6.7	1.87	0.63	0.77	18.18	4	27.15

The lower concentrations of the two surfactants decreased compressibility with alginate and gelatin as binders, while the higher ones increased it (Tables 6.3.1 and 6.3.3). In the case of PVP as binder, it was increased, indicating that the addition of the surfactants would result in the formation of more archs and bridges within the powder bed. The angle of repose was relatively unaffected by surfactant treatment when gelatin was used as binder except at the high (0.4%) T80 concentration where it was increased (Table 6.3.3).

The relative lack of effect of surfactant treatment on granule flow (Tables 6.3.1 - 6.3.3) could be as a result of the large surface area of acrosil and its inherent lubricant activity which would tend to balance out the effect of the surfactants.

6.3.2 **Tablet Properties**

6.3.2.1 Lactose as diluent

Surfactant treatment reduced the tablet hardness and increased the friability, thus reducing the physical strength of the tablets irrespective of the binder type used (Fig 6.1.1). Similar observations have been made by Nasipuri and Omotosho (1985) in their work with SLS and polysorbate 80 treatment of sulphadiazine tablets. Schott *et al* (1982) also found a decrease in tablet hardness with octoxynol (a surfactant) treatment of prednisolone. Wan and Heng (1986) similarly found that surfactant treatment reduced tablet hardness.

It is possible that the presence of surfactants in the formulation reduced the strength of the interparticulate bonds by increasing their wetness beyond levels required for the

formulation of strong bonds. The addition of surfactant - treated starch as exodisintegrant might also have increased this effect. It is also possible that the wetting (softening) effect of the surfactants would reduce the degree of fragmentation (which is a major step in compact formation for this granulate) since dry brittle materials will tend to fragment more easily and to a larger extent than soft ones. The presence of excess moisture on the granule surface which would be encouraged by the presence of surfactant would also tend to discourage bond formation by 'sandwiching' the drug particles, thus reducing the interparticulate attraction. A similar explanation would explain the friability values. Only 0.2% SLS with starch paste, alginate and gelatin as binders had tablets of satisfactory hardness. All the surfactant treated granules with starch paste as binder had unacceptably high friability. In terms of tablet physical strength the relative relationship between the surfactants depended on the binder and surfactant concentration (Figs. 6.1.1 and 6.1.2).

With PVP as binder, only the 0.2% T80-treated granulates produced tablets with good friability and fairly good hardness, all the others had very high friabilities. There was no difference in the effect of the two different surfactants on tablet hardness using alginate as binder with all the tablets having high friability although the 0.2% T80-treated granulate tablets had a fairly good value. Of all the treated granulates with gelatin as binder only the 0.2%SLS had satisfactory hardness, although it still had poor friability like all the others.

Surfactant - treatment resulted in reduced tablet disintegration time at all concentrations with starch paste and PVP as binder (Fig 6.1.3), the extent, however depended on the particular surfactant and the concentration used.

This observation agrees with that of Wan and Heng (1986) who observed that the

Fig. 6.1.3. Effect of Surfactant Type and Conc. on Disintegration Time(Lactose as diluent)

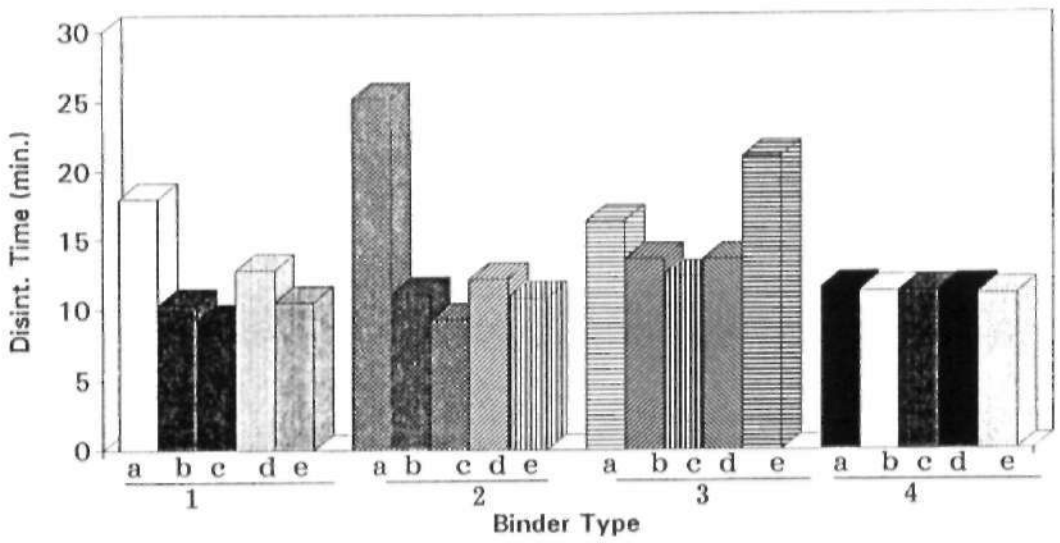
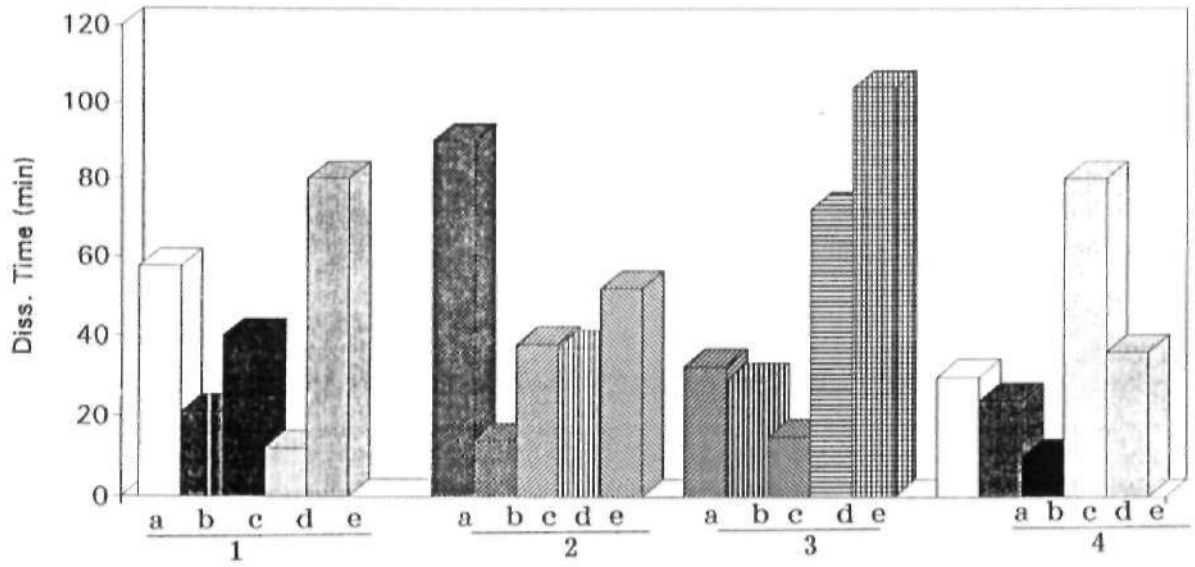


Fig. 6.1.4. Effect of Surfactant Type and Conc. on Dissolution Time, T75% (Lactose as Diluent)



key

1- Starch paste as binder
2 - PVP "" "
3 - Na alginate " "
4 - Gelatin

a - 0 Surfactant
b - 00.2% SLS
c - 0.4% SLS
d - 0.2% T80
e - 0.2% T80

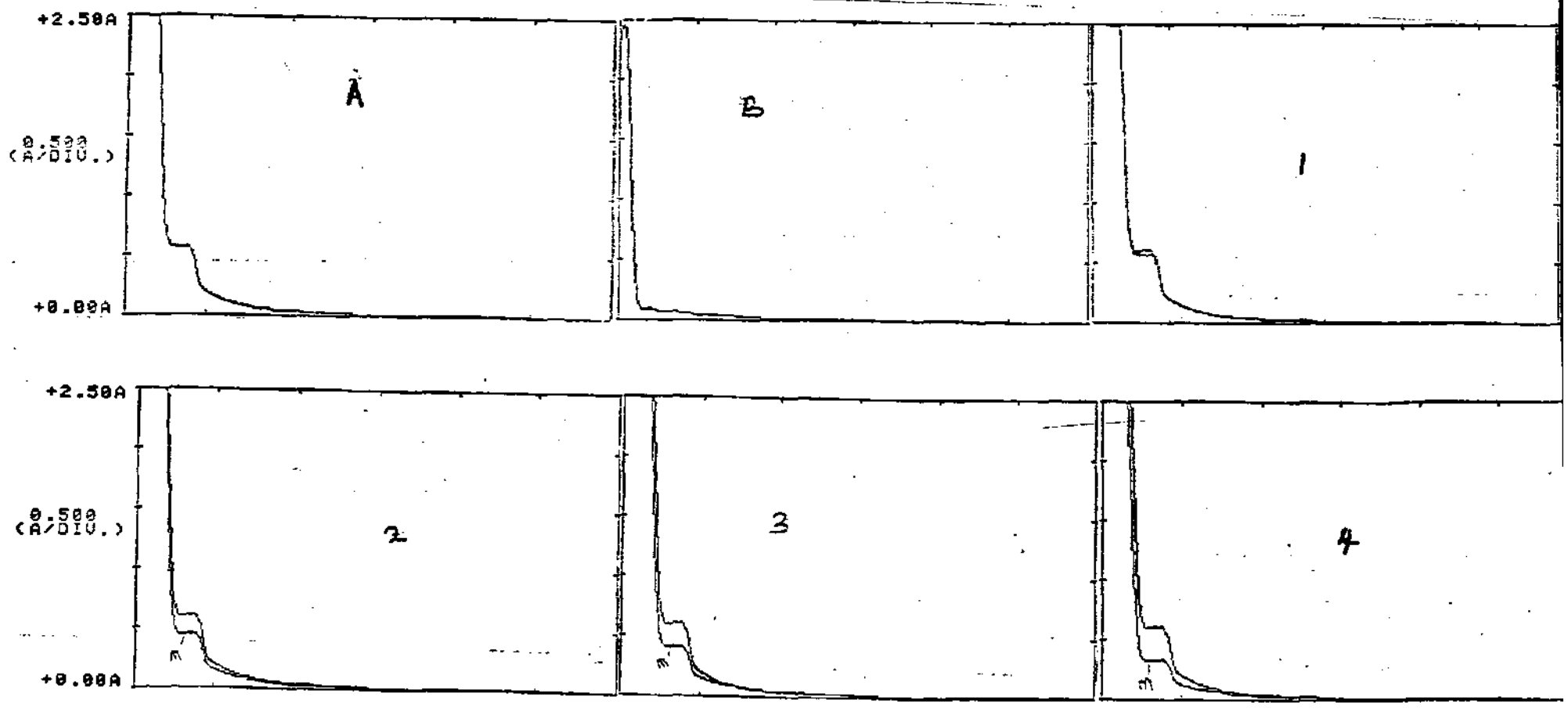
inclusion of T80 and SLS in sulphanilamide tablets helped to improve tablet disintegration. Esezobo (1984) also found that the disintegration and dissolution rates of paracetamol tablets increased with the increase in surfactant concentration. They proposed that this was probably due to the surface activity of the surfactant rendering the tablet mass more easily wetted by lowering interfacial tension. The reduced tablet physical strength might also be an additional factor in this respect. Nasipuri and Omotosho (1985) have also stated that treatment with surfactant reduced disintegration time. Increasing the concentration of the surfactants resulted in further decrease in the tablet disintegration time, the change was however slight in both cases.

The effect of surfactant treatment on reduction of disintegration time was slight with alginate as binder. At the 0.2% surfactant concentration level, both surfactants produced tablets with similar disintegration times. Increasing the SLS concentration reduced the disintegration time slightly.

Treatment with 0.4% T80 increased the disintegration time. Wan and Heng (1986) explained a similar observation as being due to the ability of the surfactant to reduce surface tension and increase the viscosity of the disintegration medium, which would reduce liquid penetration according to the Washburn equation resulting in possible retardation of the tablet disintegration process. They also postulated that the dissolved surfactant may also act on the disintegrant altering its properties, like in the case of starch, restricting the grain swelling.

Fig. 6.1.3 shows that the inclusion of surfactants in the formulation with gelatin as binder did not affect the disintegration time of the tablets inspite of the reduced hardness. In addition to the reasons earlier given, it could also be that there was some form of physical

Fig. 6.1.5 Effect of addition of SLS to the spectra of gelatin solution



Key

A - Gelatin solution (5mg/ml
B- SLS solution (4mg/ml)

1. 0.1ml + 1ml (SLS + Gelatin)
2. 0.3ml + 1ml (" ")
3. 0.6ml + 1ml (" ")
4. 1.0 + 1ml (" ")

interaction between gelatin and the surfactants when wetted by the disintegration medium thus 'inactivating' the liquid penetration - enhancing activity of the surfactant. Below its isoelectric point of pH 4.7, gelatin is positively charged. One of the surfactants used, SLS, being anionic, could therefore form a coacervate with the binder. Further investigations confirmed that the presence of SLS affected (reduced) the spectrum of gelatin in a concentration dependent manner (Fig. 6.1.5). Coacervation could also have resulted from the presence of a macromolecular substance like starch, which might explain the observed result with the non ionic surfactant T80.

With all the binders used, treatment with SLS resulted in decreased dissolution times for the tablets (Fig. 6.1.4). This agrees with the results of other workers (Nasipuri and Omotosho, 1987; Wen and Heng, 1986 and Eszobo, 1985) who also observed increased dissolution rates with surfactant treatment. This accords with the effect of the surfactants on the tablet disintegration time which is because the drug dissolves mainly from granular particles obtained by disintegration thus increasing the surface area. It seems the effect of the surfactant is also achieved by producing a very fine dispersion of disintegrated particles, thus increasing the surface area available from which dissolution will occur. Increasing the SLS concentration resulted in increased dissolution time when starch and PVP were used as binder, although this change was slight. This was inspite of the reduction observed in disintegration time with increased surfactant concentration. It would therefore seem that while the faster disintegration time could have a positive effect on dissolution time, this could be limited. A reason for this observation could be because dissolution could also take place from the intact tablet and agglomerates thus reducing the strength of the relationship between disintegration and dissolution rates. Also the factors earlier proferred to explain delayed disintegration of tablets such as increased medium viscosity which would increase with increased surfactant concentration, could contribute to the observed results. Micellar complex formation has also been proposed as a possible

cause of decreased drug dissolution (Miyamoto *et al*, 1983). Any or all of these could have contributed to the results obtained.

Treatment with T80 had different effects depending on the concentration of surfactant and the binder type used (Fig.6.1.4). The higher concentrations, (0.4%), retarded tablet dissolution with all the binders used relative to the untreated tablets. Goldberg (1974) is of the opinion that surfactants are only effective at low concentrations in improving drug dissolution. At the lower concentration (0.2%). with starch paste and PVP as binders, the dissoltuion rate increased significantly relative to tablets from untreated granules. However with alginate and gelatin, as binders, the dissolution time virtually doubled, which can be because these binders interacted with this nonionic surfactant in a way that prevented it from wetting the tablet adequately enough to increase the dissolution rate.

In virtually all the formulations tested, the SLS-treated granules produced tablets with the best dissolution profiles when compared to the T80 treated tablets. Differences in the relative behaviour of surfactants have also been obtained by other workers. Kurosaki *et al* (1989) observed decreased absorption of salicylic acid with T80 while the reverse was the case with the ionic surfactant, SLS. They explained that this was due to intermolecular electrosstatic interaction with the T80 which resulted in reduced thermodynamic avtivity of the drug, thus reducing absorption. Nogami *et al* (1963) also found that the charges on the drug particles will affect the rate and extent of water penetration with the opposite charges tending to reduce penetration. Nasipuri and Omotosho (1987) found that T80-treated granules produced tablets with better dissolution properties than those treated with SLS. Polysorbate 80 is a nonionic surfactant with a higher water solubility than the anionic SLS. Since these workers used an insoluble drug - sulphadiazine in their study, it would be understable that improved water solubility would be important and might have resulted in their observation. In the case of HWE

with a good water solubility coupled with high solubilty of lactose, this advantage of T80 over SLS would become unimportant, thus explaining our results.

6.3.2.2 Heavy Magnesium Carbonate as diluent

Treatment with SLS did not significantly affect the tablet hardness at the two surfactant concentrations used irrespective of binder type, although slight increases were observed at the lower concentrations with all the binders except starch paste (Fig. 6.2.1). Increasing the surfactant concentration resulted in a slight decrease in tablet hardness except with starch paste as binder where there was no change. This is inspite of the increased granule moisture content observed with the addition of SLS which would have been expected to result in harder tablets. It would seem that the use of an insoluble diluent, magnesium carbonate, could have reduced the effect of the high moisture content by absorbing it without much physical change.

The use of T80 as the surfactant did not also affect the tablet hardness significantly. This observation seems to support the explanation above of the poor water solubility of the diluent being responsible. With three of the four binders used, there was a decrease, although very slight, in tablet hardness with increased T80 concentration (Fig 6.2.1). It was observed that all the tablets formulated with magnesium carbonate with or without surfactant did not generally have very good hardness.

The effect of surfacant treatment of tablet friability was inconsistent (Fig. 6.2.2). It was however noted that some of the treated granules had lower friability than the untreated ones. This could be as a result of the insoluble diluent reducing the bond-softening property of the surfactants.

Fig. 6.2.1. Effect of Surfactant Type and Conc. on Tablet Hardness(MgCo3 as diluent)

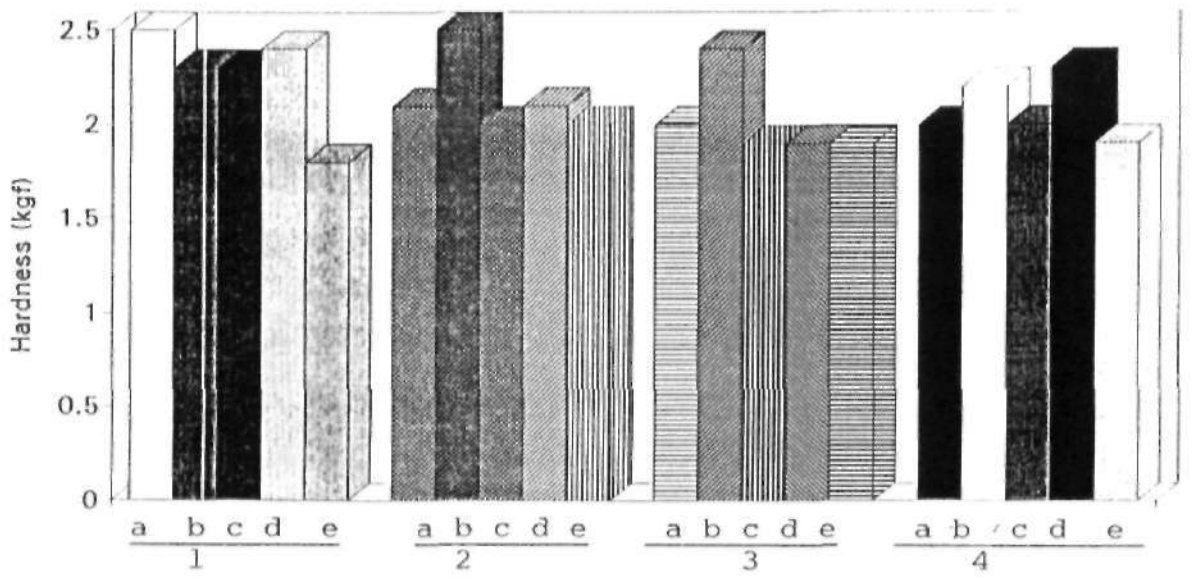
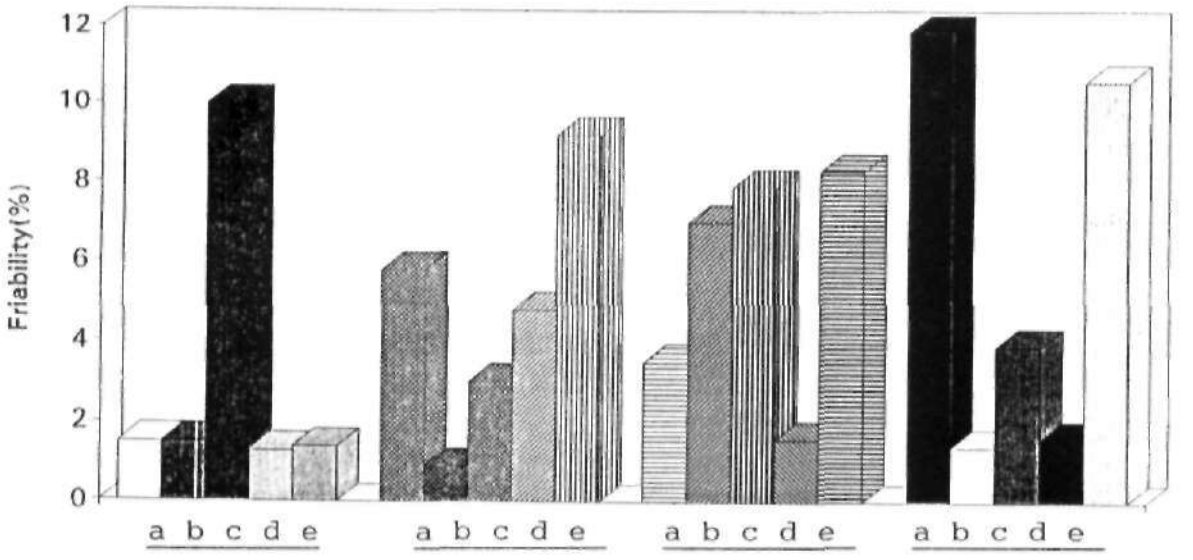


Fig. 6.2.2. Effect of Surfactant Type and Conc. on Tablet Friability (MgCo3 as diluent)



Key

1 - Starch paste as binder
2- PVP " "
3 - Na alginate " "
4 - Gelatin as binder

a - 0 Surfactant
b - 0.2% SLS
c - 0.4% SLS
d - 0.2% T80
e - 0.2% T80

In virtually all the formulations, treatment with surfactants resulted in increased tablet disintegration times (Fig 6.2.3). In addition to the reasons already proferred, the solubility of magnesium carbonate might also have contributed. Selkirk and Ganderton (1970) have found that rapid penetration of liquid into large pores isolates other areas of finer pore structure from which air cannot escape. These areas then do not contribute to the overall uptake of liquid into the tablet. It could be that the presence of the surfactant resulted in isolated areas that encouraged such rapid uptake of water into the tablet thus delaying tablet disintegration. The extent of this however depended on the type and concentration of the surfactant used as well as the binder type.

With starch paste as binder (Fig. 6.2.3) the lower surfactant concentrations (0.2% SLS and T80) increased the disintegration time much more than the higher concentrations. Considering the reasons earlier adduced for disintegration time would be expected to increase with increased surfactant concentration. It could be that with the doubling of the surfactant concentration, its wetting ability as well as surface tension lowering property were able to effectively counteract these factors. A similar result was obtained with all the other binders. The change was however much less with PVP and gelatin.

While all of the surfactants at both concentrations increased the dissolution times of the gelatin granulate tablets, they, with the exception of 0.4% T80 reduced the time slightly for the starch granulate tablets (Fig. 6.2.4). In the case of PVP and alginate granulate tablets, while SLS reduced the dissolution time T80 increased it with both effects occuring in a concentration dependent manner.

Fig. 6.2.3. Effect of Surfactant Type and Conc. on Disintegration Time (MgCo3 as diluent)

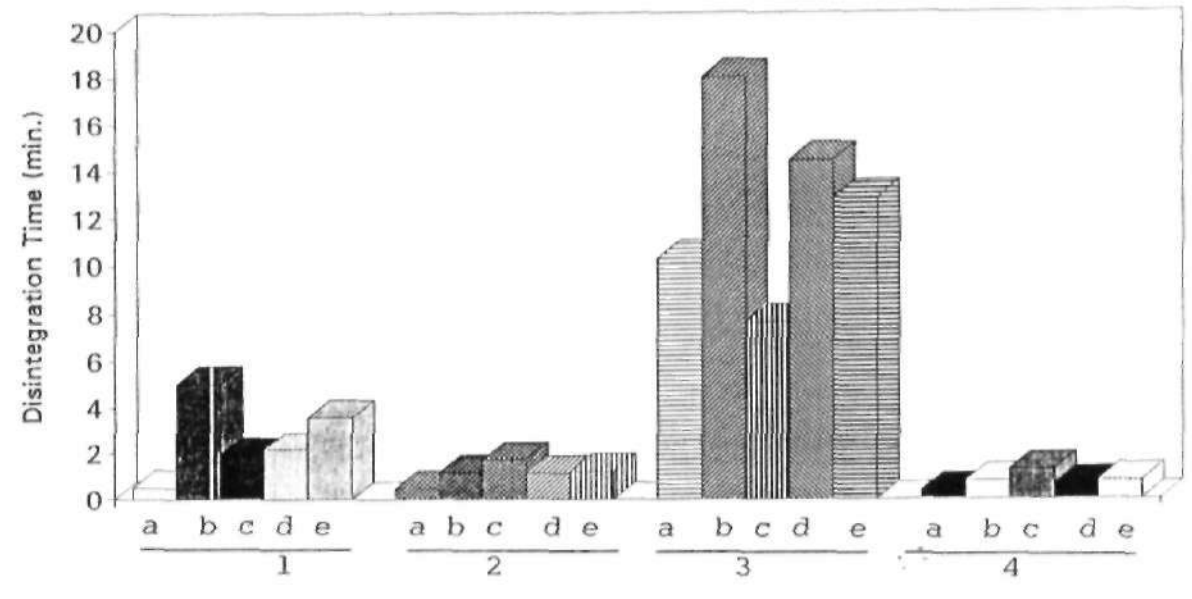
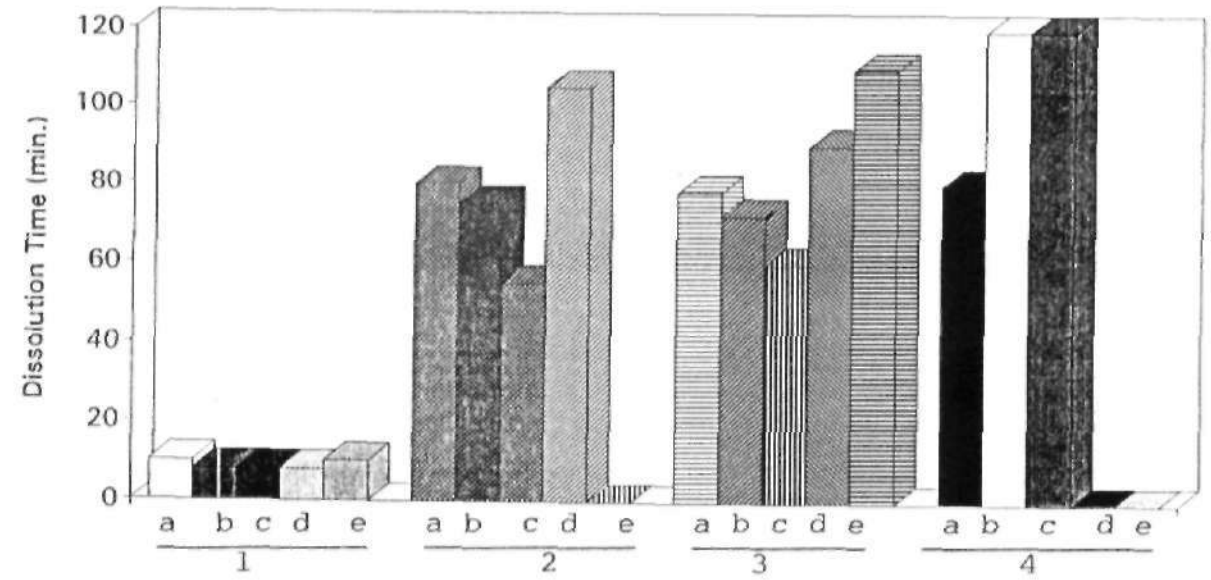


Fig. 6.2.4. Effect of Surfactant Type and Conc. on Dissolution Time, T75% (MgCo3 as diluent)



Key

1 - Starch paste as binder
2 - PVP " "
3 - Na alginate " "
4 - Gelatin as binder

a - 0 Surfactant
b - 0.2% SLS
c - 0.4% SLS
d - 0.2% T80
e - 0.2% T80

6.3.2.3 Aerosil as diluent

The tablet hardness was relatively unaffected by the addition of surfactants to the formulation, irrespective of its type or concentration, when PVP was used as binder. The friability of the tablets was also unaffected by surfactant treatment. Disintegration time was reduced with the surfactant treatment, with the extent increasing with increase in the concentration of both SLS and T80 as would be expected.

With alginate as binder, treatment with SLS and T80 resulted in decreased hardness at the two concentration levels used (Fig.6.3.1), while tablet friability increased (Fig.6.3.2). Increasing the surfactant concentration in both cases resulted in further decrease in hardness and increased friability. All the surfactant-treated granules did not produce tablets with satisfactory physical characteristics. SLS treatment reduced the tablet disintegration time (Fig. 6.3.3) significantly at both concentrations. T80 treatment however, increased the disintegration time at 0.4% concentration level, while it did not affect it at the 0.2% concentration level.

When gelatin was used as the binder, surfactant treatment did not significantly affect the tablet hardness, although friability increased in an inconsistent manner. While increasing the SLS concentration reduced the tablet friability, it increased with increase in T80 concentration. The increased friability of the surfacant-treated tablets, inspite of similar hardness values compared with the untreated tablets, could be because the wetting action of the surfactants reduced the strength of the bonds formed by allowing easy water penetration and retention within the bonds.

Disintegration time increased with surfactant treatment of the granules (Fig. 6.3.4). The T80 granulate tablets had longer disintegration times than the SLS granulate tablets. In

Fig. 6.3.1. Effect of Surfactant Type and Conc. on Tablet Hardness (Aerosil as diluent)

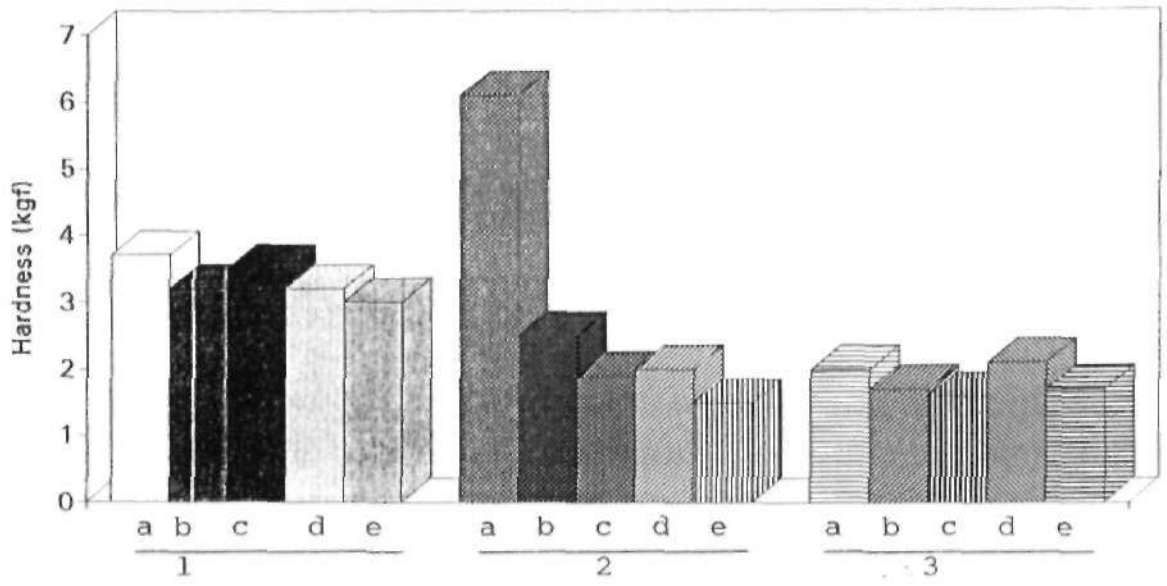
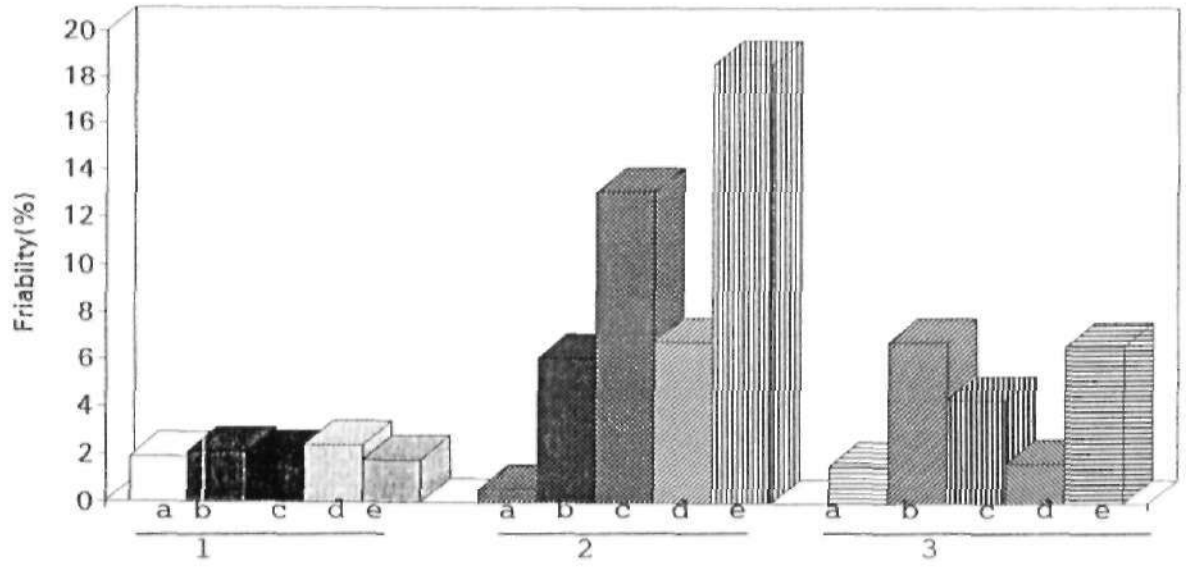


Fig. 6.3.2. Effect of Surfactant Type and Conc. on Tablet Friability (Aerosil as diluent)



Key

1 PVP as binder
2 Na alginate as binder
3 Gelatin as binder

a - 0 ;Surfactant
b - 0.2% SLS
c - 0.4%
d - 0.2% T80
e - 0.2% T80

Fig. 6.3.3 Effect of Surfactant Type and Conc. on Disintegration Time (Aerosil as Diluent)

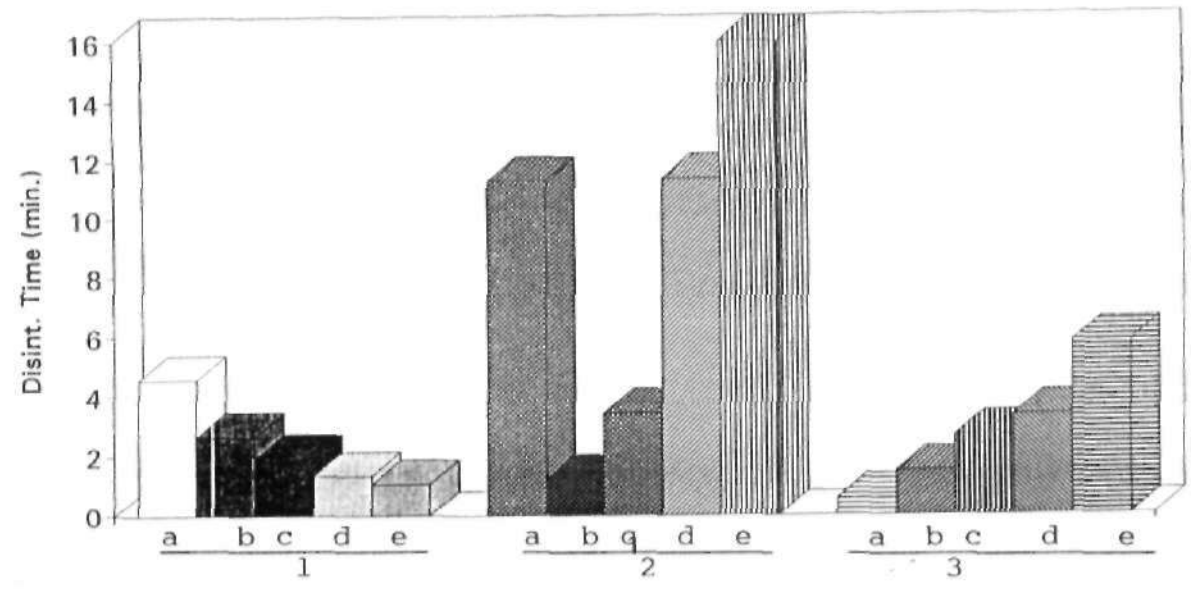
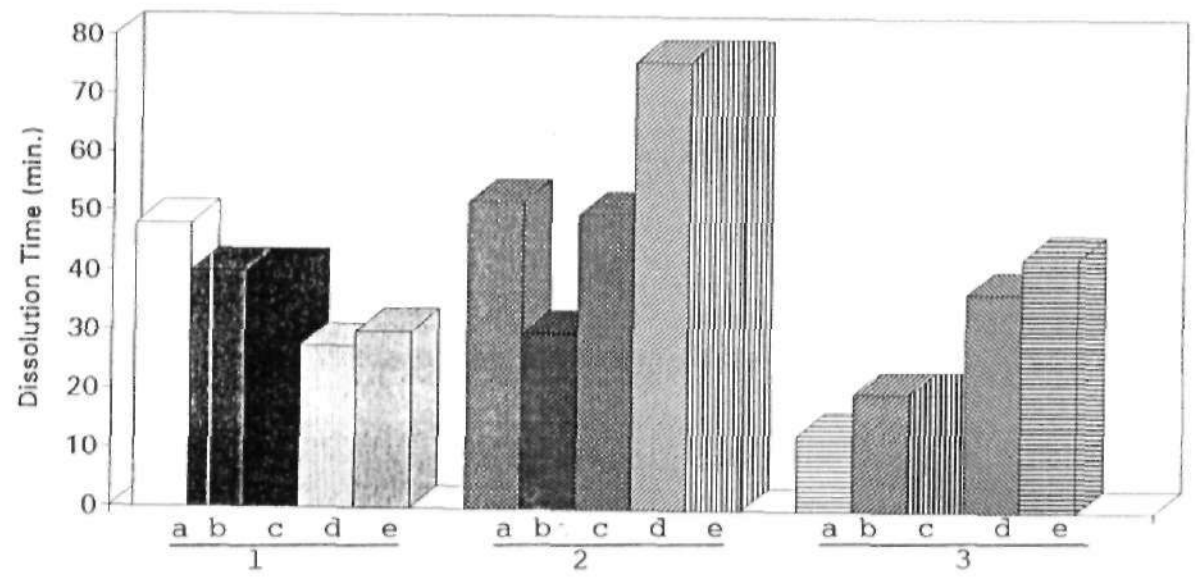


Fig. 6.3.4. Effect of Surfactant Type and Conc. on Dissolution Time, T75% (Aerosil as Diluent)



Key

1 - PVP as binder
2- Na alginate as binder
3 - Gelatin as binder

a - 0 Surfactant
b - 0.2% SLS
c - 0.4% SLS
d - 0.2% T80
e - 0.2% T80

both cases, the disintegration time increased with increase in surfactant concentration.

The dissolution time was reduced with the addition of surfactant to the formulation with PVP as binder (Fig. 6.3.4), probably due to increased liquid penetration as seen from the disintegration test results due to reduced surface tension. T80 was more effective in this respect than SLS. In the case of the alginate granulate tablets, SLS reduced the dissolution time, with the lower concentration being most effective while both concentrations of T80 increased it to the same extent. Both surfactants increased the dissolution time of the drug when gelatin was used as binder with T80 doing this in a concentration dependent manner.

6.4 CONCLUSION

Surfactant treatment was found to affect all the granule properties tested. The effect and its extent depended on the property and the type and concentration of surfactant used. The type of diluent used also contributed to the effect.

With lactose as diluent, surfactant treatment reduced the physical strength (hardness/friability) of the tablets; with only a few of the batches having satisfactory physical characteristics. The addition of surfactant did not affect these properties significantly with the insoluble diluents - heavy magnesium carbonate and aerosil - although friability was increased in a few cases with both and hardness decreased with aerosil.

With lactose, surfactants increased the disintegration and dissolution rates. In the case of aerosil and magnesium carbonate (heavy) however, the effect was inconsistent with decreased rates being obtained with some batches. Explanations have been proferred for these unexpected observations.

aerosil and magnesium carbonate (heavy) however, the effect was inconsistent with decreased rates being obtained with some batches. Explanations have been proferred for these unexpected observations.

The relative effect of T80 and SLS depended on their concentration, the type of diluent and binder used.

Based on the overall effect on the tablet properties, 0.2% SLS will be suitable for inclusion in the forrmulation of the HWE with lactose as diluent using any of the binders except alginate. In addition to this, 0.2% T80 can also be used with PVP as binder.

CHAPTER SEVEN

EFFECT OF MAGNESIUM STEARATE AS LUBRICANT ON GRANULE AND TABLET PROPERTIES

7.1 INTRODUCTION

Lubricants are added to drug formulations to improve the flow of powders or granules and in some cases to aid the ejection of tablets. They are therefore essential additives in tablet formulation. However, most of the lubricants commonly used in drug formulation are hydrophobic in nature. They can therefore result in reduced drug adsorption. It is therefore important to optimise the amount of the lubricant added to a formulation with respect to its drug release properties.

Some studies have also shown that they affect the physical properites of tablets (Esezobo, 1985) and granules (Irono and Pilpel, 1982).

The aim of this section is to determine the optimum amount of the lubricant, magnesium stearate, suitable for the formulation of HWE tablets. This is by assessing the effect of different concentrations of magnesium stearate on granule and tablet properties using three different diluents and four binder types.

7.2 MATERIALS AND METHODS

7.2.1 Materials

Hot water extract, Lactose BP, Magnesium carbonate, Maize starch BP, Aerosil Magnesium stearate B.P

Table 7.1.1: Tablet Composition (Lactose as diluent)

	A	B	C	D
Hot water Extract (HWE)	250mg	250mg	250mg	250mg
Lactose (diluent)	375mg	375mg	375mg	375mg
Maize starch powder (endodisintegrant)	7.5% w/w	7.5%	7.5%	7.5%
Binder	*	*	*	*
Maize starch powder (Exodisintegrant)	7.5% w/w	7.5%	7.5%	7.5%
Mg stearate (lubricant)	0%w/w	0.1%	0.2%	0.30%

** Four (4) different binders were used for each of the tablet compositions A, B, C and D i.e 5% starch paste, 5% PVP, 5% Na alginate and 7.5% gelatin.*

Table 7.1.2: Tablet composition (Heavy magnesium carbonate as diluent)

	A	B	C	D
Hot water Extract (HWE)	150mg	150mg	150mg	150mg
Mg carbonate (diluent)	450mg	450mg	450mg	450mg
Maize starch powder	7.5%w/w	7.5%	7.5%	7.5%
Binder	*	*	*	*
Maize starch powder	7.5%w/w	7.5%	7.5%	7.5%
Mg stearate	0%w/w	0.1%	0.2%	0.30%

Table 7.1.3: Aerosil as diluent

	A	B	C	D
Hot Water Extract	350mg	350mg	350mg	350mg
Acrosil (diluent)	210mg	210mg	210mg	210mg
Maize starch powder	7.5%w/w	7.5%	7.5%	7.5%
Binder	*	*	*	*
Maize starch powder	7.5%w/w	7.5%	7.5%	7.5%
Mg stearate	0%w/w	0.1%	0.2%	0.30

7.2.2. **Methods**

(a) The wet granulation method of massing and screening was used with exactly the same

procedure as earlier outlined followed. The dried granules were mixed with the required amount of lubricant for about 5 minutes in a tumble mixer.

(b) The bulk and tapped densities, percent compressibility, flow rate and angle of repose of the granules were determined as stated earlier.

(c) The tablet weight variation, hardness, friability, disintegration and dissolution times were determined as earlier outlined.

7.3RESULTS AND DISCUSSION

7.3.1 Granule Properties

7.3.1.1 Lactose as diluent

Bulk and tapped densities were increased by the addition of magnesium stearate to the PVP and gelatin granulates at 0.20 and 0.30%, (Table 7.2.1). Podezeck and Miah (1996) have stated that magnesium stearate forms a film around particles. The results could therefore be because the complete coating of the particles by the lubricant increased the ease with which the particles slid over each other, due to the smoothening of the rough points or asperities. This would result in closer packing of the particles, reduced volume and consequent increase in density. This effect increased with increase in concentration probably because the higher the concentration, the better will be the coating around the particles. The PVP granulate which was relatively unaffected by concentration changes was an exception probably because the optimal coating had been achieved at the lower concentration. As would be expected from the foregoing, percent compressibility was

reduced by the addition of lubricant except with the alginate granulates where the 0.10 and 0.20% concentrations resulted in increased values (Table 7.2.1).

In the case of the starch paste granulates, the bulk and tapped densities were reduced by the addition of lubricant. It could be that with this set of granulates, the lubricant film did not completely coat the particles, explaining the difference from the other granulates. It could also be that the coating was such that shearing action between the particles was able to remove at least a part of it. From the results, however (Table 7.2.1), where the densities were found to increase with increased lubricant concentration, the latter explanation might be more valid, since the thicker the coat the less will be the effect of this on the granules. With these granulates (starch as binder), the percent compressibility decreased with the addition of lubricant. This is an indication that the granulates should have good flow properties, with the addition of lubricant changing the flow from very good to excellent (Carr,1965).

All the granulates with the other binders also showed decreased angles of repose with the addition of lubricant. While in the case of PVP and gelatin as binder (Table 7.2.1), it decreased in a concentration dependent manner, it unexpectedly increased between 0.20 and 0.30% when sodium alginate and starch were used. Jones and Pilpel (1966) and Irono and Pilpel (1982) have found that excessive lubricant results in granules that have too thick a coat, or excessive fines all resulting in reduced flowability. Dodezeck and Miah (1996) explained that at the point at which $\propto_2$ (the ratio between the shear stress and the normal pressure at the contact area between lubricant film and asperties of the powder particles) is greater than the constant $\propto_1$ (the ratio between the shear stress applied and the normal pressure at the contact points of the surface asperities), any further increase in film thickness will result in increased friction and thus a decrease in powder flow. It would therefore seem that for these granulates (starch and alginate),

Table 7.2.1:Effect of Mg stearate conc. on Granule Properties with Lactose as Diluent

Binder Type	Mg stea-rateconc. %w/w	Bulk Density (g/ml)	Tapped Density (g/ml)	%Compressibility	Flow Rate (g/sec.)	Angle of Repose,θ
Starch paste	0.00	0.84	0.98	16.60	4.00	26.23
	0.10	0.64	0.74	13.51	5.22	25.70
	0.20	0.72	0.78	7.69	7.80	23.67
	0.30	0.78	0.87	10.35	6.37	24.78
PVP	0.00	0.69	0.79	12.66	7.5	25.41
	0.10	0.73	0.81	9.88	6.67	25.02
	0.20	0.73	0.82	10.98	7.53	20.75
	0.30	0.73	0.81	9.88	7.45	18.57
Na alginate	0.00	0.69	0.84	17.86	6.00	26.60
	0.10	0.70	0.86	18.61	6.14	22.70
	0.20	0.82	1.05	21.91	6.90	21.95
	0.30	0.98	1.06	7.55	5.14	25.93
Gelatin	0.00	0.69	0.83	16.86	4.88	28.07
	0.10	0.67	0.80	16.25	5.01	25.20
	0.20	0.73	0.84	13.10	6.79	24.78
	0.30	0.75	0.84	10.71	7.50	23.67

0.20% magnesium stearate concentration is the optimum for lubricant activity. The results of the flow rate experiment where the 0.2% lubricant concentration granulates had the best flow tends to support this.

Flow rate was increased with the addition of lubricant to the other granulates, PVP and gelatin (Table 7.2.1), with the rate increasing with increased lubricant concentration. It is possibly a result of a reduction in the van der Waals forces between the particles (Gold *et al*, 1968) and/or the reduced shearing and rupture of the materials at the contact points and the surrounding area during sliding (Tabor, 1981). The increase in rate with increased concentration of magnesium stearate is because the optimal effect is obtained when a complete film has been formed surrounding each individual particle, which would be approached or achieved as the quantity of the lubricant available per particle (magnesium stearate concentration) increases up to a limit. This would explain the very minimal effect of the 0.1% concentration on the flow rate of the gelatin granulate.

The 0.1% magnesium stearate concentration with the PVP granulate resulted in decreased flow rate (Table 7.2.1). It could be that as the particles rolled over each other, there was shearing and rupture of the film at the contact points (Tabor, 1981) which resulted in the partial removal of the lubricant film. This will result in the exposure of some rough edges and asperities on the particles which could increase interparticulate interaction thus reducing flow. This probably explains why it was observed with only the lower lubricant concentration where the film would be thinnest.

7.3.1.2 Heavy Magnesium Carbonate as diluent

The bulk and tapped densities increased with the addition of magnesium stearate (Table

Table 7.2.2.: Effect of Mg stearate conc. on Granule Properties (Diluent : Heavy $MgCo_3$)

Binder Type	Mg stea-rate conc. %w/w	Bulk Density (g/ml)	Tapped Density (g/ml)	%Compres sibility	Flow Rate (g/sec.)	Angle of Repose,θ
Starch paste	0.00	0.64	0.81	20.99	5.00	21.67
	0.10	0.82	1.03	20.39	6.46	17.68
	0.20	0.92	1.09	15.59	6.15	15.14
	0.30	1.01	1.19	15.46	6.54	13.86
PVP	0.00	0.73	0.87	16.09	5.56	22.41
	0.10	0.87	1.01	13.86	6.10	15.52
	0.20	0.87	1.00	13.00	6.98	15.32
	0.30	0.84	0.99	15.15	6.16	17.68
Na alginate	0.00	0.50	0.63	20.64	5.00	25.00
	0.10	0.69	0.86	19.77	6.89	20.27
	0.20	0.75	0.85	11.77	6.81	24.78
	0.30	0.77	0.86	10.47	6.91	20.56
Gelatin	0.00	0.67	0.82	18.29	6.25	23.55
	0.10	0.82	0.94	12.77	6.64	16.77
	0.20	0.83	0.93	10.75	6.55	14.42
	0.30	0.84	0.97	13.40	6.32	17.59

7.2.2). The percent compressibility decreased in all cases with the addition of lubricant. With the PVP granulate, it increased between 0.20 and 0.30% concentrations, probably indicating reduced lubricant efficiency at the higher concentration. This was also reflected in the angle of repose value where there was an increase between 0.20 and 0.30% rather than a decrease as would have been expected. The flow rate also decreased slightly between the two concentrations. It would therefore seem that 0.2% is the optimal concentration of lubricant for this formulation in agreement with Podizeck and Miah (1996), that the optimal magnesium stearate concentration is found at the minimum of any friction characteristics. At this optimal concentration, the friction occuring is only partially due to shearing of the lubricant film but mainly due to deformation of the surface (Bowden and Tubor, 1973).

With gelatin as binder (Table 7.2.2), percent compressibility and angle of repose increased between 0.20 and 0.30% lubricant concentration rather than decrease as would have been expected. This is an indication that 0.20% might be the optimal concentration. With these granulates, flow rate increased only slightly with the addition of lubricant. It was relatively unaffected by concentration changes as was also the case with the alginate granulate.

7.3.1.3 Aerosil as diluent

As was expected the bulk and tapped densities increased with the addition of magnesium stearate, while percent compressibility and angle of repose (Table 7.2.3) decreased, all indicating better sliding of the particles over each other. This probably resulted in the improved flow rate observed with the addition of lubricant to the granulates. All of these effects increased to different extents with increased lubricant concentration depending on the binder used and mg stearate concentration. Increasing the lubricant concentration

Table 7.2.3. : Effect of Mg stearate conc. on Granule Properties with Aerosil as diluent

Binder Type	Mg stea-rate conc. %w/w	Bulk Density (g/ml)	Tapped Density (g/ml)	%Compres sibility	Flow Rate (g/sec.)	Angle of Repose, θ
PVP	0.00	0.70	0.79	11.39	5.25	22.87
	0.10	0.72	0.81	11.11	5.80	19.32
	0.20	0.82	0.90	8.89	6.00	16.64
	0.30	0.84	0.92	8.69	6.02	14.56
Na alginate	0.00	0.81	1.04	22.12	6.67	18.98
	0.10	0.84	1.04	19.23	6.72	18.14
	0.20	0.91	1.06	14.15	6.94	13.64
	0.30	0.91	1.06	14.15	7.03	12.03
Gelatin	0.00	0.65	0.77	15.58	5.50	25.23
	0.10	0.71	0.82	13.42	5.94	20.77
	0.20	0.80	0.89	10.11	6.54	18.39
	0.30	0.82	0.91	9.89	6.62	16.38

from 0.2 to 0.3% did not seem to affect the properties of the alginate granulates significantly.

7.3.2 **Tablet Properties**

7.3.2.1. Lactose as diluent

Tablet hardness was reduced and friability increased by the addition of magnesium stearate to most of the formulations, irrespective of the binder used (Table 7.3.1). Similar observations have been made by others (Esezobo, 1985; Shotton and Ganderton, 1961) who have found that there is a weakening of the inter-particulate bond between particles on addition of a lubricant such as magnesium stearate. Gold *et al* (1968) have proposed that magnesium stearate reduces particle adhesion due to long-range van der Waals forces between the particles of a powder bed. This could result in the weakening of the interparticulate bonds and consequently low tablet hardness and high friability.

The extent of the effect on hardness and friability, however, depended on the binder type used (Table 7.3.1). In the case of the PVP granulate, only the 0.3% concentration had any substantial effect while there was even a slight, although insignificant, increase with 0.1% lubricant.

Tablet disintegration time increased with the addition of magnesium stearate (Table 7.3.1). This effect increased with increased lubricant concentration except with the PVP granulate between 0.1 and 0.2% where it was unchanged. Sixsmith (1977) similarly observed that the addition of magnesium stearate has a marked effect on the disintegration

Table 7.3.1. Effect of Mg stearate Conc. on Tablet Properties (Diluent:Lactose)

Binder Type	Mg stearate conc. %w/w	Av.Weight, mg (SD)	Hardness (kgf)	Friability %	Disint. Time (min)	Dissolution Time (min.) T50	T75	T90
Starch paste	0.0	759.50(6.88)	7.8	0.16	18.30	32	49	60
	0.1	730.42(36.64)	7.0	0.25	21.09	32	49	75
	0.2	739.82(22.34)	7.2	0.36	26.98	32	49	90
	0.3	763.35(27.63)	7.1	0.30	28.59	49	86	120
PVP	0.0	757.41(8.22)	14.5	0.10	25.13	45	90	107
	0.1	704.44(21.02)	14.0	0.10	27.95	50.5	96	110
	0.2	722.67(29.66)	14.0	0.10	27.69	50.5	90	110
	0.3	739.82(22.34)	12.0	0.10	28.98	60	104	-
Na alginate	0.0	740.94(15.06)	8.82	0.52	16.20	17.5	26	35
	0.1	748.44(22.11)	9.0	0.60	18.72	18	34	48
	0.2	716.51(20.50)	7.8	0.62	24.67	18	35	60
	0.3	742.88(28.93)	8.0	0.58	26.44	26	86	120
Gelatin	0.0	737.12(24.60)	8.68	0.52	11.50	18	30	55
	0.1	697.61(25.18)	8.0	0.50	12.28	18	33	55
	0.2	693.95(30.95)	8.1	0.60	18.80	18	30	60
	0.3	706.67(24.51)	7.9	0.80	19.6	29	90	120

time of tablets which effect increased with increase in lubricant concentration. He concluded that this was as a result of the inability of water to penetrate the tablet probably because of the coating of the particles by the hydrophobic magnesium stearate. The relative lack of effect between the 0.1 and 0.2% concentrations in the case of the PVP granulate is, probably because the increase was not enough to change the nature or thickness of the coating enough to affect the disintegration time.

As would be expected from the disintegration times, drug dissolution was generally delayed by the addition of magnesium stearate (Table 7.3.1). At the lower lubricant concentrations (0.1 and 0.2%) especially, the effect on dissolution was not as much as would be expected from the disintegration times in most cases. This is possibly because at these concentrations, the hydrophobic film of magnesium stearate does not envelope the granules completely and therefore as proposed by Desai *et al* (1993), the action of the disintegrants is not inhibited once in contact with the dissolution medium.

The delay in dissolution time was most pronounced on the T90% (time taken for 90% of the drug content to dissolve). This would tend to indicate that while the medium could penetrate the tablet relatively easily, it was more difficult to penetrate the granules and aggregates formed after the breakup of the tablet. This could be because the coating would tend to be more complete at this micro level due to increased surface area than with the larger tablet mass. With gelatin as binder only the 0.3% concentration significantly increased dissolution time.

7.3.2.2 Heavy magnesium carbonate as diluent

Tablet hardness was decreased while friability, disintegration and dissolution times

Table 7.3.2 : Effect of Mg stearate Conc. on Tablet Properties (Diluent:HeavyMgCo3)

Binder Type	Mg stearate conc. %w/w	Av.Weight, mg (SD)	Hardness (kgf)	Friability %	Disint. Time (min)	Dissolution Time (min.) T50	T75	T90
Starch paste	0.0	723.98(35.21)	2.60	2.20	0.22	18	28	45
	0.1	764.56(25.53)	2.50	2.40	0.32	20	35	75
	0.2	774.26(22.05)	2.26	2.40	0.48	20	45	75
	0.3	693.95(30.59)	1.82	3.10	2.28	25	115	-
PVP	0.0	712.32(28.27)	2.48	2.30	2.37	38	78	100
	0.1	768.80(27.75)	2.26	2.80	3.75	40.5	78	120
	0.2	768.62(26.21)	2.30	3.00	4.33	38	78	120
	0.3	801.60(21.43)	2.26	2.40	7.22	72	-	-
Na alginate	0.0	714.43(14.14)	3.00	3.50	10.13	40	73	105
	0.1	788.62(22.64)	2.30	4.00	10.78	42	87	105
	0.2	753.27(24.73)	2.62	3.80	11.39	42	78	105
	0.3	799.95(27.16)	2.40	3.90	15.92	50	94	120
Gelatin	0.0	753.34(19.83)	3.00	8.90	0.16	27	60	90
	0.1	739.63(17.88)	2.26	10.0	0.25	30	72	-
	0.2	783.37(23.95)	2.62	11.9	0.33	30	82.5	-
	0.3	757.76(24.70)	1.62	*	0.32	49	100	-

* Completely shattered on commencement of the test

increased with the addition of magnesium stearate (Table 7.3.2). In the case of starch paste as binder, these effects were most pronounced at the 0.3% lubricant concentration, with the tablets not even releasing up to 90% of their drug content within the duration of the test. When PVP was used as binder, the 0.3% lubricant concentration unexpectedly produced tablets with lower friability than was the case at 0.2% concentration. It was also observed that the T50% value decreased with increased lubricant concentration from 0.1 to 0.2%. This is possibly because both concentrations of lubricant did not completely envelope the granules, thus it was possible for the dissolution media to penetrate at about the same rate, the effect of this penetration would then depend on a number of other factors such as the particle configuration and surface area which are independent of lubricant concentration.

The tablets with 0.3% magnesium stearate concentration and gelatin as binder were very soft and could not withstand handling, being completely shattered as soon as the friability test was commenced (Table 7.3.2). Inspite of this however, it still had about the longest disintegration and dissolution times, not even releasing up to 90% of its drug content in 2 hours. Desai *et al* (1993) have stated that the dissolution of granules is dependent, amongst others, on the hydrophobic lubricant concentration. It would therefore seem that at this concentration, the lubricant so completely surrounded the particles that it prevented the formation of bonds and the penetration of fluids even after the disintegration of the tablet.

7.3.2.3 Aerosil as diluent

Irrespective of the binder type used, tablet hardness decreased, while the friability,

Table 7.3.3. : Effect of Mg stearate Conc. on Tablet Properties (Diluent:Aerosil)

Binder Type	Mg stearate conc. %w/w	Av.Weight, mg (SD)	Hardness (kgf)	Friability %	Disint. Time (min)	Dissolution Time (min.) T50	T75	T90
PVP	0.0	686.90(29.10)	3.90	1.60	9.32	22.5	51	87
	0.1	694.27(24.09)	3.70	1.40	10.85	22	41	72
	0.2	699.00(18.75)	3.40	1.80	11.18	22	48	120
	0.3	701.39(23.97)	3.00	2.00	13.29	48	89	-
Na alginate	0.0	673.51(38.75)	6.70	0.40	9.32	20	40	72
	0.1	663.06(17.13)	6.00	0.60	10.85	20	48	78
	0.2	652.80(12.46)	5.90	0.60	11.18	33	55	87
	0.3	670.17(19.63	5.00	0.90	13.29	42	88	-
Gelatin	0.0	679.94(23.31)	3.00	1.00	0.48	6	13	23
	0.1	685.37(15.68)	2.70	1.50	1.64	7.5	28	41
	0.2	684.87(25.75)	2.00	1.60	1.93	10	27	60
	0.3	688.29(17.98)	1.30	1.90	2.18	12.5	50	-

disintegration and dissolution times increased with the addition of magnesium stearate (Table 7.3.3). All of these effects generally increased with increased magnesium stearate concentration. The effect of changing the lubricant concentration was most pronounced between 0.2 and 0.3% concentration levels.

The T75% values unexpectedly decreased with the 0.1 and 0.2% magnesium stearate concentration relative to the unlubricated formulations when PVP was used as binder (Table 7.3.3). As suggested by Deboer *et al* (1978), it could be that during compression, the hydrophobic film (which might not be too thick at these concentration levels) is disrupted and the granules are fragmented resulting in new, fresh, uncoated surfaces which could result in unimpeded drug dissolution. Esezobo (1977) has also found that aerosil (the diluent in this case), when added to tablet formulations internally i.e. before granulation, can have effects similar to those of lubricants. It could therefore be that this effect, coupled with that of the lubricant (magnesium stearate), complicated the dissolution process in an unpredictable manner, giving rise to this unexpected observation.

7.4 Conclusion

The addition of magnesium stearate (lubricant) to the granules resulted in the improvement of all the flow indicating properties tested. There was generally a substantial improvement in flow properties when the lubricant concentration was increased from 0.1 to 0.2%, while the effect of increasing the concentration to 0.3% was not that much and even resulted in lower values for some of the indicators. It would therefore seem that the optimum magnesium stearate concentration is around 0.2%. These observations were valid irrespective of the diluent and binder used, although the magnitude of the effect differed depending on which diluent or binder was used.

The addition of mg stearate affected the properties of the tablets formulated generally reducing the physical strength while these effects were minimal with the 0.1 and 0.2% concentrations the 0.3% affected the tablets to a larger extent. The extent of these effects depended on the diluent and binder used.

Based on the results of the investigations on the granule and tablet properties, the 0.2% concentration of mg stearate seems to be best suited for use in the formulation of the hot water extract without reducing the strength and increasing the disintegration and dissolution times.

CHAPTER EIGHT

EFFECT OF FORMULATION ON HWE

8.1 INTRODUCTION

The most important stage in the development of a pharmaceutical product is the selection of the material/excipients to be included in the formulation. Various investigations have shown that the excipients used in the formulation of a drug can affect its physical properties (Mckenna and McCafferty, 1982; Alderborn and Nystrom, 1982; Shubair and Dingwall, 1976; Kunle and Bangudu 1990; Jaminet, 1969). The goal of every formulation scientist involved in tablet dosage form development is to find excipients that will confer positive properties such as improved flow and compressibility on the granules and also produce tablets of adequate physical strength and release characteristics. Such excipients should not interfere in any way with the activity of the drug on biological systems i.e they should be inert.

Hence in developing any formulation, when additives are selected, it is extremely important to consider whether they interact with drug materials or other additives, form a complex with the drug, adsorb the drug or get adsorbed by the drug or alter the absorption characteristics of the drug after administration. This is necessary because there have been many reports of some excipients either interacting, forming complexes, adsorbing the drug or being adsorbed by it.

For herbal drug formulations, since the drug is either crude or an extract with the chemical substances producing the effect not known, it may be impossible to determine these incompatibilities by the conventional chemical means. Nasipuri (1997) has therefore

suggested that it would be necessary to establish some kind of "fingerprinting" method for determining the effect of the additives. These could be either UV or TLC or even a pharmacological or biological finger print. The aim of this investigation is to determine the effect of the excipients used in the formulation of the tablets on the drug using three "finger printing" techniques-thin layer chromatography, UV spectroscopy and pharmacological activity.

8.2 MATERIALS AND METHOD

8.2.1 Thin Layer Chromatography (TLC)

The hot water extract was reconstituted in hexane to give a concentration of 75mg/ml. This preparation served as the "pure" drug to which the formulations were compared. Enough tablets to give 750mg of the extract were crushed in a mortar with a pestle, which was then reconstituted in 10 ml of hexane.

Glass plates coated with Kieselgel 60HF 254 and 366 were used for the test. The plates were spotted, each with the "pure" drug and a formulation to be tested. They were then developed with hexane: acetone (70:30) as the mobile phase and were examined under UV light at a wavelength of 366nm after being air dried. The retardation factor (R_f) was then calculated for each spot.

8.2.2 UV spectroscopy

The extract was reconstituted in hot water at a concentration of 400mg/ml. Enough tablets were crushed from each formulation to be tested; the required amount was weighed and reconstituted in hot water. The disperson of the tablet in hot water was

allowed to stand for 24 hours as was the solution of the extract. The supernatant (in the case of the formulations), was decanted and filtered through a 0.2μm filter before being used for the test. The solutions were scanned on a Shimadzu UV 160A spectrophotometer between 800nm to 200nm. The spectrum for each formulation was superimposed on that for the "pure" extract.

8.2.3 **Pharmacological Assessment**

The same method as earlier described was used to induce ulcer using acetyl salicylic acid (ASA) and to determine the ulcer index.

8.2.3.1 Sample preparation: Ten (10) tablets were selected from each batch. They were then crushed and powdered in a mortar using a pestle. Equivalent quantities of the powder to give the required amount of the hot water extract (HWE) was then weighed out. This was dissolved in hot water to give the solution used for the test. The batches tested were coded as below:

LSC -	Lactose	as	diluent,	starch	as	binder (10%w\v)
LPC -	"	"	"	PVP	"	" (7.5%w/v)
LAC -	"	"	"	Alginate	"	" (7.5%w/v)
LGC -	"	"	"	Gelatin	"	" (17.5%w/v)
MSC -	$MgCo_3$	"	"	Starch	"	" (10% w/v)
MPC-	"	"	"	PVP	"	" (7.5%w/v)
MAC-	"	"	"	Alginate	"	" (7.5%w/v)
MGC-	"	"	"	Gelatin	"	" (7.5%w/v)
APC-	Aerosil	"	"	PVP	"	" (7.5%w/v)
AAC-	"	"	"	Alginate	"	" (7.5% w/v)
AGC-	"	"	"	Gelatin	"	" (17.5%w/v)

Table 8.1.1.Effect of Formulation on the R_f values of the various formulations (Diluent: Lactose)

Spot No.	1IWE	LSC	HWE	LPC	HWE	LAC	HWE	LGC
1	0.79	0.8	0.87	0.87	0.6	0.60	0.64	0.63
2	0.61	0.61	0.53	0.54	0.55	0.55	0.57	0.57
3	0.55	0.55	0.48	0.49	0.48	0.50	0.50	0.53
4	0.49	0.50	0.40	0.42	0.41	0.43	0.44	0.45
5	0.42	0.43	0.31	0.36	0.35	0.37	0.38	0.37

Table 8.1.2. Effect of Formulation on the R_f values of the various formulations (Diluent: Heavy $MgCo_3$)

Spot No.	HWE	MSC	HWE	MPC	HWE	MAC	HWE	MGC
1	0.81	0.83	0.73	0.75	0.75	0.79	0.79	0.80
2	0.49	0.49	0.55	0.58	0.59	0.59	0.62	0.65
3	0.42	0.47	0.49	0.50	0.52	0.53	0.55	0.57
4	0.39	0.40	0.42	0.44	0.45	0.46	0.46	0.43
5	0.33	0.31	0.37	0.38	0.39	0.41	0.37	0.34

Table 8.1.3. Effect of Formulation on the R_f values of the various formulations (Diluent: Aerosil)

Spot No.	HWE	APC	HWE	AAC	HWE	AGC
1	0.79	0.78	0.83	0.84	0.77	0.75
2	0.61	0.59	0.75	0.74	0.61	0.61
3	0.53	0.49	0.66	0.64	0.55	0.52
4	0.47	0.43	0.56	0.58	0.49	0.45
5	0.40	0.39	0.49	0.49	0.42	0.42

8.3 **RESULTS AND DISCUSSION**

8.3.1 TLC

Tables 8.1.1 - 8.1.3 shows the R_f values for the various spots obtained on examining the chromatograms.

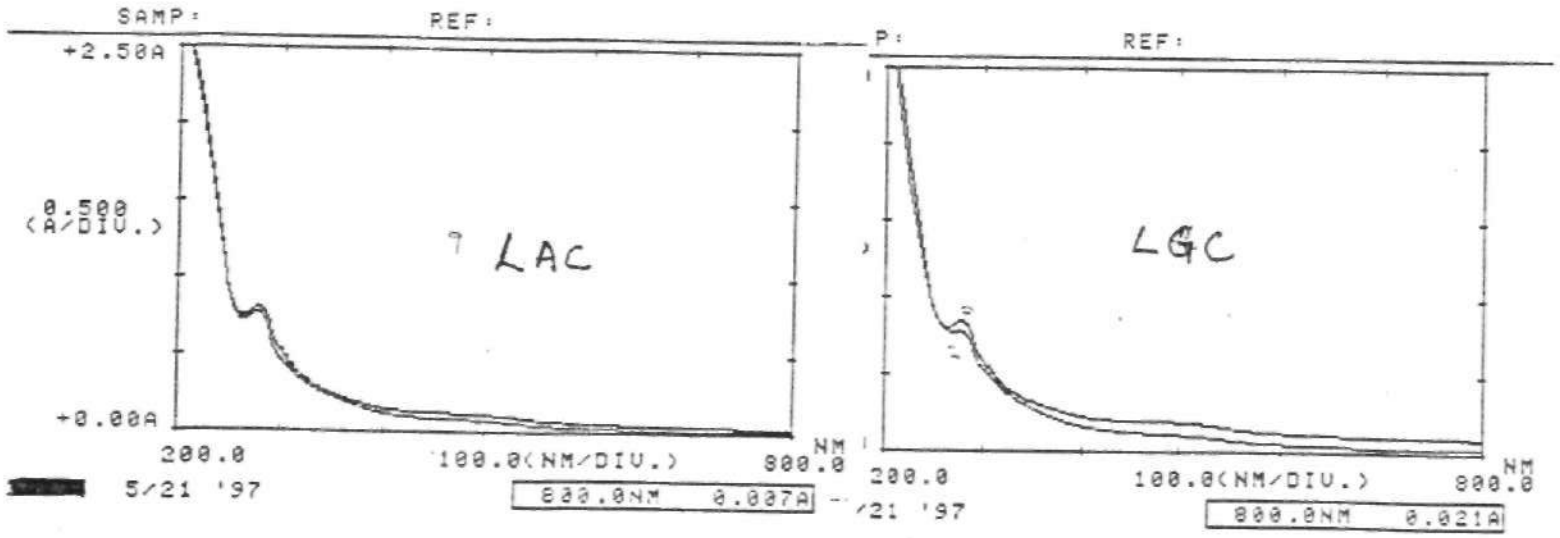
The results indicate that the unformulated (pure) extract was separated by the solvent system to give 5 (five) distinct spots. Two of these spots A_1 and E_1 were whitish while the other three were brown spots when viewed under UV light. The number and color of the spots were found to be consistent in all of the ten chromatograms that were prepared. The formulations tested also gave similar number of spots with the same color characteristics.

Based on the consistency in the nature of the spots and R_f values for the "pure" extract in all the chromatograms it is possible to use these characteristics as fingerprints for the assessment of the effect of the formulation on the extract.

The retardation factor (R_f) value is a measure of the distance travelled by a spot relative to the solvent front. Since the distance travelled by the spot will depend on the chemical nature of the compounds that are giving the spot relative to the coating material, it can give an idea of the nature of the compounds. In this case the coating material used, silica gel, is slightly acidic, so the more basic the compounds the higher their retention time and therefore the lower will be their R_f value.

All the R_f values were between 0.3 and 0.8, an indication that the solvent system was suitable for this separation (Vogel 1987). The results indicate that the extract contained both basic (low R_f) and acidic (high R_f) compounds.

Fig. 8.2.1.: Effect of formulation on the spectra of the HWE (Lactose as diluent)



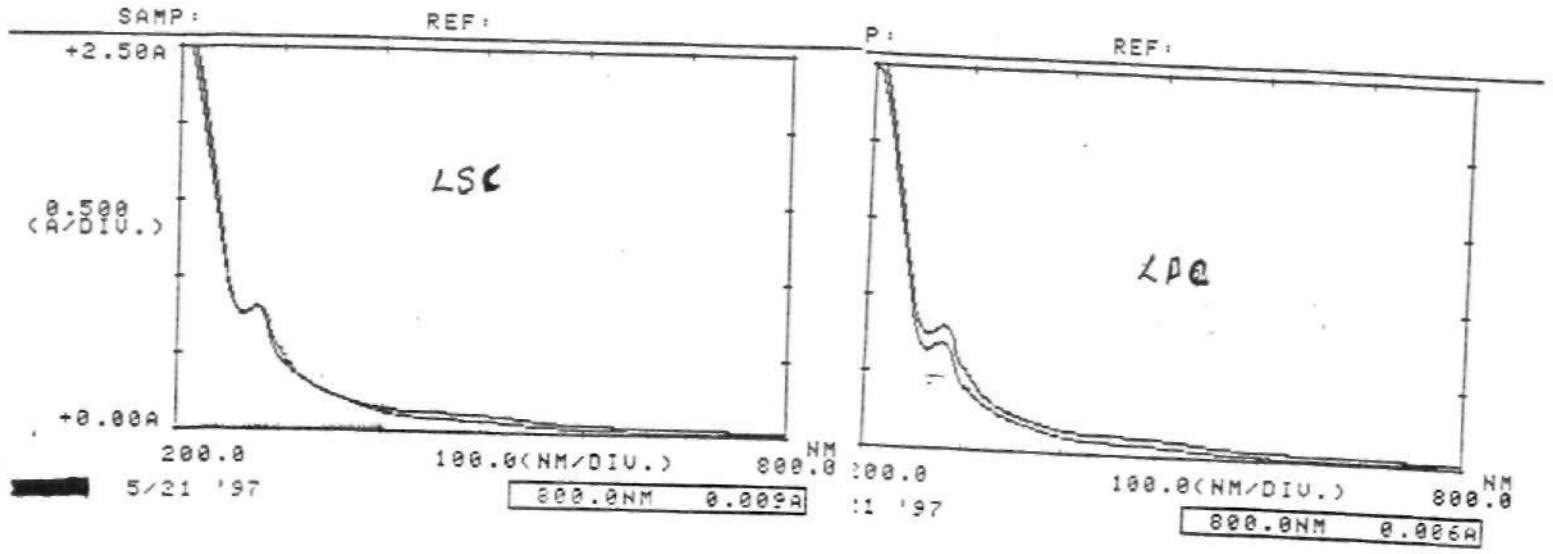
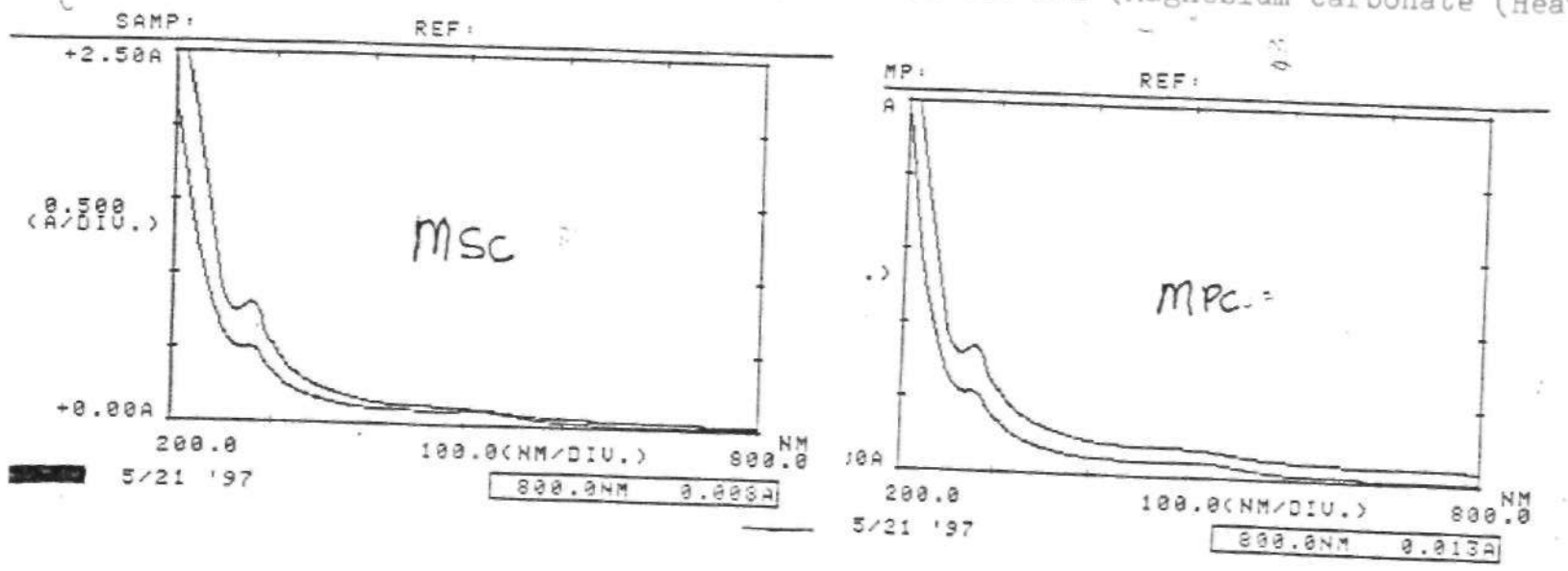


Fig. 8.2.2. Effect of formulation on the Spectra of the HWE (Magnesium carbonate (Heavy as diluent)



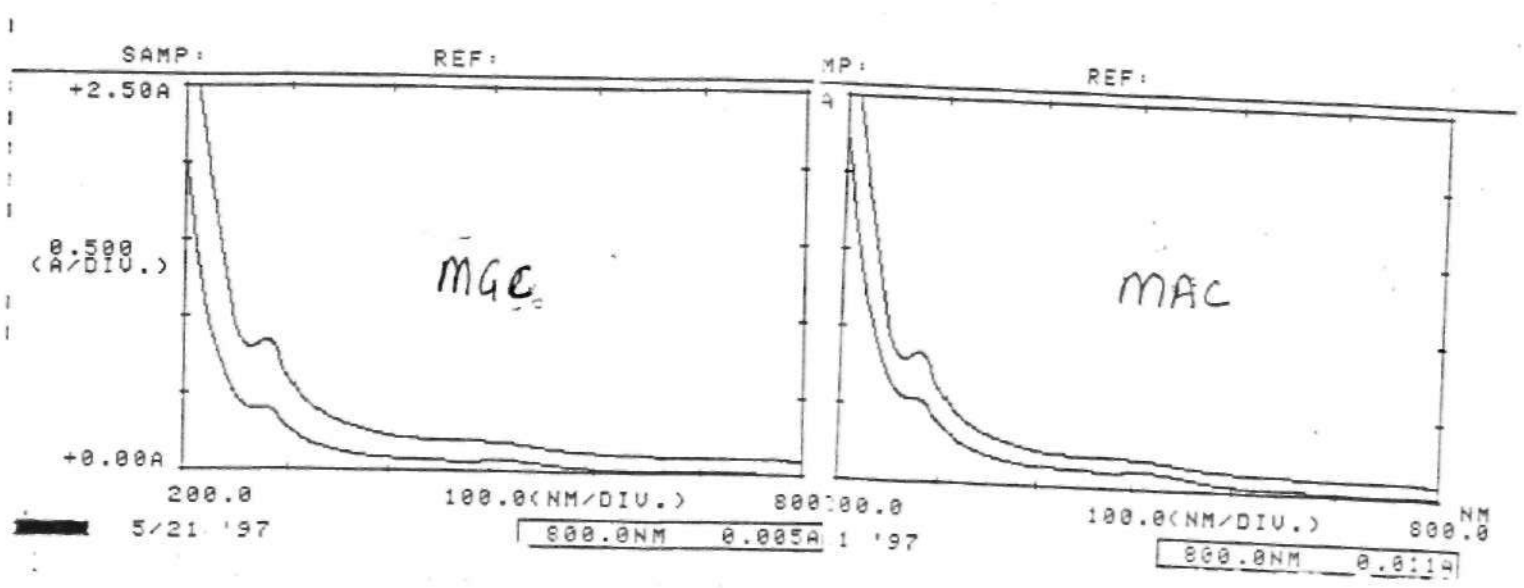
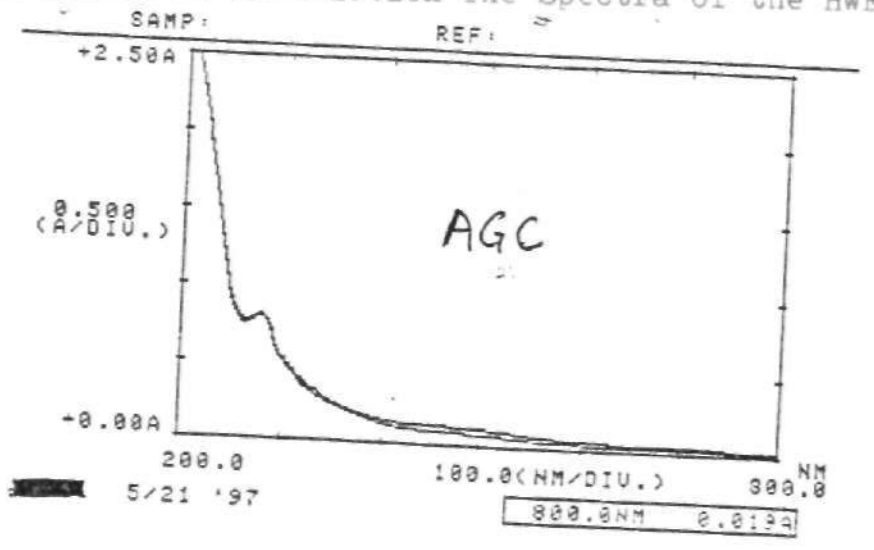
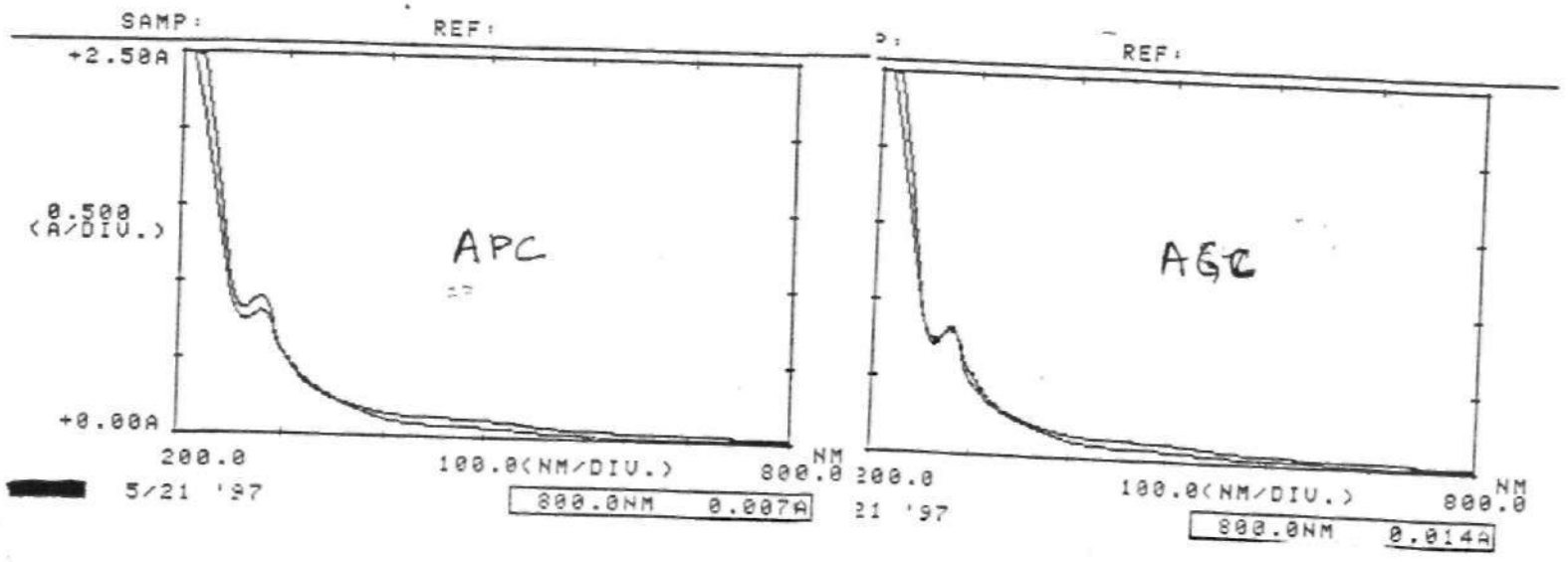


Fig. 8.2.3. Effect of formulation The Spectra of the HWE (Aerosil as diluent)





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There was no significant ($P<0.01$) difference between the R_f values obtained for the "pure" (unformulated) extract and those of the formulations. This is an indication, when considered along with the number of spots, that the formulation process and the additives did not qualitatively affect the extract.

8.3.2 UV-Visible Spectroscopy

Figs 8.2.1 to 8.2.3 show the comparative scan of the extract (unformulated) and the formulations. The results show that those tablets with lactose and aerosil as diluent had spectra that were virtually completely superimposed on those of the unformulated extract. Those formulated with magnesium carbonate as diluent however had spectra that were qualitatively similar to that of the 'pure' extract but quantitatively different. Their spectra were consistently below those of the pure drug.

8.3.3 Pharmacological

The results indicate that ASA at 250mg/ml was able to induce ulcer in all the control rats with an ulcer index of 2.7 ± 0.51 (Figs. 8.3.1 - 8.3.3).

As expected, the extract reduced the ulcer index to 0.36 ± 0.13, supporting the earlier results obtained that the HWE has the ability to protect the gastric mucosa from damage by ASA.

Fig. 8.3.1 shows that all of the formulations with lactose as diluent retained the cytoprotective (antiulcer) activity of the diluent, irrespective of the binder type used. They

Fig. 8.3.1. Effect of Formulation on Anti-ulcer Activity of HWE
(Lactose as diluent)

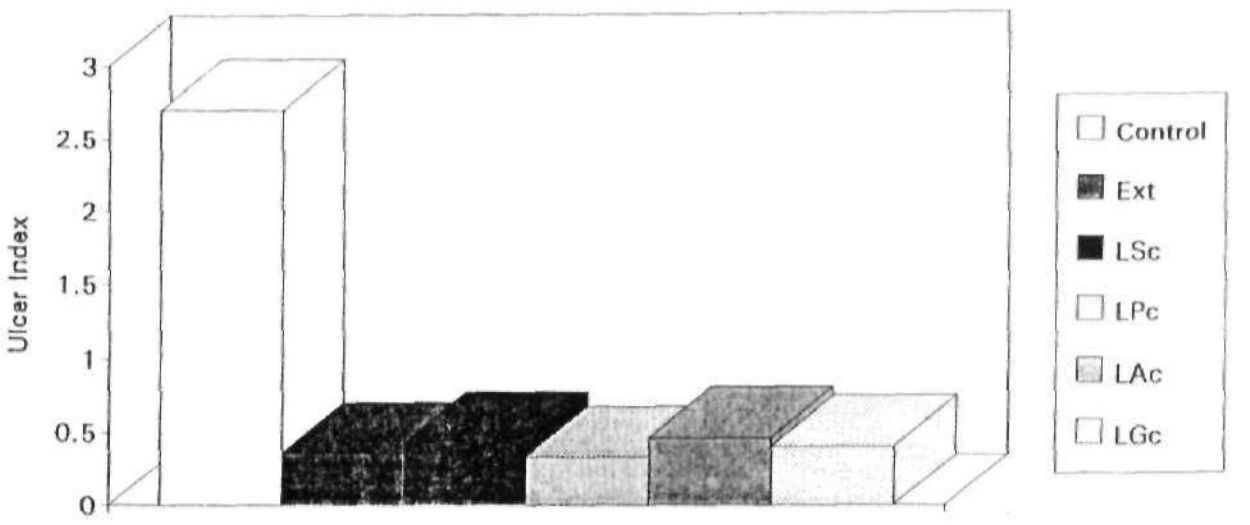


Fig. 8.3.2 Effect of Formulation on Anti-ulcer Activity of HWE
(Aerosil as diluent)

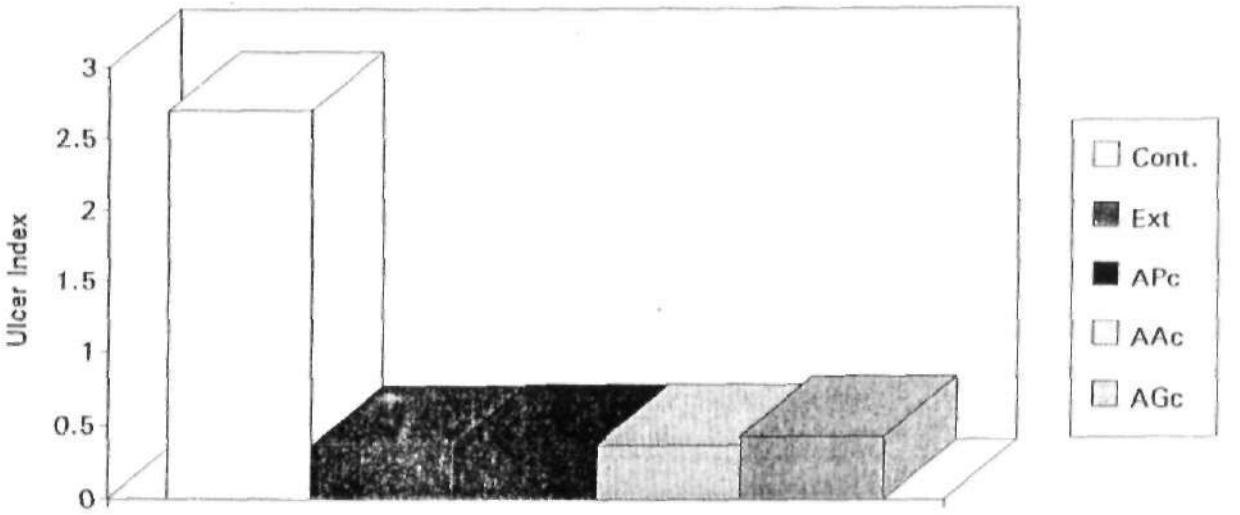
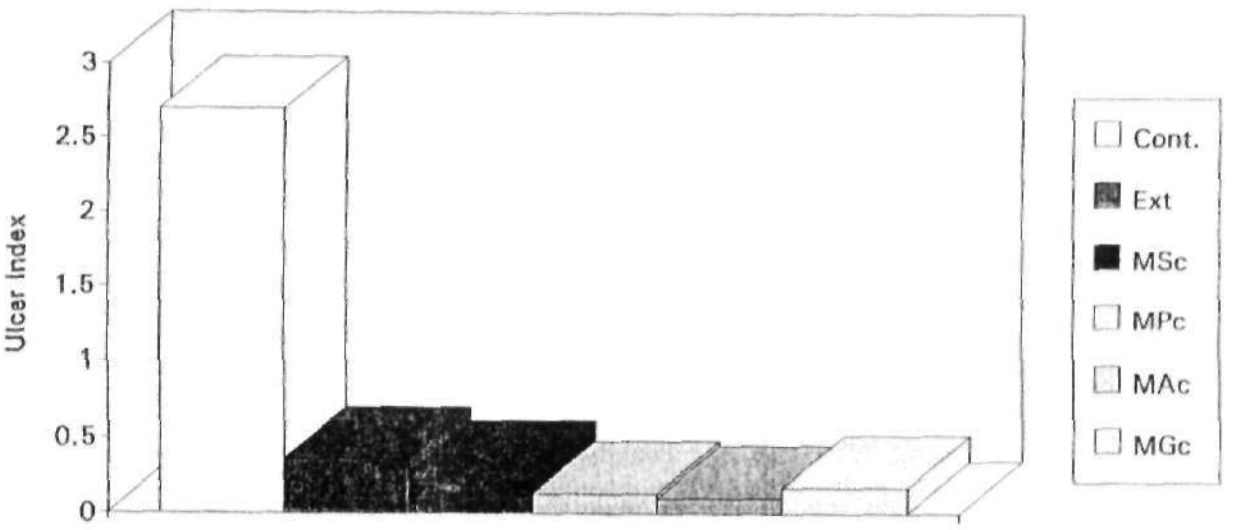


Fig. 8.3.3. Effect of Formulation on Anti-ulcer Activity of HWE
(MgCo3 as diluent)



(the formulations) reduced the ulcer index significantly ($P<0.5$). Although there were slight differences in the extent of reduction of the ulcer indices by the different formulations and the extract, statistical analysis showed that these differences were not significant.

Fig. 8.3.2 also shows that the use of magnesium carbonate (heavy) as diluent, and starch paste, PVP, sodium alginate and gelatin as binders did not affect the antiulcer activity of the extract. The differences in the extent of reduction of the ulcer index between the binder types were found not to be statistically significant ($P<1.0$). The extracts formulated with heavy magnesium carbonate as diluent however had the best antiulcer effect relative to the other diluents used. Magnesium has some antacid activity and is in fact administered along with aluminium hydroxide to improve its activity but mainly to reduce its ($AlOH_3$) constipating side effect. This might explain this observation.

The use of aerosil as diluent with the various binders did not affect the antiulcer activity of the extract (Fig.8.3.3). As in the other cases, all the formulations had similar properties with the unformulated extract, with the slight differences between them not being significant.

8.4 CONCLUSION

Fingerprints were established for the extract using three different methods - TLC, spectroscopy and pharmacological means.

The results from the TLC and biological studies indicate that none of the formulation additives had any significant effect on the "finger prints" of the extract. This is as would be expected since these additives are expected to be inert and not interact with the drug.

Tablets with magnesium carbonate as diluent however had some effect on the antiulcer activity.

While tablet formulations containing aerosil and lactose as diluent also did not affect the spectral finger print of the extract, those with heavy magnesium carbonate as diluent had quantitatively different spectra. This probably indicates some interaction (adsorption) between magnesium carbonate and the extract and would indicate the need for the use of more than one "fingerprinting" method since the other two methods did not detect this difference. It could also be that the effect was so minimal as not to be detected by the others.

8.5 INVESTIGATIONS INTO THE QUANTITATIVE REDUCTION OF HWE BY MAGNESIUM CARBONATE (HEAVY) RELATIVE TO UNFORMULATED EXTRACT

8.5.1 Introduction

On spectral scan of the various formulated products, it was found that those tablets that were formulated with heavy magnesium carbonate as diluent had spectra that were less than those obtained for the 'pure' drug. Although this did not result in any loss of biological activity it was thought necessary to carry out some further investigations into this observation. Since magnesium carbonate (heavy) is an adsorbent with a large surface area, it is possible that the observation could have been a result of some irreversible adsorption of the extract to the diluent.

Adsorption is a surface phenomenon and may be defined as the concentration of a substance on the surface of another substance or at the interface of two substances. The substance that attracts the molecules to its surface is called the adsorbent and the attracted molecules, the adsorbate. The degree of adsorption is largely dependent on the amount of the adsorbate, although other factors, such as temperature, pressure, concentration and physical state are also important. Adsorption is usually physical in nature and is associated with van der Waal's forces. There are however a few cases where adsorption is due to chemical reaction and is referred to as chemisorption. Adsorption from a gas or liquid onto a solid interface can be considered as an attempt to reduce the surface free energy of the solid (Martins and Camarata, 1983) Non-specific adsorption will occur if the solute is surface active and if the surface area of the solid is high (Zografi *et al*, 1990).

The adsorption of solute molecules from solution can be treated in a manner analogous

to the adsorption of molecules at the solid/gas interface. This has resulted in the description of a number of equations, to define the best isotherm by substituting solute concentration for vapor pressure in the gas equations. Based on these assumptions and equations, two types of isotherms are recognised - Type I isotherms which assumes the formation of a monolayer, and Type II, which results from the formation of a monolayer followed by multilayer formation. The Type I isotherms are described by the Langmuir adsorption isotherm which can be expressed as

$$\frac{C}{x/m} = \frac{1}{ab} + \frac{1}{b} C$$

Where x = weight of adsorbate (mg) adsorbed by m grams of adsorbent; C = the equilibrium concentration (mg/100ml) while a and b are constants.

A plot of $\frac{c}{x/m}$ against C should yield a straight line, where the smaller the slope, the better is the adsorption.

Type II isotherms are described by the BET equation,

$$\frac{P}{(p_0-p)} = \frac{1}{ym^b} + \frac{b-1}{ym^b} \frac{p}{p_o}$$

Where P is the pressure of the adsorbate in mmHg at which mass y of vapor/gm of adsorbent is adsorbed; p_o is the vapor pressure when the adsorbate is saturated with vapor, ym^b is the quantity of vapor adsorbed/unit of mass of adsorbent when the surface is covered with a monomolecular layer, and b is a constant proportional to the difference between the heat of adsorption of the gas in the first layer and the latent heat of condensation of successive layers.

Approximate adsorption from solution can be measured by separating solid and solution and either estimating the amount of adsorbate adhering to the solid or the loss in

concentration of adsorbate from solution (Zografi *et al*, 1990). In this investigation the loss in concentration of adsorbate from solution was determined.

8.5.2 Materials and method

8.5.2.1 Materials

HWE, Heavy magnesium carbonate

8.5.2.2 Method

(a) Enough of the hot water extract was dissolved in boiling water in order to obtain a solution of the required concentration

(b) The hot water extract powder was mixed with heavy magnesium carbonate in a blender. Different proportions as shown on Table 8.2 were used. The mixtures were then transferred into enough boiling water to give the required concentration of hot water extract in solution. This suspension was left to stand for 24 hours, and filtered through a membrane filter of 0.2μm pore size. The filtrate was analysed for hot water extract content spectrophotometrically at a wavelength of 274nm.

Table 8.2: Composition of hot water extract (HWE) and heavy magnesium carbonate mixtures.

S/No	HWE : $Mgco_3$	
1	10	0
2	20	0
3	25	0
4	30	0
5	40	0
6	10	30
7	20	30
8	25	30
9	30	30
10	40	30

8.5.2.3 Results and discussion

A loss in concentration of HWE was observed at all the concentrations of HWE used.

Table 8.3: Comparative concentrations of HWE and HWE/MgCo3 mixture.

Conc. of HWE mg/ml	Conc. of HWE in HWE/$Mgco_3$ mixture
151.84	112.13
307.70	290.06
379.18	314.72
455.86	369.08
599.22	511.38

Fig. 8.4 shows the plot of C/x/m versus C for the hot water extract (HWE) - heavy magnesium carbonate mixture.

Fig. 8.4. PLOT OF C/x/m VERSUS C

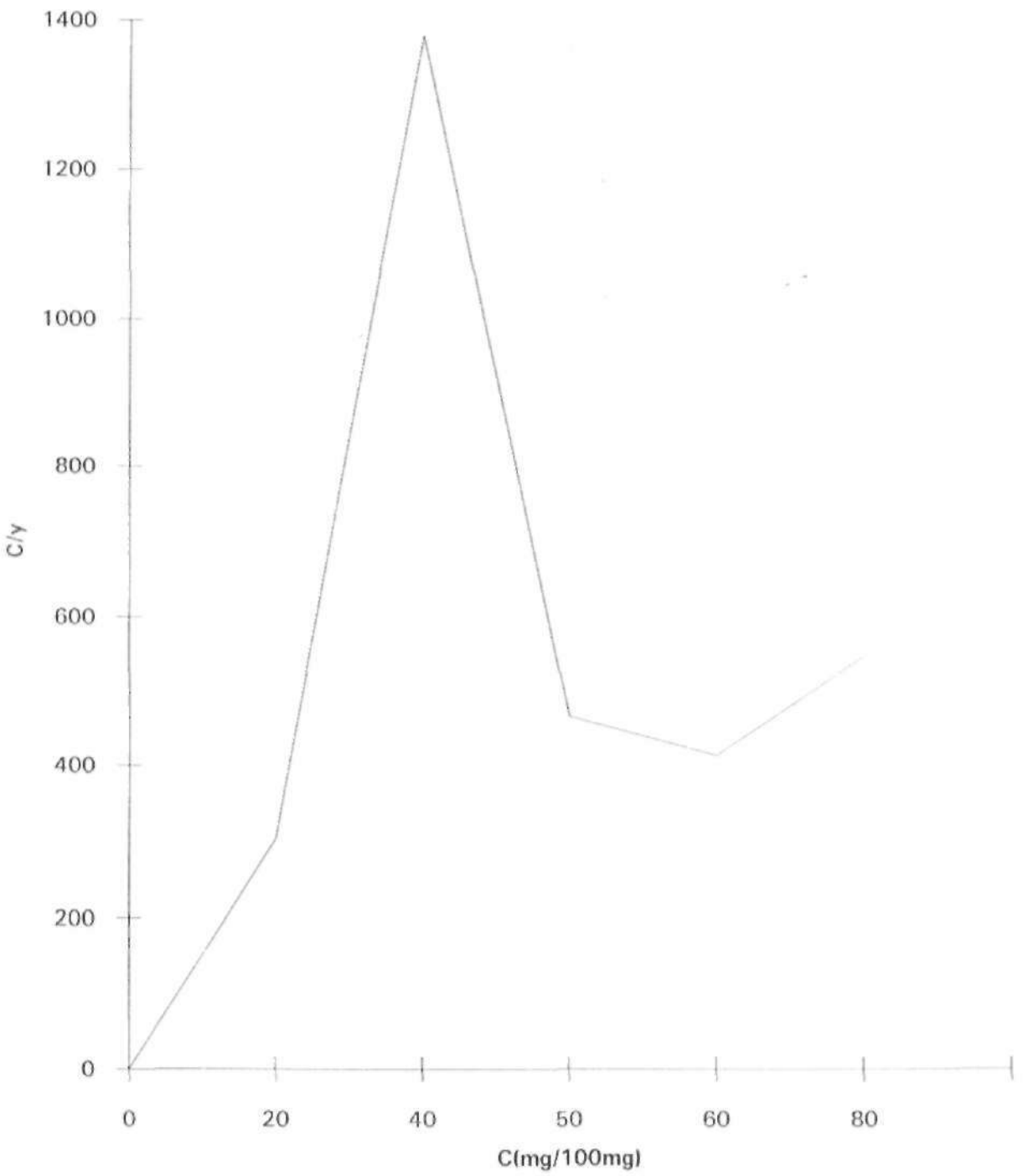


Table 8.4: Values from the Plot of C/x/m against C

C (mg/100ml)	x (mg)	m (g)	y	c/y
20	1.99	30	0.066	303
40	0.88	30	0.029	1379.3
50	3.22	30	0.107	467.29
60	4.34	30	0.145	413.79
80	4.39	30	0.146	547.95

Note : (1) x is the difference between the acutual conc. of HWE and the conc of HWE in HWE/$MgCo_3$ mixture expressed in mg.
(2) m is the amount of adsorbent, magnesium carbonate.
(3) y = x/m

The c/y values did not have a consistent pattern, with an initial rise and then subsequent decrease in the values and finally another slight increase. The non -linear nature of the plot indicates that the uptake of the HWE by heavy magnesium carbonate did not follow the Langmuir adsorption isotherm.

8.5.2.4 **Conclusion**

If the assumption that the fall in concentration of HWE with the addition of heavy magnesium carbonate is due to adsorption, the results would therefore indicate that it is not a Type I adsorption since it did not fit the Langmuir isotherm. It is most probably a Type II adsorption with multilayers of the HWE molecules on the adsorbent (heavy magnesium carbonate).

CHAPTER NINE

CONCLUSION

Extracts of the leaf of *Ficus sur* have been investigated for ulceroprotective (antiulcer) activity in rats. All of the extracts tested as well as the mixture of all four extracts were found to possess significant antiulcer activity. The only exception was the hexane extract which seemed to have ulcerogenic activity. The extracts were also found to be safe at the doses used, which was well below their LD_{50}. As would be expected of an antiulcer drug, the water and methanol extracts possessed reversible smooth muscle relaxative effect comparable to nor-adrenaline. The hot water extract was the best of the extracts with respect to these properties.

The methanol extract was also found to posess activity against the Gram positive bacillus, *E. coli*, which is similar to *H. pylori*. This would indicate the need to investigate the anti-*H. pylori* activity of this extract.

Compaction studies using the Heckel equations showed that most of the formulations had Type B characteristics. This would imply that good strong compacts would be expected from them. Some of the formulations, 5% starch paste/lactose and 12.5 and 17.5% gelatin/$MgCo_3$, modified the behaviour of the diluents to give Type C-like characteristics indicating a softening of these diluents.

Several formulations were prepared in order to develop a suitable formula for tablets of the HWE. Three different diluents - lactose, heavy magnesium carbonate and aerosil - with four binders, starch paste, PVP, sodium alginate and gelatin, at three concentration levels were used. All the granules had good flow properties. Formulations containing

lactose as diluent produced tablets with good physical strength irrespective of the binder type or concentration used. Some of them, however, failed the disintegration test, while those with magnesium carbonate were not very strong although they had good disintegration and dissolution properties. With aerosil, the tablets with sodium alginate as binder had the best physical properties.

The surfactants - sodium lauryl sulphate and Tween 80 - included in the formulations, reduced the tablet physical strength but improved the disintegration and dissolution in some cases, depending on the surfactant type, concentration, as well as the binder and diluent types.

In order to improve the disintegration rate of the tablets containing lactose as diluent without excessively reducing the physical strength, 0.2% SLS will be suitable for inclusion in the formulation as binders except sodium alginate. 0.2% Tween 80 can also be included with PVP as binder.

The optimal lubricant (magnesium stearate) for most of the formulations was between 0.1 and 0.2%w/w.

Three "fingerprints" were developed for the formulations. They were UV spectroscopy, thin layer chromatography and a pharmacological one. They showed that the formulation process and additives did not affect the extracts with respect to those containing lactose and acrosil as diluents. With heavy magnesium carbonate, however, there seemed to have a multi-layer adsorption of the extract detected by UV spectroscopy, while it seemed to have potentiated the antiulcer activity of the HWE.

A formulation with lactose as diluent, maize starch as disintegrant, 7.5% PVP or gelatin

as binder and 0.2%w/w magnesium stearate as lubricant can be used in formulating suitable tablets of HWE. Where the other binders must be used, 0.2% SLS should be added to the disintegrant. Aerosil can also be used as diluent,especially with sodium alginate as binder. Heavy magnesium carbonate can be included in the formulation of this extract, as it seems to improve its antiulcer activity. The amount used must however be carefully determined to ensure the production of tablets with good physical strength and elegance.

The results have shown that suitable tablets can be produced from the hot water extract of the leaves of *Ficus sur* once the additives are carefully selected. It also shows that efforts in the development of formulations of herbal medicines should be encouraged.

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Table 1.1. Result sheet for weight variation test

QUICKPharma V2.2 Copyright 1993 CGS-GmbH-Hamburg CW406001

Ident no. >
Batch / Lot-No. > 002
Nominal/Filling > 730
Tolerances (+/- 5 +/- 10) according to average:
upper T2 limit > 828.5
upper T1 limit > 790.9

Product > ANTIULCER
Type/Form > Tablet
Tare-/Capsuleweight > 0
lower T2 limit > 677.9
lower T1 limit > 715.6

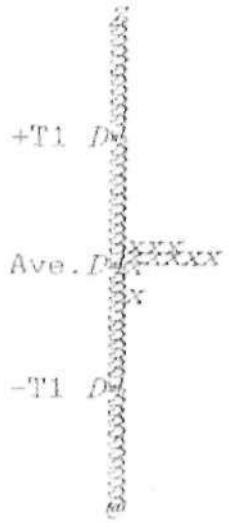
Number of tests already done > 1 Number/Test > 10
Total amount of weighed parts > 10

Test results: Date 19.09.1996 at 15:20:09

753.9	754.3	754.1	755.5	742.3	751.6	755.2	756.2	754.2	754.3

maximum weight	> 756.2
minimum weight	> 742.9
average	> 753.22
parts higher than +T2	> 0
parts higher than +T1	> 0
parts within T1 range	> 10
parts lower than -T1	> 0
parts lower than -T2	> 0
max. + deviation from nominal	> 26.2
max. - deviation from nominal	> 0.0
max. + deviation from average	> 2.98
max. - deviation from average	> 10.32
Span	> 13.3
Variance	> 14.51
Standard deviation	> 3.81
relative standard deviation	> 0.51

+ max. line: 5 pcs.

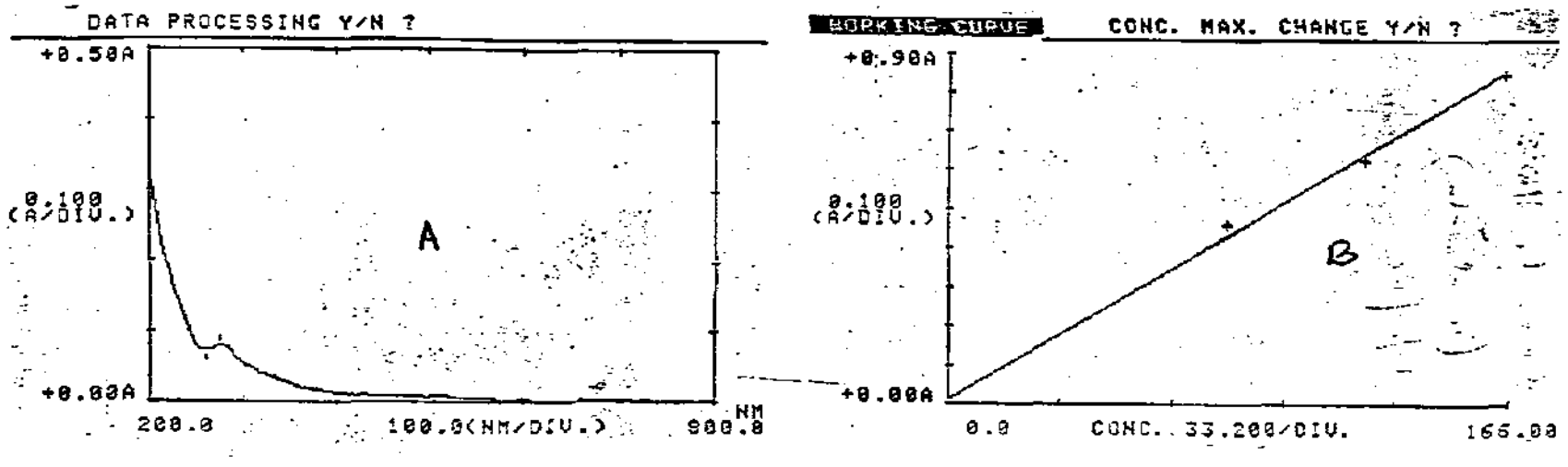


Operator: KUNLEMOSS

IG:I2421 STAV:1 TARE:20 POFF:0 VIB1:4 FQU1:4 VIB2:4 FQU2:4 DELY:1 +/-%:50 PULS:4 SING:1 CONF:5 GRAF:1

Appendix 1

Fig. 2.1. Spectral characteristics for dissolution studies



A. Scan of the HWE

B. Beer Lambert's Curve for HWE

Appendix 2