TABLETING AND COMPACTION PROPERTIES OF *ANOGEISSUS LEIOCARPUS* AND *PROSOPIS AFRICAN A* EXTRACT SCREENED AS AN ANTIASTHMATIC.

ISIMI CHRISTIANAH YETUNDE
BSc Pharm. MSc Pharmaceutics.

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Department of Pharmaceutics and Pharmaceutical Microbiology,
Faculty of Pharmaceutical Sciences, Ahmadu Bello University,
Zaria- Nigeria

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, Dr. J.E. Ojile and Dr. Y.K.E. Ibrahim both 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.

Ctisimi 3/7/2001
ISIMI, CHRISTIANAH YETUNDE
Department of Pharmaceutical Technology and Raw Material Development, National institute for Pharmaceutical Research and Development, Idu -Abuja

CERTIFICATION

This thesis titled, TABLETING AND COMPACTION PROPERTIES OF *ANOGEISSUS LEIOCARPUS* AND *PROSOPIS AFRICANA* EXTRACT SCREENED AS AN ANTIASTHMATIC by ISIMI, CHRISTIANAH YETUNDE meets the regulations governing the award of degree of DOCTOR OF PHILOSOPY (pharmaceutics) of AHMADU BELLO UNIVERSITY, ZARIA, NIGERIA, and is approved for its contribution of knowledge and literary presentation.

EXTERNALEXAMINER Date
Prof. T.A. Iranloye
B.Pharm (Ife), M.Sc (Iowa), Ph.D. (London)
Department of Pharmaceutics and Pharm. Technology.
Faculty of Pharmaceutical Sciences, University of Jos,
Jos, Nigeria.

INTERNAL EXAMINER 3/07/2007 Date
Prof. I. Abdu-Aguye; MBBS (Ibadan)
M.Sc Pharmacology (A.B.U), FMCP
Prof. Of Clinical Pharmacology
Dean, Faculty of Medicine
Ahamadu Bello University, Zaria

INTERNAL EXAMINER 31/07/2007 Date
Dr. Y.K.E. Ibrahim
B.Sc.Pharm(ABU,Zaria),M.Sc.Pharm(ABU,Zaria),Dr.Sc.hum.(Heidelberg, Germany)
Department of Pharmaceutics and Pharmaceutical Microbiology,
Ahamadu Bello University, Zaria

HEAD OF DEPARTMENT Date

Dr. Y.K.E. Ibrahim
B.Sc.Pharm(ABU,Zaria),M.Sc.Pharm(ABU,Zaria),Dr.Sc.hum.(Heidelberg, Germany)
Department of Pharmaceutics and Pharmaceutical Microbiology,
Ahamadu Bello University, Zaria

DEAN., POST-GRADUATE SCHOOL Date

Prof. S.B. Ojo
B.Sc., M.Sc., Ph.D., FNIP
Ahamadu Bello University, Zaria

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DEDICATION

TO MY CHILDREN

OLUBUKOLA

BABATUNDE

YEWANDE

OLUWASEUN

ABSTRACT

Anogeissus leiocarpus and *Prosopis africana* are popular herbal anti-asthmatic drugs used in Northern Nigeria. However there is always the problem of standardisation. This can be over come by formulating the plant extract into a pharmaceutical dosage form. Tablets offer several advantages over the other oral medications such as precision of dosage, durability of physical characteristics for extended period of storage and stability of chemical and physiological activity of drugs.

The stem barks of *Anogeissus leiocarpus* and *Prosopis africana* were extracted using cold (maceration) and hot water extraction methods. R_r values of spots obtained on the TLC plates and the Àmax on the UV were similar for extracts obtained from both methods of extraction, indicating that the heat involved in the extraction process did not affect the extract chemically. *Anogeissus leiocarpus* was found to contain saponins, tannins, flavonoids, and glycosides, while Prosopis africana was found to contain in addition alkaloids. The combined extract was found to contain glycosides, alkaloids, saponins, tannins and flavonoids.

To justify the use of the stem barks of *Anogeissus leiocarpus* and *Prosopis africana* in the management of asthma, the hot water extracts of *Anogeissus leiocarpus; Prosopis africana* and the 50:50 combinations were investigated for anti asthmatic activity using different laboratory animals and pharmacological models. The LD_{50} of the combination was found to be higher than either of the LD_{50}'s of individual extracts indicating that an interaction which lead to the formation of a less toxic extract may have taken place. The three extracts were found to have a dose dependant relaxation on the isolated rabbit jejunum, isolated guinea pig trachea and guinea pig bronchospasm. A synergistic effect was observed when the combined extract was used on the rabbit jejunum. A dose dependant anti-inflammatory activity on the induced rat paw oedema was observed with all three extracts, and combination of the extracts produced an additive anti-inflammatory effect. The anti-inflammatory activity of the extract was used as a biological 'fingerprint' to test the effect of

formulation process and additives on the activity of the extract and it was observed that the excipients did not have negative effect on the anti-inflammatory activity of the extract.

Two diluents, lactose (water soluble) and $MgC0_3$ (water insoluble), were used for the formulations. The granules produced using $MgCO_3$ were generally smaller, had lower moisture content but had better flow properties. While those produced with lactose as diluent had higher moisture content, were bigger and had lower flow properties. The tablets produced with $MgC0_3$ were softer (lower hardness), more friable and had longer disintegration and dissolution rates when compared to those produced with lactose.

Four binders (water, starch, gelatin and PVP) were used and Binder type and concentration were found to affect the properties of resulting granules and tablets. Granule size, true density, % compressibility and moisture content were found to generally increase with increasing binder concentration. Granules produced with starch as binder gave the best flow properties and angle of repose. There was a general increase in tablet hardness, disintegration and dissolution times with increase in binder concentration from 2.5 -5.0%.

Three disintegrants (starch, cross-linked PVP and treated starch) were used. The type and concentrations of the disintegrants were varied with intention of improving the disintegration and dissolution rates of the formulation. Inclusion of sodium lauryl sulphate in the formulation was found not to have produced the expected decrease in disintegration and dissolution rates. Cross- linked PVP (a super disintegrant which has been reported to be a very effective disintegrant even in low concentrations) significantly reduced the disintegration and dissolution times of the tablets but these tablets were softer and more friable when compared with those produced with starch as disintegrant. Pharmaceutically acceptable tablets were produced when lactose as diluent (60%) and starch as binder (2.5%) and disintegrant (5%) are used.

Compaction studies using the Heckel equation showed that formulations prepared with lactose consolidated mainly by plastic deformation, characteristic of type A material, while those formulated with $MgC0_3$ as

diluent consolidated by an initial fragmentation followed by plastic deformation; which is characteristic of type B material. This finding suggested that the extract modified the consolidation characteristics of lactose, which is a known type B material. The tensile strength of the tablets formulated with $MgC0_3$ increased with increasing compression pressure from 56.58 to 113.16 MNm^{-2} while tensile strength of tablets formulated with lactose was highest at the compression force of 84.87 MNm^{-2}.

The results have shown that the use of the plants *Anogeissus leiocarpus* and *Prosopis africana* in the management of asthma is justified. The main research objective of formulating these plants into a pharmaceutically acceptable dosage form was also accomplished.

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CHAPTER ONE

1.0 GENERAL INTRODUCTION

Disease treatment and prevention in Nigeria were for many years handled solely by traditional healers. The healers evolved various methods for preventing and treating prevalent diseases. It is an established fact that many diseases were and are still being treated in traditional medical practice with great success. The diseases that have or claimed to have been treated with success include mental illness, asthma, diabetes, hypertension, pains, sickle cell anaemia, etc (Akubue, 1986)

Traditional medicine is used by a large number of the Nigerian population for their physical and psychological health needs. Medicinal plants have become the focus of intense study recently in terms of conservation and also to know if their traditional uses are supported by actual pharmacological effects or merely based on folklore. With the increasing acceptance of traditional medicine as an alternative form of health, the screening of medicinal plants for pharmacological activity is very important.

Combination of *Prosopis africana* and *Anogeissus leiocarpus* is widely used in the northern part of Nigeria in the treatment and management of asthma. Preliminary investigations showed that this herbal remedy is tremendously useful in asthma therapy (Mallama Azija–Personal communication). However because of absence of specific standards of quality and dosage for traditional medicine portions, there have been some skeptism and fear about them. To ensure standardization in the dosage regimen, formulation into a suitable dosage form that will ensure proper handling and reproducibility of dose is called for. Formulation of these plants into tablets will ensure proper standardization and improve acceptance, thus ensuring

cheaper management of asthma as well as allay the fear and skeptism associated with the use of traditional herbal medicines.

1.1 HERBAL MEDICINE.

Herbal medicines refer to plant-derived materials or preparations with therapeutic or other human health benefits that contain either raw or processed ingredients from one or more plants. Herbal medicines, as the major remedy in traditional medical systems, have been used in medical practice for thousands of years and made great contributions to maintaining human health. More than 70% of the world's population in developing countries still rely on herbal medicines to meet their health needs.

Plants have been serving the animal kingdom as its source of energy (food, fuel) as well as its means of shelter and sustenance since the very beginning of its existence on earth. Apart from providing food, fuel and shelter, plants synthesise a large variety of chemical substances. These substances (secondary metabolites) differ from plant to plant thus providing a tremendous reservoir of various chemical substances with potential therapeutic properties (Ghani, 1986).

A survey by UNCTAD has shown that 33 percent of drugs produced by the industrialized nations are plant-derived (UNCTAD/GATT, 1974). Sofowora, (1981) put the figure at 60% with the inclusion of microbes. According to Myers (1982), about 80% of present day medicines are directly or indirectly derived from plants, and out of the estimated 250,000 - 500,000 species of higher plants less than 15% are known to have been investigated pharmacologically (Farnsworth and Bengel, 1977). Only seven drugs of natural origin used in USA are known to be synthesized commercially, namely emetine, caffeine, theobromine, theophylline, pseudoephedine, ephedrine and papaverine (Farnsworth and Morris, 1976)

1.1.2 Standardization of Herbal Potions.

The WHO has shown a lot of support and interest in the use of herbal medicines that have been tested to be safe and pharmacologically effective. To encourage research into traditional medicines a paper on guidelines aimed at setting standards for evaluation of quality, safety and efficacy has been published. Traditional medicine is the most ancient art of medical practice on which even today 80% of the rural population of many developing countries of the world depend for maintaining their health and well being. But because of the absence of specific standards of quality and dosage for traditional medicine portions, there have always been some scepticism and fear about them. The major criticism against them is that they are not standardised by any specific parameters nor are they dispensed to patients in specified doses or with specific directions for use.

Even with these shortcomings, traditional medicine has been practiced quite commonly throughout the world for centuries and the world, particularly the third world countries, cannot afford to do away with this system in maintaining the health of the teaming millions. Thus there is an urgent need for developing some systems and methods of standardization of traditional medicine potions in order to improve their general acceptability, allay the scepticism and fear of people, avoid dangers of toxicity, side effects and over-dosage and ensure a certain minimum level of hygiene in their preparation (Abdul- Ghani 1986).

Sofowora (1979) suggested that for the country to become self-reliant in their pharmaceutical services, it must promote the use of locally available medicinal plants for the preparation of drugs. He also made proposals listed below through which this self- reliance would be achieved.

1. Developing countries must reduce unwarranted importation of drugs- only essential drugs should be imported (WHO 1977). Drug import bill for Nigeria alone was about ₦ 120 billon (US $ 200 million) in 1977 (Ekunife, 1978).

2. They should attempt to produce some pharmaceuticals locally,
3. They should utilise locally available medicinal plants as substitutes for other drugs.

A lot of effort has been put towards research in terms of investigation of biological activity but very little has been done to formulate these products into suitable dosage forms. Moreover, most of these herbal medicines even though pharmacologically effective are usually unhygienic, bulky and lack reproducibility of dose. These short falls can only be over come by standardization and formulation into suitable dosage forms.

1.2 The Plants

1.2.1 *Anogeissus leiocarpus*

Anogeissus leiocarpus (D.C.) Gull & Perr belongs to the family Combretaceae. The plant grows widely in most of the savannah area, from the driest region to the borders of the forest zone. The bark is generally grey, scaly and exudes a not very soluble gum called marike in Hausa.

The gum is of very good viscosity and useable as a substitute for, or adulterant of gum arabic. It can be used in pharmacy as an emulsifying agent (Oliver, 1960). The plant has found a wide use among Nigerian herbalists and its infusion or decoction is used as cough medicines, while the pulped roots are applied to wounds and ulcers. The leaf decoction is also used for washing and fumigation. Some parts of the tree are boiled in water together with potash to cure stomach pains and for schistomiasis in Northern Nigeria (Mantosh, 1979).

The hot water extract of the bark is used in Guinea to disinfect syphilitic ulcers (Vasilera, 1969). In Niger, the hot water extract is also reported to being used as an antitussive (Baoua *et al*, 1976). The hot water extract of the leaf is used in Guinea against diarrhea for women after parturition. The decoction of the leaf is used in Nigeria to treat malaria (Bhat *et al*, 1990). While the root extract is used as an emmenagogue in Senegal (Berhault, 1974). The root is used as chewing stick (El-Said, *et al* 1971; Odusanya *et al*, 1979; Asubiojo *et*

al, 1982; Sanni and Okor 1983; and Bhat *et al,* 1990). In Senegal, the bark decoction is used in treating diarrhea. The powdered bark in combination with Terminalia sp. (Combretaceae) is applied to gums for toothache whereas the decoction of the bark from the twig is used to clean sores and syphilitic chancres (Dalziel 1937).

Ibrahim (1992) studied the antihelmintic activity of the hot water extract of the aerial parts of the tree and found it to have a lethal concentration (LC_{50}) of 84.6 mg/ml. The antitrypanosomal activity of the decoction and the hot water extract of the plant were investigated by Yaian *et al,* (1997). The hot water extracts and decoction were found to be inactive against Trypanosoma Brucei Gambiense at 0.01, 0.03, and 0.10 ml/gm. and have weak activity against Schistomosa at a concentration of 1000 PPM (Elsheiku *et al*, 1990). Ibrahim *et al,* (1997) studied the antibacterial effects of the leaf, stem and root bark and they found the plant to have useful antimicrobial properties that tend to support its traditional use. The hot water extract of the leaf has been found to have antibacterial activity against *Staphylococcus aureus* at 62.5 mg/ml, *Staphylococuss (pyogenes and pneumoniae*) at 125 µg/ml, and against *Haemophilus influenzae* and *Moraxella Catarrhalis* at 250.0 µg/ml. The Methanolic extract was found to be more effective against all these organisms at a lower concentration (Sanogo *et al* 1998) The benzene, chloroform, ether and petroleum ether extracts of the seeds have been found to be active against plant pathogens (Bhatt and Saxena, 1979).

The general toxic effect of the extract on mice was studied and an intragastric dose of 50.0 gm/Kg was found to be inactive, while a dose of 20.0 gm/kg i.p was active and led to death within 60 seconds. With the i.v route a dose of 8.0 gm/kg was found to be effective and lead to death in 5 seconds. The ethanol (95%) extract of the stem bark has been found to have some CNS depressant activity on mice at dose of 25.0mg/kg i.p (Fong *et al*, 1972).

Adegoke *et al,* (1968) reported the leaves and barks to be rich in tannin and containing in addition saponin, sterol and trace of alkaloid (Basua *et al*,

(1976) reported the absence of alkaloids in the bark extract. Ibrahim *et al*, (1997) also reported the presence of tannins, saponins, flavonoids and glycoside in the water extract of the bark.

1.2.2 *Prosopis africana*

Prosopis africana Taub-Hall belongs to the family Mimosaceae and is popularly called Kiriya in the Northern part of Nigeria. It is a Savanna tree readily distinguished by the rough bark, pale drooping foliage with small pointed leaflets and sausage shaped fruits. It is about 12-18m high and up to 1m in girth (Dalziel 1937). The seeds are used for food in Northern Nigeria.

The bark has been used as a dressing or to make a lotion for wounds. In Northern Nigeria the decoction of the bark is used for the treatment of back pain (personal communication). The hot water leaf extract is reported as being used as an aphrodisiac in Sudan (Lewis and Elvin-Lewis, 1977). The hot water extract of the combination of fresh leaves of *Prosopis africana* and those of *Tamarindus indica* are reported as used in the treatment of malaria in Nigeria (Oladipo, 1990). In Dahomey, the water infusion of the leaf, root and stem bark is used to treat sleeping sickness (Kerharo, 1974). While in Senegal, the hot water extract of the dried stem bark is been used as a cardiotonic. In Mali and in Nigeria the dried root and stem are been used as chewing sticks (Wolinsky *et al*, 1983 and Delaveau *et al*, 1979). The teeth cleaning effect of the half dried twig has also been reported by Sote and Wilson, (1999).

The antibacterial activity of the ethanolic extract has been investigated and it was found to be active against *Pseudomonas aeruginosa* and Staphylococcus species with MIC of 1.0 mg/ml, but was inactive against *Escherichia coli*, *Klebsiella* species, *Proteus vulgaris* and *Salmonella* species (Adoum *et al*, 1997) The methanol extract of the dried stem bark was found to be active at 15.0 mg/ml against *Sarcina lutea* (Laurens *et al*, 1985). The hot water extract of the half dried twig was found to be active against *Camphylobacter rectus* and *Porphyromonas gingivalis* at MIC of 4.0 mg/ml and > 10.0 mg/ml respectively (Sote and Wilson, 1999).

Quite a number of research work have been carried out on the use of materials derived from P*rosopis africana* as tablet excipients. e.g. the binding, and disintegrant properties of the gum from the seeds have been studied (Adikwu *et al*, 1992a,Adikwu *et al*, 1992b), Suspending and emulsifying properties of the seed gum as well as the evaluation of the seed gum as an excipient for sustained release tablets have been carried out (Adikwu, 1994; Adikwu *et al*, 1994: Adikwu *et al*, 1997). Chukwu and Chukwu (1996) also studied the swelling properties of polymer obtained from *Prosopis africana* and its disintegrant mechanism of action.

Several authors have reported the presence of alkaloid in different parts of the plant. Among alkaloids isolated are prosopine and prosopinine by Chimque (1966) and cassinine in the entire plant by Qui *et al* (1982), Khuong-Huu *et al* (1982), isolated three alkaloids prosafrine in addition to prosopine and prosopinine from the stem bark of P*rosopis africana*. Protein (25.74%) was reported to be present in the seeds (Balogun and Fetuga, 1986). Delaveau *et al*, (1979) reported the absence of quinones but the presence of saponins, sterols, tripertenes and tannins in the stem.

1.2.3 *Anogeissus leiocarpus* & *Prosopis africana*

The two plants Prosopis africana & Anogeissus leiocarpus are commonly combined in the treatment of various disease conditions caused by bacteria, fungi and helminthes (Iwu, 1993). The combinations of different parts of the plants have been used to treat diseases such as respiratory tract infections, gonorrhoea, boils, and wounds in the Hausa societies (Jinju, 1990). Traditional healers use a 1:1 infusion of the combined plants as a remedy for asthma management. The infusion is prepared by boiling the powdered stem barks in a quantity of water. The supernatant is taken, half a glass two times a day (personal communication) Mallama Azija Ayhu (Herbal consultant with N.I.P.R.D Idu- Abuja)

1.3 ASTHMA.

Asthma is a disease of the airways, (the tubes through which people breathe). The causes of airflow obstruction in asthma are swelling of the airways, excessive mucus production, and inflammation of the airways with eosinophils and neutrophils, and airway smooth muscle contraction. Asthmatic airways are full of secretions, mucus-containing eosinophils- (white blood cells) that reflect an underlying inflammation. In such cases, the epithelial cells that line the airways have been lifted off and the airways are denuded. The muscles contract, closing the airways, stimulating the glands (which are very reactive) to produce large quantities of mucus.

Asthma is characterized by sudden or insidious paroxysms of expiratory dyspnoea and wheezing, over inflation of the lungs, and cough, which may be brief or may last for weeks. Hypertrophy of the bronchial wall, oedema of the bronchial mucosa, and accumulation of secretions in the bronchial lumens are due to generalized bronchial airway obstruction (Norman, 1970). Grant,(1978) on the other hand defined asthma as being characterized by an increased responsiveness of the airways to various stimuli including immunological, physical, chemical, infectious and emotional factors.

In asthma, it is probable that bronchi spasm, mucosal oedema and bronchial secretions are the principal mechanism producing airway obstruction, which is localized primarily in the small bronchioles. The expiratory airways obstruction leads to hyperinflation or emphysema of the lungs (Norman, 1970).

Asthma has become one of the most common non- communicable diseases in industrialized and non-industrialized countries of the World and epidemiological studies suggest that its prevalence, severity and mortality are rising at a time when mortality from other common treatable conditions is falling (Barnes, 1991). While the reasons for these situation is not yet clear, there is increasing evidence that environmental factors, such as increased exposure to allergen (particularly house dust mite, antigens) and atmospheric pollutants may be important.

Asthma exists worlds wide and affects individuals of all ages. The incidence of asthma is about 5% or more in the general population (Amos 1996). Saul Rosen, (1997) reported that asthma affects one in every five house-hold, and one in every seven children are thought to be a victim; a higher incidence of asthma is reported in developed countries and in the upper socio-economic classes. More than 2,000 deaths each year is directly attributed to asthma, but this figure considerably under-estimates the morbidity caused by this illness. Taken as a whole, the allergic diseases are a major cause of absenteeism from schools and work place and absorb a large share of the national health in the United States (Grant, 1978).

1.3.2 Inflammation and Asthma

Inflammation is the response of the host to tissue damage, which may have a variety of causes including infection, physical injury or toxic chemicals. In asthma, inflammatory process is an integral part of the host's response to insult and is designed to protect the host against pathogens that threaten its integrity. Asthma as a disease is characterized by airway inflammation, thus Barnes (1989) stated that asthma even in its mildest form is an inflammatory condition.

The cardinal features of inflammation are present in asthma, and are important in the disease; cellular infiltration and activation participate in the airflow obstruction as well as increasing airway reactivity. Oedema is a major contributor to airflow obstruction and leads to increased airway fluid, which is often the cause of death in acute asthma (Kaline, 1976). There has recently been increasing emphasis on the use of anti-inflammatory treatment, such as inhaled corticosteriods, and Cromolyn sodium early in the treatment of asthma (Barnes, 1989).

The principle of modern therapeutic system in treatment of asthma is that treatment should be matched to severity of disease with emphasis on anti-inflammatory drugs to help prevent symptoms rather than over reliance on

bronchiodialators, which only provide short-term relief. However, both types of treatment obviously have a complimentary role to play in asthma management. The National Asthma Education Prevention Program (NAEPP) in a report on Guidelines for the diagnosis and management of asthma recommended a new stepwise approach to using medications that put a heavier emphasis on early use of anti-inflammatory medication (NAEPP, 1977)

Drugs used in the Management of Asthma.

1. β-adrenoreceptor agonist

Sympathomimetic or β- Adrenergic agents are group of medications that are widely used in the treatment of asthma. The stimulation of the sympathetic or adrenergic system produces a decrease of mucous gland production, a decrease in capillary permeability, and relaxation of bronchial smooth muscle.

Most of the β- adrenoceptor agonists used in management of asthma have activity on β-1, β-2 and α- receptors. Activity on the β-1 and α- receptors are considered as side effects. For over thirty (30) years, β- adrenoceptor agonists have been used routinely in the treatment of bronchial asthma and this therapeutic use is derived from their ability to prevent and reverse bronchoconstriction (Amos, 1996). Examples of β-adrenoceptor agonists are: -

a) Epinephrine Hydrochloride (Adrenalin), which has been used in the treatment of asthma since the work of Beyer and Dale in 1910;
b) Ephedrine Sulphate (an alkaloid derived either from the plant *Ephedra equistina* or produced synthetically);
c) Terbutaline Sulphate (Bricanyl). This is the most effective β_2 anti asthmatic drug currently in the market. It has relative selectivity for β_2-receptor but has skeletal muscle tremor as side effect.
d) Salbutamol (Ventolin) Administered by inhalation or orally. The oral administration may produce limb tremor as a side effect.

2. Methyl-xanthenes:

The use of theophylline (a potent bronchodialator), effective in relieving the signs and symptoms of asthma has long been recognized. Methyl-xanthines inhibit destruction of intracellular Cyclic-AMP in the mast cell and basophil and secondarily block the release of histamine and other mediators.

Aminophylline is the most commonly used drug of this group, and is the ethylene diamine salt of theophylline. Side effects of all theophylline preparation include gastric irritation, nausea, vomiting headache, syncope hyperactivity and occasional diarrhoea.

3 Cromolyn Sodium.

Cromolyn Sodium is an important advancement in asthma management. The mechanism of action of cromolyn sodium is not entirely known but it inhibits phosphodiesterases and appears to stabilize the membranes of the mast cell; thereby preventing the release of mediators of anaphylaxis (Guy *et al*, 1979). Cromolyn sodium is administered by inhalation and is not of use in the management of acute asthma. The adverse reactions consist of dermatitis, gastroenteritis, myositis, urethral burning and pulmonary allergic granulomatosis (Guy *et al*, 1979).

4 Anticholinergic Drugs.

The use of anticholinergic drugs in asthma management is due to their bronchodilatory effect. In the past subcutaneous administration of atropine sulphate has been used to treat asthmatics, but the frequent side effect such as central nervous system stimulation, mydriasis and depression of salivary secretion, has restricted its clinical use. Ipratropium bromide (Alupent) is a newer drug, which lacks the deleterious effects of atropine but retains some of its beneficial properties.

5 Corticosteroids.

Corticosteroid therapy may be looked upon as a double-edged sword in the treatment of asthma. They are quite effective in alleviating asthmatic symptoms but the administration of these drugs may be fraught with a multitude of serious complications.

6 Herbal Drugs.

Many claims have been made as to the use of herbal drugs in the treatment of respiratory diseases in general and in particular, management of asthma. However, only a few of these herbs have been tested pharmacologically to verify their acclaimed potency.

Pavelta crasisipes has been investigated for its antiasthmatic activity and it was found to relax the guinea pig tracheal muscle, showed profound anti-inflammatory effects and had bronchodilatory activity in guinea pigs. These findings by Amos (1996) led to his conclusion that there is a correlation between the pharmacological activity and the use of the plant as antiasthmatic by the traditional herbalists. Investigations are currently being carried out on *Cammiphora africana, Prosopis africana*, *Anogeissus leiocarpus* and *Euphorbia hata* at NIPRD,Idu-Abuja

1.3 COMPRESSED TABLETS.

Drugs in their pure form are hardly ever directly administered because of certain inherent disadvantages. They are therefore formulated into different dosage forms, such as compressed tablets. Compressed tablets, which are the most popular dosage form, are solid dosage forms prepared by compaction of a formulation containing the drug with or without certain excipients (USP, 1990). The term, compressed tablet generally refers to a plain, uncoated tablet for oral ingestion, prepared by a single compression. The excipients, which are selected to aid the processing and improve the properties of the product, are binders,

fillers, disintegrants and lubricants. Tablets can be made in many sizes and shapes, with a variety of properties.

Tablets remain the most frequently employed dosage form throughout most parts of the world, because they offer several advantages over the other oral medications such as precision of dosage, durability of physical characteristics for extended period of storage, stability of chemical and physiological activity of drugs (Lachman *et al*, 1986).

Tablets are prepared by three (3) general methods; wet granulation; dry granulation (roll compaction or slugging) and direct compression. The purpose of both wet and dry granulations is to improve the flow of the mixture and/or enhance its compressibility. Whatever the method of tablet production the desire of a good formulator is to end up with pharmaceutically acceptable tablets. Such tablets should have qualities that include; ability to withstand the rigors of the mechanical treatment involved in production, packaging, shipment, and dispensing, freedom from defects such as cracks, chipped edges, discolouration, and reasonable chemical and physical stability under storage conditions. Such tablets should also posses the ability to release medicament in a reproducible and predictable manner.

1.4.1 Tableting

Most powders cannot be compressed directly into tablets because they lack inherent binding characteristics and often times exhibit poor flowability. Wet granulation is the traditional means which attempts to gather small particles into large, permanent aggregates resulting in improved flow and binding potentials (Lachman *et al*, 1986).

1.4.2. Wet Granulation

This is the oldest and most conventional method of tableting (Lachman *et al*, 1989). Despite the labour intensive and expensive nature, it persists because of its versatility. The process involves the addition of a liquid system (suspension, slurry, or solution) containing a binder to a powder, resulting in

agglomeration or granules, and formation of liquid bridges between particles. The tensile strength of the bond increases as the amount of binder liquid is increased (Banker and Anderson, 1989).

Formulation of tablets usually involves series of compromises in order to produce the desired properties. Correct selection and balance of excipient materials for each active or a combination of active ingredients is paramount to the formulator so as to achieve the desired objective (safe, effective, and highly reliable product).

To produce an affordable product, the cost of a new material or a particular processing step must be considered before a final tablet formulation is selected. Tablet product design thus required two major considerations; identification of excipients most suitable for a prototype formulation and secondly the level of such excipient must be optimally selected to satisfy all process and product quality constraints.

1.5 TABLET EXCIPIENTS AND THEIR EFFECT ON TABLET PROPERTIES.

The process of wet granulation involves the addition of several excipients to produce a free flowing material with good compression characteristics. Correct selection and balance of these excipients is necessary to achieve the desired objective. The knowledge of the effect of each excipient is therefore necessary to adequately control the granulation process (Kristensen and Schaefer, 1987).

1.5.1 Binders

Binders are substances that impart cohesiveness and structural strength to a powdered material and provide the bonding property required to produce tablets that can withstand handling. They can be added either dry or wet (as a solution). The concentration of binder varies from binder to binder and also depends on the properties of the material to be granulated.

Binders have been found to affect the properties of both granules and tablets. Several research works have been carried out on the effect of type, concentration and quantity of binder on such parameter as disintegration, dissolution, mean granule size, friability and hardness.

Binder concentration has been found to have a direct effect on the granule size, hardness and disintegration time in lactose tablets. Mean granule size, hardness and disintegration times of lactose have been reported to increase with increase concentration of binder (Nasipuri and Akala, 1986).

It has also been reported by Sakr *et al* (1972) that the friability of tablets decrease with increased gelatin (binder) concentration. This was also the conclusion made by Nasipuri and Akala (1986) using cassava starch mucilage.

The volume of binder solution used in granulation has been shown to have a significant effect on granule property. Zayic and Bukton (1990) found that the granule size distribution was not affected by the concentration of PVP but increase in the volume of PVP led to an increase in size of granules formed.

Kurup and Pilpel (1977) working on the effect of binder concentration using griseofluvin found that tensile strength of griseofluvin tablets is dependent on the binder concentration. Niskanen *et al* (1990) while evaluating the effect of two independent process variables on granulation of potassium chloride found that mean granule size and granule flowability of potassium chloride granules increased with increase in binder solution. Esezobo and Pilpel (1977) found that tensile strength increased with increased gelatin concentration. The increase in gelatin was also found to reduce the capping tendency of the tablets, while disintegration and dissolution times increased with increase in binder concentration.

1.5.2 Disintegrants

A disintegrant is a substance or mixture of substances added to most tablet formulations to facilitate its break-up or disintegration after administration. The active ingredient must be released from the tablet matrix as

efficiently as possible to allow for its rapid dissolution. Tablet disintegration may be taken as the initial stage of availability of the drug in the system.

No matter how elegant a tablet may appear or however accurate the dose of drug contained in it, it will be medically useless, unless the active ingredient is made available for absorption by the system. This can be achieved by including in the formula a disintegrating agent. Basically, the disintegrant's major function is to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the mechanical body of the tablet.

The importance of quick tablet disintegration and dissolution to ensure rapid availability of the active ingredient(s) for absorption is well recognized. (El-khawas. M and El-khodiary K.A, 1995). A number of agents have been formerly used as tablet disintegrant but are now archaic. Only a few acceptable disintegrants are currently available to pharmaceutical scientists. The plain starches, which were the most widely used disintegrants, are unable to effectively break apart tablets when used in low concentrations.

Most Compendia and Industrial standard for the disintegration time of a compressed tablet are considerably shorter than they were in the early 1970's. This shorter disintegration time requirement, stimulated continuous efforts in the search for new, more efficient, disintegrating agents other than the most widely used plain starches (Deshpande and Panya, 1987; Bhargava *et al*, 1991; El-khawas and El-Khodiary, 1995 and Duri *et al*, 1995).

Traditional tablet disintegrants can be classified as starches (e.g. corn, wheat, potato, rice and pregelatinized starch), macromolecules (e.g. alginic acid, sodium alginate, and guar gum), finely divided solids (e.g. colloidal silicon dioxide and magnesium aluminium silicate), cellulose (e.g. powdered cellulose, microcrystalline cellulose, carboxyl-methylcellulose, methylcellulose and low substituted hydroxypropylcellulose), surfactants and recently super disintegrants (e.g. cross linked PVP and Sodium starch glycolate).

1.5.2.1 Mechanism of Disintegrant Action.

Many theories relating to the mechanism of action of tablet disintegrants have been proposed, but none has fully explained the disintegrant properties of all the agents. Lowenthal (1973), discussed in detail the different mechanisms and factors affecting tablet disintegration. Three major mechanisms of action have been proposed for disintegrant action: (A) swelling (B) porosity and capillary action and (C) deformation. Even though these factors are listed separately, inter-relationships probably occur in almost all tablet formulations.

A. Swelling

This is perhaps the most widely accepted general mechanism of action for tablet disintegrant (Carli *et al*, 1986; Takewiech *et al*, 1987). Primarily, this is because almost all disintegrants swell to some extent and swelling has been reported quite universally in literature (Lowenthal, 1972; Couvreur and Rowland, 1976).

Many attempts have been made to quantify swelling, but only recently have sophisticated methods been brought to bear on the problem (Erdos, 1986; Chukwu and Chukwu, 1996). For water insoluble materials like aspirin, disintegration was found to be due to swelling. (Caramella, 1991), while Van Kamp *et al*, (1986) observed that mechanisms other than swelling might be responsible for disintegration process for insoluble or partly soluble drug formulations.

Kanig and Rudnic, (1984) found swelling and wicking to be the primary mechanism of action for tablet disintegrants, while other mechanisms, such as deformation, recovery, particle repulsion theory, heat of wetting and evolution of gas etc may play a role in particular cases.

B Porosity and Capillary Action (Wicking)

Tablet porosity, have an important influence on water penetration and tablet disintegration depends on the pressure at which tablets are compressed as well as on the nature of the material being tabletted. Curlin (1955) reported that

while aspirin tablets containing starch disintegrated in 15 sec, the starch grains were not swollen, He suggested that the disintegration action of starch was due to capillary action rather than to swelling.

Khan and Rhodes (1975) studied the sorption properties of various disintegrants and they concluded that the process of wicking was essential for efficient disintegration. Similar work by Mitrevej and Hollenback (1982) also supported these claims.

Bolhuis *et al* (1981) and Lerk *et al* (1982) studied the effect of the rate of wetting of disintegrants by coating the disintegrants with a hydrophobic substance (Magnesium stearate). In both studies, the authors concluded that if wetting of disintegrant particles was slowed, disintegration of the tablets also slowed. These researchers have conclusively demonstrated that the rate of water up take is of critical importance for a number of tablet disintegrants.

Kornblum and Stoopak (1973) observed that cross-linked PVP swells very little but it takes up water into its network quite rapidly. These authors concluded that the mechanism of action of this disintegrant is wicking.

C. Deformation

Plastic deformation of starch grains under high pressure has been reported by a number of investigators. Starch grains are generally thought to be elastic, therefore, any grains that are deformed under pressure tend to return to their original shape and size when the pressure is removed. However, it has been suggested that compression may cause more permanent deformation, the deformed starch grains gaining energy, which are released when exposed to water (Fehrer, 1977). These energy rich grains swell more rapidly than the undeformed grains.

Hess (1978) using electron photomicrographs of potassium chloride and aspirin tablets clearly showed that the starch grains returned almost instantaneously to their original shape when the tablets are exposed to moisture. This mechanism appears to be more convincing than the idea of simple swelling.

1.5.3 Lubricants

Gunsel *et al* (1970) defined lubricants, as those agents that act between surfaces in relative motion to prevent friction and wear. Although granules are naturally freer flowing than powdered materials, their flow properties can be improved by coating them with lubricants added in the form of fine powder.

Lubricants have a number of functions in tablet manufacture. They improve the rate of flow of tablet granulations, prevent adhesion of the tablet material to the surface of the dies and punches, reduce inter-particle friction and facilitate ejection of the tablet from the die cavity.

Mixing time is very critical in lubricant addition and has been found to affect several properties of the tablets formed. Hersey and Rees (1973) while studying density changes in lactose tablets showed that materials that fragment during compaction show little or no reduction in tablet strength when lubricant is added due to creation of new, fresh, uncoated surfaces that are able to form bonds between the particles.

Desai *et al* (1973) reported that increasing mixing time led to decrease in drug dissolution rate. Sixmith (1977) observed that an increased in concentration of magnesium stearate led to a decreased dissolution rate.

1.6 COMPRESSION AND COMPACTION OF PHARMACEUTICAL POWDERS.

The process of compression as encountered in the preparation of tablets has received a lot of attention by various authors. Train (1956) was one of the first to study the compression process and he related applied pressure to relative volume of powder and suggested four (4) stages for the compression process. Other researchers Heckel (1961a & 1961b), Hancock and Zografi, (1997) and Hyunjo *et al*, (1998) have defined the stages of the compression process as filling and rearrangement of particles in the die, elastic and plastic deformation of particles, fracture of particles and cold welding or bonding.

1.6.1 Stages of Compression Process

1.6.1.1. *Filling and Rearrangement of Particles*

Paroren and Juslin (1983) while studying the compression characteristics of four starches observed that the initial packaging and bulk density of a powder in the die cavity depends on the particle size distribution and shape. They found that potato starch, with the highest mean particle diameter exhibited the best packing potential in the die filling stage because it has the least electrostatic forces that could prevent the packaging of the particles. The degree of particle slippage and rearrangement taking place during compression increases as the powder particle size decreases. York (1979) found this effect to be more significant for powders composed of non-spherical particles due to the increased number of contact points per unit area and higher inter-particulate cohesive forces.

1.6.1.2 Elastic and Plastic Deformation

A material under pressure can deform either due to plastic or elastic deformation. If the deformation disappears entirely on release of the stress, it is said to be elastic. Rippie and Danielson (1981) classified a material as plastically deformed if it does not completely recover after release of stress. The force required to attain plastic deformation is referred to as the yield pressure (Py) Heckel (1961a & 1961b).

The ability of a powdered material to undergo plastic deformation during the compaction process is essential in tablet formation. Edward and Danielson (1981) defined the stage at which a material yields plastically as the point where the system undergoes an instantaneous and total irreversible response to an applied pressure. Newtonian flow is considered to occur, where the strain rate is directly proportional to the applied stress. Total energy applied at the irreversible state (E_t) was described by the expression.

$$E_t = E_1 + E_2 + E_3. \quad \text{----------} \quad 1$$

Where E_1 is the work lost in the form of friction, E_2 is the net energy spent in the formation of the tablet, while E_3 is the elastic deformation energy. The E_2 is affected by the physico-chemical nature of the material, and E_3 on the compaction mechanism. Cole *et al* (1973) and Hess (1978) observed that potassium chloride mainly consolidated by plastic deformation and this was ascribed to the presence of highly symmetrical ionic crystal lattice.

The ability of formulated powders to form satisfactory tablets depends on their plastic deformation during compression and elastic recovery during decompression. David and Augsberger (1977). Armstrong and Haines-Nutt (1972) studied elastic recovery in compact powder system and defined elastic recovery (E.R) as

$$ER = \frac{Ho - Hc}{Hc} \times 100 \quad \text{.....2}$$

where H_c and H_o represent compact height under pressure and after compression forces has been removed respectively.

Krycer *et al* (1982) similarly proposed an expression for elastic recovery as:

$$ER = \frac{Ho - Hp}{Hp} \times 100 \quad \text{.....3}$$

Where Hp and Ho are the thickness of the tablets at maximum pressure and after final decompression respectively.

Malamataris *et al* (1984) proposed an expression for stress relaxation (S.R) of the powder, which is the percentage reduction in force that occur when as a result of plastic deformation, the applied force decays with time as:

$$SR = \frac{Hp - Ht}{Ht} \times 100 \quad \text{.....4}$$

Where Hp and Ht represent the thickness of the tablet at maximum pressure and after being held for 30 secs at maximum pressure respectively.

The effect of elastic recovery in pharmaceutical compact caused a lot of concern in recent times. Paracetamol for example does not form satisfactory tablets due to elastic recovery. Bangudu (1985) studied the effects produced on the ratio of elastic recovery to stress relaxation (E.R/S.R) on tablet strength, by varying ratio of paracetamol/Avicel^{R} in the formation. Hiestand *et al,* (1977) studied the influence of the die wall and punch pressure on compression. They showed that stress relief was a function of time and proposed a brittle fracture expression to quantify the lamination tendency of materials during ejection.

$$B.F.I. = 0.5\left[\frac{Ts}{To} - 1\right] \quad \text{.....5}$$

Where T_o and T_s are tensile strength of square compacts with or without hole respectively. B.F.I measures the stress relaxation that takes place due to plastic flow of materials during compression and its value ranges between 0 and 1. Plastic materials have low brittle fracture, while high brittle fracture (close to 1) represent elastic tendency with possibility of capping and laminating.

1.6.1.3 Fracture of Particles

Fragmentation occurs as a result of increased pressure during compression, the deformed particles may fragment into smaller parts to produced new clean surface that serves as potential bonding areas (Ritter and Sucker, 1980). Parrott *et al* (1990) showed that not all materials fragment due to stress relieved by plastic deformation.

The fragmentation process is of importance when determining the effect of additives in direct compression formulations. Hersey *et al* (1973) observed that materials that fragment during compaction show little or no reduction in tablet strength when lubricants are added, due to the creation of new fresh, uncoated surfaces that are able to form bonds.

1.6.1.4 Cold Welding on Bonding

The exact explanation of interpaticule bonding in tablet compaction has not yet been fully known but several authors here made attempts to explain it. Carstensen (1980) suggested that asperity melting occur primarily in materials with low melting points. Parrott *et al* (1990) proposed three forces -mechanical, intermolecular and liquid surface film to be responsible for bonding in compacts.

Greenwood and Johnson (1981) attempted to explain particle bonding based on the mechanism of plastic deformation and fragmentation. They attributed bond formation to plastic deformation and molecular rearrangement of one particle with respect to another.

1.6.2 Compaction Characteristic of Pharmaceutical Powders

Physicochemical properties of the particles, such as morphology of material, moisture content, particle size/distribution, affect the compatibility of the material. Hyunjo *et al* (1998) and Hancock and Zografi (1997) observed that most crystalline materials tend to exhibit elasticity and brittleness while amorphous materials exhibit varying degrees of viscoelasticity.

Several methods have been proposed to distinguish the consolidation mechanisms in powder (Leigh *et al*, 1967; Carstensen and Toure, 1980), but pressure-volume relationship used by Heckel (1961a &1961b), Macleod (1983) and Kawakita and Ludde (1970/97) is most popular in studying compression and compatibility of materials.

Kawakita and Ludde (1970) while considering powder compression equations concluded that Heckel's equation though deviating slightly from linearity at low compression pressures was most informative on mechanism of powder consolidation. Heckel (1961) considered the compaction of powders to be analogous to a first order reaction, the pores being the reactants and densification of the bulk as the product.

Heckel came out with an equation:

$$\ln\left[\frac{1}{1-D}\right] = KP + A \quad \text{.....6}$$

The Heckel equation has been found to be qualitatively valid except at the lowest pressure levels (Kawakita and Ludde, 1970). The constant A, represents the degree of packing achieved at low pressure as result of rearrangement process before appreciable amount of interparticle bonding takes place. D is the relative density at applied pressure P. The constant K, which is the slope of the linear region, gives a measure of the ability of the material to density by plastic flow. The reciprocal of K is the mean yield pressure (Py).

On the basis of the Heckel's plot, Roberts and Rowe (1986) determined K and A from the slope and intercept of the extrapolated linear portion. They also derived an equation whereby the relative density D_A, can be calculated from the value of A.

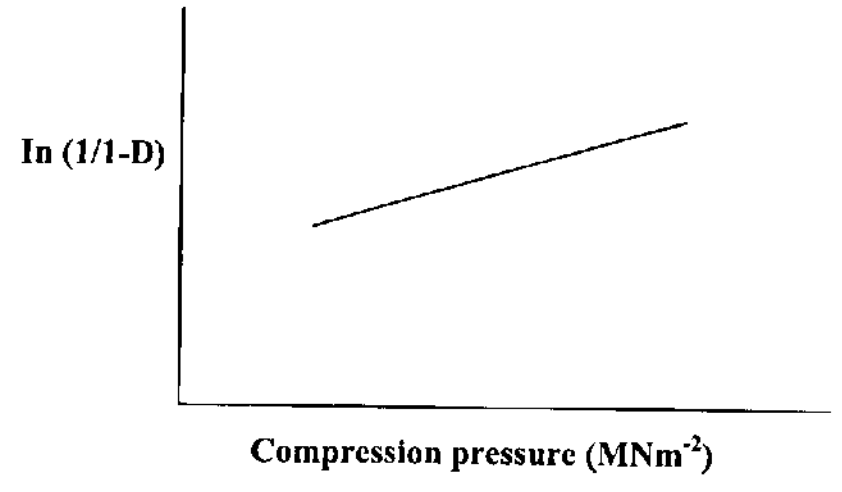
$$D_A = 1 - e^{-A} \quad \text{.....7}$$

Do, the relative density at nil pressure, has been used to described 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 rearrangement depends on the theoretical point of densification at which deformation of particles begin, D_B is obtained from the relationship.

$$D_B = D_A - D_0 \quad \text{.....8}$$

The Heckel's equation has been used to classify powders based on their compaction behaviours. York and Pilpel (1973), Hersey and Rees (1971) classified powders into three types, referred to as type A, B and C.

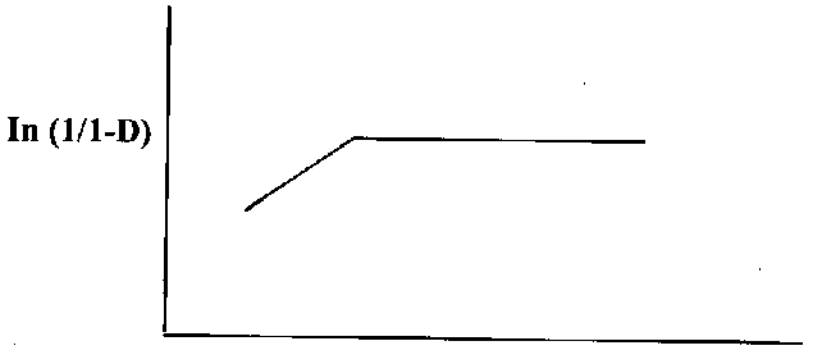
With type A materials such as sodium chloride, a linear relationship is observed at all applied pressures indicating densification apparently occurs due to plastic deformation.



TYPE A



TYPE B



TYPE C

Fig. 1.1 Schematic representation of Heckel plots for different materials

For type B materials (e.g lactose), there is an initial region, usually curved, followed by a linear portion. This indicates that the particles are fragmented at the early stage of the compaction process followed by plastic deformation. Hersey *et al* (1973) and Mackenna and Mcattety (1982) found that hard materials fall in this category and this is associated with high yield pressures.

Type C behaviour, which was proposed by York and Pilpel (1973) while studying the compression of fatty acids and lactose-fatty acid mixture is believed to be due to the absence of a rearrangement phase and densification is due to plastic deformation and asperity melting. The type C materials do not exhibit the curved region but rise linearly and then flattens out as the packing fraction approaches unity

1.7 EFFECT OF SOME PHYSICOMECHANICAL PARAMETERS OF MATERIALS ON POWDER COMPACTION.

During compression, solid particles rearrange, deform and fragment to form a compact. Several physico mechanical parameters of the material being compressed, such as crystallinity, moisture content, tensile strength, particle size, surface area and density, that influence the compaction characteristics of solids have been identified (Vijay and Kothari, 1999).

1.7.1 Particle Size

The deformation mechanism of a material may be determined by its particle size and this will influence the consolidation and compaction properties of its elastic and plastic component. The effect of particle size on the compaction characteristics of solids can be studied using the equation put forward by Heckel (1961) in which he considered the consolidation process to be analogous to a first order chemical reaction where the pores are the reactants.

Several authors have studied the effect of particle size on the compaction of pharmaceutical powders. Hersey and Rees (1973) studied the effect of particle size on the consolidation of powders and they acknowledged that Heckel's equation facilitated their study. The effect of particle size on the mechanical strength of compacts was found to be dependant on the material property (Alderborn and Nystrom, 1982). They found that lactose and acetylsalicylic acid undergo plastic flow or formation of solid bridges at contact points forming tablets with mechanical strengths increasing with decrease in particle size, while the mechanical strength of Emcompress and saccharose that undergo extensive particle fragmentation were almost independent of particle size variation.

The material dependence effect of particles size on strength of compact was also observed by Alderborn *et al* (1988) while studying the effect of particle properties on the mechanical strength of sodium bicarbonate tablets. They observed a decreased tablet strength with increase in particle size of Sta - R_X 1500 and attributed this to the increase in the number of contact points and a probable increase in stress at each particle contact point resulting in the formation of solid bridges.

The effect of particles size and size distribution of Avicel^R PH 101 and magnesium carbonate with dissimilar compaction mechanisms were studied by Armstrong and Cham (1987). They observed that the particle size of the disintegrated compact was affected by both the initial particle size and the difference in the mechanism of the two materials.

Carless and Sheak (1976) studied the effect of particle distribution of sulfathiazole powder during compaction. They observed that the bigger sized particles are crushed to fines agglomerate, while the intermediate sized are not significantly affected. They therefore suggested that a critical particle size exist, at which bonding and fragmentation equalise but this vary with the nature of the material used. They found 76 μm to be the critical particle size for sulfathiazole.

1.7.2 Moisture Content

The properties of pharmaceutical powders (granules) are greatly affected by the moisture content. Moisture content affects the bulk density of the material and this will in turn affect its flow and also compressibility. Absorbed water film expressed during the compaction process is thought to be responsible for the decrease in the adhesion of tablets to the die wall due to decrease in particle surface energy (Jaffe and Foss, 1959).

Eaves and Jones (1972) studying the effect of moisture on tensile strength, observed an increase in tensile strength of the coarse, non-cohessive fractions of sodium chloride as the moisture content was increased. The increase was observed up to critical moisture content after which there was a decrease. Khan *et al* (1981), who studied the effect of moisture content of some excipients on compression properties of formulations of Paracetamol and Potassium Phenethicillin, found that 7.3% moisture content of microcrystalline cellulose gave the strongest tablet. Similarly, Pilpel and Ingham (1988) while studying effect of moisture on the compaction and tensile strength of microcrystalline cellulose observed a decrease in yield pressure with increase moisture content.

Giordano *et al* (1990) studied the role of adsorbed water on powder compatibility and they found that amount of water present in cyclodextin produces different binding compacts. Li and Peck (1990) and Sebhatu *et al* (1997) who studied the effect of moisture on compression properties of maltodextin produced by different degrees of hydrolysis of cornstarch and amorphous lactose respectively, observed a decrease in yield pressure and improved densification with increase in moisture content of powder.

Armstrong and Griffiths (1970) observed that presence of moisture in a compact led to a reduced surface area due to improved lubrication and recrystallisation permitting the formation of interparticulate bonds.

1.7.3 Shape and Surface Area

The shape and surface area of a particle play very important roles in the flow and dissolution behaviour of materials. (Brittain *et al*, 1991). Alderborn *et al*. (1988) studied the effect of particle size and shape on the mechanical strength of sodium bicarbonate tablets and found that the milled powder fractions gave the highest tablet strength, which they attributed to surface area and surface irregularity.

Ridgway and Rupp, (1969) observed an increase in angle of repose and decrease in bulk density and flowability with increased departure from spherical shape. Ridgway and Scolton (1970) while studying the effect of particle shape on die fill, observed an increase in mean tablet weight with increase irregularity of particle shape.

Wong and Pilpel (1990), while studying the effect of particle shape on compression characteristics observed a decrease in yield pressure and elastic recovery when shape of material changed from regular to irregular for Starch Rx-1500, which consolidates principally by plastic deformation. Powders that consolidate mainly by fragmentation were not affected by shape.

1.8 STATEMENT OF OBJECTIVE

The high incidence of asthma makes it one of the most important prevalent respiratory diseases in industrialized and non-industrialized countries. The synthetic drugs used in the management of asthma are associated with several and often serious side effects, sometimes leading to death. The complexity of the disease often calls for combined therapy; which is usually expensive and poses compliance problem.

With the renewed interest in use of phytomedicines as source of medical care, especially in developing countries, focus on the search for an-ideal antiasthmatic agent from medicinal plants will not only reduce side effects but also cost, as natural products are cheaply procured and are believed to have less side effects (Amos, 1996). Combination of *Prosopis africana* & *Anogeissus leiocarpus* is widely used in the northern part of Nigeria in the treatment and management of asthma. Preliminary investigations showed that this herbal remedy is tremendously useful in asthma therapy. However there is standardization problem as the dosage often prescribed by the herbalist are imprecise, variable, non-reproducible and unreliable. To ensure standardization in dosage regimen, formulation into a suitable dosage form that will ensure proper handling, quantification and monitoring is called for. Formulation of these plants into tablets will ensure proper standardization and improve acceptance, thus ensuring cheaper management of asthma in our environment.

The objectives of this study are therefore: -

1 To screen the extract of (*Anogeissus leiocarpus* and *Prosopis africana)* for antiasthmatic properties using pharmacological models;

2 To conduct formulation studies on the extract by using different excipients and excipient combinations, with the aim of selecting the most suitable excipients for an acceptable formulation;

3. To study the compaction characteristics of the different formulation with a view to understanding the interplay of forces affecting the properties of formulated tablets;
4. To propose a suitable formulary for the formulation of the extract (*Anogeissus leiocarpus /Prosopis africana*).

CHAPTER TWO

PHYTOCHEMICAL SCREENING OF BARK EXTRACT

2.1 INTRODUTION

Several researchers have reported on the phytochemical properties of the plants *Anogeissus leiocarpus* and *Prosopis africana* (Adegoke, *et al* 1968. Basua, *et al* 1976 and Delaveau, *et al* 1979). This section of the work is primarily to develop a phytochemical "finger print" for the extract and also to confirm the secondary metabolites that have been previously reported and possibly relate them to the pharmacological activities of the extract.

2.2 MATERIALS.

2.2.1 Equipment

U.V. Spectrophotometer type 160A Shimadzu

UV. Lamp. Cart bury (Model Cm-10), Network

Water Bath (Type (1083) Karl Kolb Germany

Oven (Type TSG 160) Salvias AG Germany

Erweka type TG2S Milling machine, Germany.

Rotary Evaporator. Puchi. W.Germany.

Freeze dryer- Film/Aqua Lyovac GT3,

2.2.2 Chemicals

The following are BDH. Chemicals. Ltd England, Sodium hydroxide, Sulphuric acid, Ammonia solution, Nitric acid, Hydrochloric acid, Acetic acid and Chloroform

Lead sub acetate, Potassium hydroxide - M&B Ltd. England.

Olive oil - Goya foods, Inc USA

Mayer's reagent

Vanillin- sulphuric Acid Spray Reagent.

Dragendoff's reagent

Fehling solution A and B

2.2.3 Glassware

Reversed phase [K_C18_F] precoated TLC plates.

Test tubes

Beakers

2.3 METHODS.

2.3.1 Plant Material Collection

The stem bark of *Anogeissus leiocarpus* was collected from Deidei village in the suburb of Abuja Nigeria while that of *Prosopis africana* was collected from National Institute for Pharmaceutical Research and Development (NIPRD) garden also in Abuja. The plants were identified and authenticated by Messrs. Ohaeri and Mazuam of the Herbarium, National Institute for Pharmaceutical Research and Development (NIPRD) Abuja. Specimen of *Anogeissus leiocarpus* and *Prosopis africana* were deposited in the Herbarium of NIPRD and assigned No 3404 and 4392 respectively.

2.3.2 EXTRACTION.

2.3.2.1 Hot Water Extraction

The stem barks of *Anogeissus leiocarpus* and *Prosopis africana* were sun dried until dry enough to be broken with bare hands. The barks were milled using the Erweka milling machine mounted on a Copley motor and mixed in a ratio 1:1 weight in volume. The mixed milled barks were then soaked in distilled water ratio 1:1 weight to weight (as used by the herbalists), boiled for 10 minutes on an electric heater and left to soak at room temperature for 24 hours. The liquid extract was filtered through a calico cloth and concentrated using a rotary evaporator. The concentrate was further concentrated on a water bath to a semi-solid mass which was transferred into a tray and dried in an oven

at 60°C until dry. The dried extract was pulverised using a pestle and mortar and passed through a 150µm sieve.(This procedure was repeated for the individual stem barks).

2.3.2.2 Cold Water Extraction (Maceration).

Portion of the milled bark from section 2.3.2.1 was soaked in distilled water in a ratio of 1:10 weight in volume and macerated for 24 hours. The liquid extract was filtered through a calico cloth and freeze-dried. The extract was then stored in a desiccator.

2.2.3 Phytochemical Tests

Phytochemical tests were carried out on the three extracts obtained from section 2.3.2.1 according to Trease and Evans (1989) for the absence or presence of saponin, glycosides, tannins, alkaloids, resins and flavonoids, as described below:

2.2.3.1 Test for Saponins

0.5 g of the powdered extract from section 2.3.2.1 was dissolved in distilled water, filtered and the filtrate used for the following tests.

(i). General

2.5 mls of the filtrate was diluted with 10 ml of distilled water, shaken vigorously for 2 minutes, and observation was made. Two drops of olive oil was added, shaken again and any sign of turbidity was observed.

(ii). Saponin glycoside

To 2.5 mls of extract was added 2.5 mls of mixture of Fehling solution A and B. Any colour development was observed and recorded.

(iii). Lieberman - Burchard Test.

Equal volume of extract was treated with equal amount of concentrated sulphuric acid and acetic anhydride and observed.

2.2.3.2. Glycosides

(I). General

To 2.5 mls of dilute sulphuric acid was added 5 ml of extract in a test tube, boiled for 15 minutes, cooled and neutralised with 10% NaOH. 5 ml of Fehling's solution A and B were then added and observed for any colour development.

(ii). Digitalis glycosides –(Keller - Killiani test.)

1 ml of glacial acetic acid containing traces of $FeCl_2$ was added to 5 mls of extract and poured over 2 ml of concentrated H_2S0_4.

(iii). Anthracene Derivatives (Borntragger's test).

5 mls of extract was shaken with equal volume of chloroform, and allowed to separate.5mls of 10% ammonia solution was added to the chloroform layer, shaken vigorously, allowed to separate and observed.

2.2.3.3. Tannins

(i) General

0.1 g of the extract was added to lead subacetate solution and observed for any precipitate formation.

(ii) Hydrolysable Tannin

4mls of extract was shaken with 4 mls of 10% ammonia solution. Observation was made for turbidity.

(iii) Pseudotannins

A stick of matches was put into the extract, placed in test tube and a drop of concentrated HCl was added down the side of the tube. Observations were made for colour change.

2.2.3.4 Resins

2 mls of the extract was added to an equal volume of acetic anhydride solution followed by drops of concentrated H_2S0_4. Observation was made for any colour change.

2.2.3.5 Alkaloids

(i) General

(a) To 0.1 gm of the extract was added 5ml of Dragendoff's reagent. Observation was made for precipitate formation.

(b) 0.1 g of the extract was added 5mls of Mayer's reagent. Observation was made for precipitate formation.

(ii) Tropane Alkaloids (Viitali - Mornin test).

0.1 g of the extract was dissolved in a few drops of glacial acetic acid, evaporated to dryness and cooled. 2-3 drops of fuming nitric acid was added to the residue, evaporated to dryness again, cooled and redissolved in acetone. To the solution, 2 drops of 3% potassium hydroxide was added. Observations were made for any colour change.

2.2.3.6 Flavanoid

(a) To the extract was added small quantity of magnesium chips. A drop of Conc. HCl was added down the side of the tube. Colour change was noted.

(b) 1 mg of the extract was dissolved in dilute sodium hydroxide, and dilute HCl was added. Colour change was noted.

2.2.4 Chromatography

0.1g of the crude extract was dissolved in methanol and spotting was made on a reversed phase [K_c18_f] precoated TLC plate. The chromatograms were developed using ethanol and water in the following arbitrary ratios: -
Ethanol: H_20 (10:0, 9:1, 4:1, 1:1, 0:10).

After development the chromatograms were dried and detections were made using U.V. light at wavelength of 254 nm.

2.2.4 U.V. Spectroscopy

The extract was reconstituted in distilled water and filtered through a 0.2 μm pore filter paper. The filtrate was scanned in a U.V. Spectrophotometer between 800 and 200 nm wavelengths.

2.3 RESULTS.

2.3.1 Extraction Results.

Table 2.1 % Yield and Nature of Extract

Extraction Method	Yield of Extract (%)	Nature of Crude Extract
Cold water	8.7	Brown fluffy and highly hygroscopic.
Hot water	10.9	Brown, powder, not obviously hygroscopic.

The two water extracts exhibited slightly different physical characteristics. The hot water extract, which is of higher % yield, was relatively a non-hygroscopic, crystalline powder while the cold-water extract was more or less amorphous and hygroscopic.

2.3.2 Phytochemical Tests

The results of the phytochemical tests are shown in Table 2.2

Table 2.2 Summaries Of Results From Phytochemical Screening.

Test	Inference		
	A. leiocarpus	*P. africana*	Combined extract
Saponin			
General	+	+	+
Saponin glycoside	+	+	+
Liebermann Burchard	+	+	+
Glycoside			
General	+	+	+
Keller-Killiani Test	+	+	+
Born tragger test	+	+	+
Tannins			
General	+	+	+
Hydrolysable tannins	-	+	+
Pseudotannins	-	-	-
Alkaloids			
General	-	+	+
Dragendoff's reagent	-	+	+
Mayer's reagent	-	+	+
Tropane alkaloids	-	-	-
Flavanoids			
General	+	+	+
Confirmation	+	+	+

The phytochemical investigation of the extract showed that several secondary metabolites namely alkaloids, glycosides, flavonoids, saponins and tannins were present. The glycosides identified are mostly digitalis, anthracene and saponin types. These findings are in line with findings of several other researchers (Adegoke *et al,* 1968;Delaveau *et al*, 1979; Ibrahim *et al*, 1997)

2.3.3 TLC CHROMATOGRAPHY

The thin layer chromatograms of both extracts were developed in the ethanol: water system and observed under UV lamp at 254 nm wave -length. An additional spot (purple) invisible under UV light was spotted when the chromatograph was sprayed with vanillin-sulphuric acid. The R_f values of the spots are indicated in Table 2.3. Generally, the R_f values of corresponding spots were similar; an indication that the heating process employed in the hot water extraction method did not alter the phytochemical composition of the extract

Table 2.3 R_f Values of Cold and Hot Water Extract Using Ethanol: Water (4:1)

Extract	No. of Spots	R_f Values
Cold water	5	0.125, 0.237, 0.375, 0.5, 0.925
Hot water	5	0.112, 0.231, 0.375, 0.487, 0.950

The chromatogram of the formulated extract was approximately similar to that of the crude extract as shown on Table2.4

TABLE 2.4 R_f values of crude and formulated extracts using Ethanol:water (4:1)

Extract	No. of Spots	R_f Values
Crude	5	0.125, 0.237, 0.375, 0.5, 0.925
Formulated	5	0.122, 0.237, 0.365, 0.487, 0.915

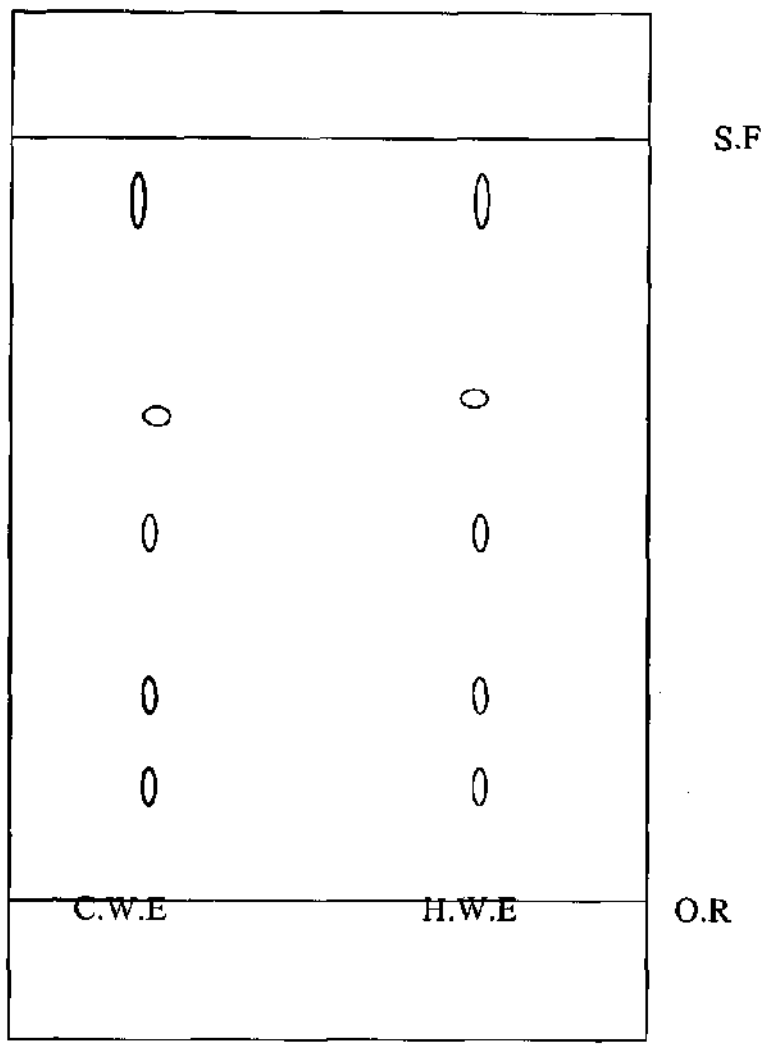


Fig 2.1 Diagram of T.L.C Plate

Key to Fig 2.1;

S.F-Solvent front

HWE-Hot water extract

CWE- Cold-water extract

OR - Origin

The TLC was used as chemical "finger print" to check if the formulation process or excipients had any effect on the chemical constituents of the extract. The similarity in R_f values for both the formulated and crude extracts is an indication that the extract was not affected chemically by the formulation process or excipients

3.3.4 Spectroscopy

The U.V. spectra of the cold water and hot water extracts are represented in Fig 2.2(A) and 2.2(B) respectively. Both extracts had their peaks at 287 and 288 nm respectively. The difference in the λmax is not significant and it can be inferred that the extraction process has not affected the phytochemical properties.

CHAPTER THREE

PHARMACOLOGICAL SCREENING OF CRUDE AND FORMULATED EXTRACTS

3.1 INTRODUCTION

The stem barks of *Anogeissus leiocarpus* and *Prosopis africana* have been used by a number of traditional practitioners in the Northern part of Nigeria in the management of asthma. There is renewed attention to the development of plants that have been in use based only on folklore. To justify this claim scientifically the antiasthmatic activity of the plants will be studied using standard pharmacological models.

3.2 MATERIALS

3.2.1 Chemicals.

Extract (prepared in the Lab)

The following are BDH Potassium Chloride, D-glucose, Sodium dihydrogen orthophosphate and Potassium dihydrogen orthophosphate while Acetylsalicylic acid, Sodium Chloride, Calcium Chloride, Sodium bicarbonate and Magnesium sulphate (M & B)

Histamine Sodium, pentobarbitone (Abbott)

Magnesium chloride (Vickers Lab. England)

Halothane (Halocarbon Lab. London)

3.2.2 Experimental Animals

The experimental animals used were as follows: -

Wister rats (male and female)

Swiss albino mice (male and female)

Guinea pig (male and female)

New Zealand rabbits (male and female)

All experimental animals were obtained from the Animal Facility Centre of the National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria.

2.2.3 Equipment

Unirecorder model 7050 with transducer model No. 7004.Ugo Basile Switzerland.

Rodent Ventilator model No. 7025 Ugo Basile Switzerland

Digital Plethysmometer LE 7500 (Leticia Scientific instrument)

Metler balance model - p165 Switzerland

Triple beam balance (Ohaus)

Water Circulator. (Churchill)

3. METHOD

3.3.1 Acute Toxicity

Toxicity studies were carried out in mice following the method of Lorke (1983), from which the mean Lethal dose (LD_{50}) of the extract was determined. A total of thirteen mice weighing between 18-25g were used, and fed *ad libitum* for about 24 hours before being exposed to drugs. The evaluation was conducted in two stages. In the first stage 3 mice each were treated with 10, 100, 500 mg/kg of the plant extract i.p to establish the range of doses producing toxic effect. Based on the percentage survival rate on first stage, 4 mice were then treated with 50, 100, 200, 300mg/kg i.p. From the results of the 2nd stage the LD_{50} was then calculated:

$$LD_{50} = \sqrt{}(\text{highest non lethal dose x lowest lethal dose})$$

3.3.2 Pharmacological effect of Extract on Isolated Rabbit Jejunum

Segment of the jejunum about 2-3 cm long were obtained and dissected free of adhering mesentery. The lumen was flushed with Tyrode solution of the following composition: (mM): Na^+ 149.2, K^+ 2.7;Ca^{2+} 3.6,Mg^{2+} 2.1; Cl^- 145.3; H_2P04^- 0.4, $HC0_3^-$ 11.9; glucose 5.0. The tissue was mounted in a 20 ml organ bath containing Tyrode solution at 37°±1C and aerated with air. One end of the tissue was tied to the stationary tissue holder at the bottom of the organ bath, while the other end was connected to the Ugo Basile force displacement transducer and a tension of 0.5 g was applied. The effect of *Anogeissus leiocarpus*, *Prosopis africana* and the combined extract at doses (100,200,400,800 µg/ml) were investigated and recorded isometrically on an Ugo Basile Unirecorder 7050 after a 60 minutes equilibrium period.

3.3.3 Pharmacological effect of Extract on Guinea-Pig Isolated Trachea

Adult guinea-pigs (350-450 g) were killed by a blow on the head, extrangulated and the thorax opened, care being taken to avoid damage to the neck and trachea. The trachea from the larynx to the bronchi was immediately removed and transferred to a petri dish containing Krebs solution at room temperature. The composition of the Krebs solution was (mM): Na^+ 132, K^+ 5.9, Ca^{2+} 2.5, Mg^{2+} 1.2; Cl^- 122.7, $HC0^-$ 2.5; $S04^{2-}$ 1.2, $H_2PO_4^-$ 1.2 and dextrose 11. The trachea was separated from the bronchial tree and cut into rings. The rings were then tied to each other in an alternate fashion with cotton thread to form a six- ringed chain. The chain was then transferred into a 20 ml organ bath containing Krebs solution gassed with 95% 0_2 and 5% CO_2 maintained at 37°C and equilibrated for 60 minutes. The combined extract (1.6×10^{-3}, 3.2×10^{-3} g/ml) and Histamine (4.5×10^{-5} 3.6×10^{-4} g/ml) were introduced into the organ bath and the relaxant effect of the combined extract on the tracheal muscles were recorded on the Ugo Basile Unirecorder 7050.The organ bath was flushed with Krebs solution after each recording.

3.3.4 Pharmacological effect of Extract on Rat Paw Oedema:

Wister rats of either sex weighing between 150 - 250 g were used. They were divided into four (4) groups of five (5) animals each. The method of Winter et al (1962) was followed. Inflammation was induced in the hind paw of Wister rats by injecting raw egg albumin in the sub-plantar region. Two acute doses of (50 and 100 mg/kg) of the hot water extract of the single and combined plant were administered intraperitoneally and 200 mg/kg of the combined extract and formulated extracts orally. 30 min after albumin injection in the different groups of animals the hind paw volume was measured before and after the albumin challenge plethysmometrically at 30min intervals for 3 h.

3.3.5 Effect of Extract on Guinea-Pig Bronchospasm.

Adult guinea pigs of either sex weighing between 350-450 g were used. The guinea -pigs was anaesthetised with sodium pentobarbitone (40 mg/kg 1.p). After a sufficient depth of anesthesia, the trachea was cannulated and the guinea pigs were artificially ventilated with the Ugo Basile rodent ventilator at 70 strokes per minute (70 SPM). The Rodent Ventilator is in turn connected to the Bronchospasm transducer (7020), and the volume of air displaced in the transducer arm containing distilled water is now recorded on the Ugo Basile Unirecorder 7050. The femoral vein of the guinea pig was cannulated for drug administration. The effect of the combined extract at doses of (10, 20, 60 mg/kg) and Acetylcholine (10 μg/kg) were investigated.

3.4 RESULTS.

3.4.1 Acute Toxicity Studies

The results of acute toxicity studies on the extract are shown in Table 3.1.

Table 3.1 RESULTS OF ACUTE TOXICITY STUDIES

Extract	LD_{50} (mg/kg)	
	i.p	oral
Prosopis africana	134.16	Not done
Anogeissus leiocarpus	69.28	Not done
Combined	282.2	> 1700

3.4.2 Effect on the Isolated Rabbit Jejunum

The effect of the extracts on the rabbit jejunum (smooth muscle) is represented in Fig 3.1,3.2,3.3 and 3.4.The Figures show that the three extracts (*Prosopis africana, Anogeissus leiocarpus* and combined) exhibited a dose dependent relaxation of the rabbit jejunum

3.4.3 Effect on the Guinea-Pig Isolated Trachea:

The effect of the combined extract on the isolated guinea pig trachea is presented on Fig 3.5. As shown the extract produced a slight but dose dependant relaxation of the guinea pig tracheal chain.

3.4.4 Anti-Inflammatory Studies using the Rat Paw Oedema

The effects of crude and formulated extracts are shown in Fig 3.6 and 3.7 respectively. As shown the extracts produced a dose dependant anti-inflammatory activity against the induced rat paw oedema. The formulated extract was also found to have an earlier unset of activity when compared to the crude extract, thereby indicating an improvement in the dissolution rate which might have led to the

3.4.5 Effect of extract on Guinea Pig Bronchospasm

The effect of the combined extract is shown on Fig. 3.8.The extract gave a dose dependent bronchodilatory effect

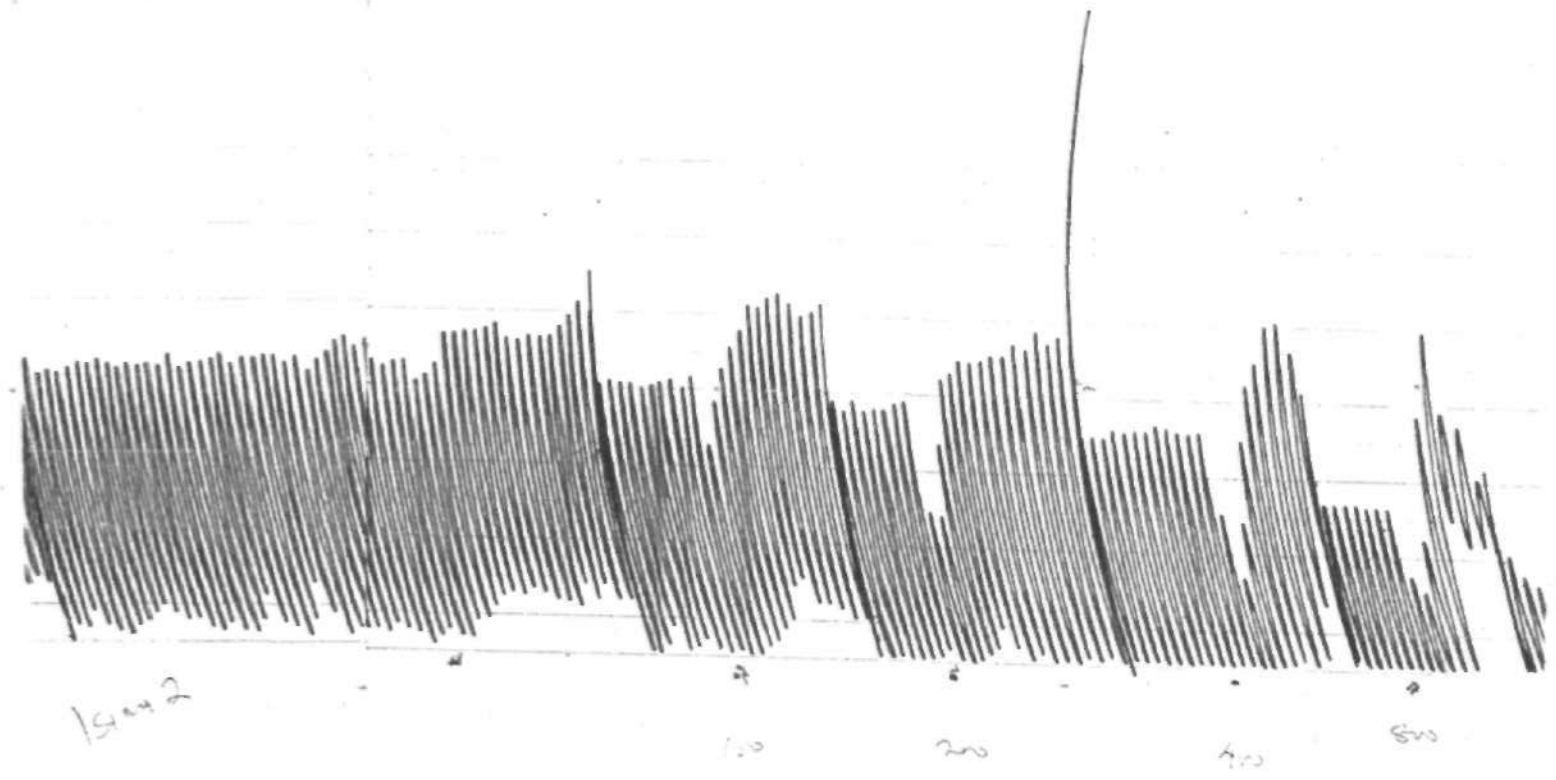


Fig. 3.1 Effect of *Prosopis africana* extract on rabbit jejunum (100, 200, 400 and 800 μg/ml)

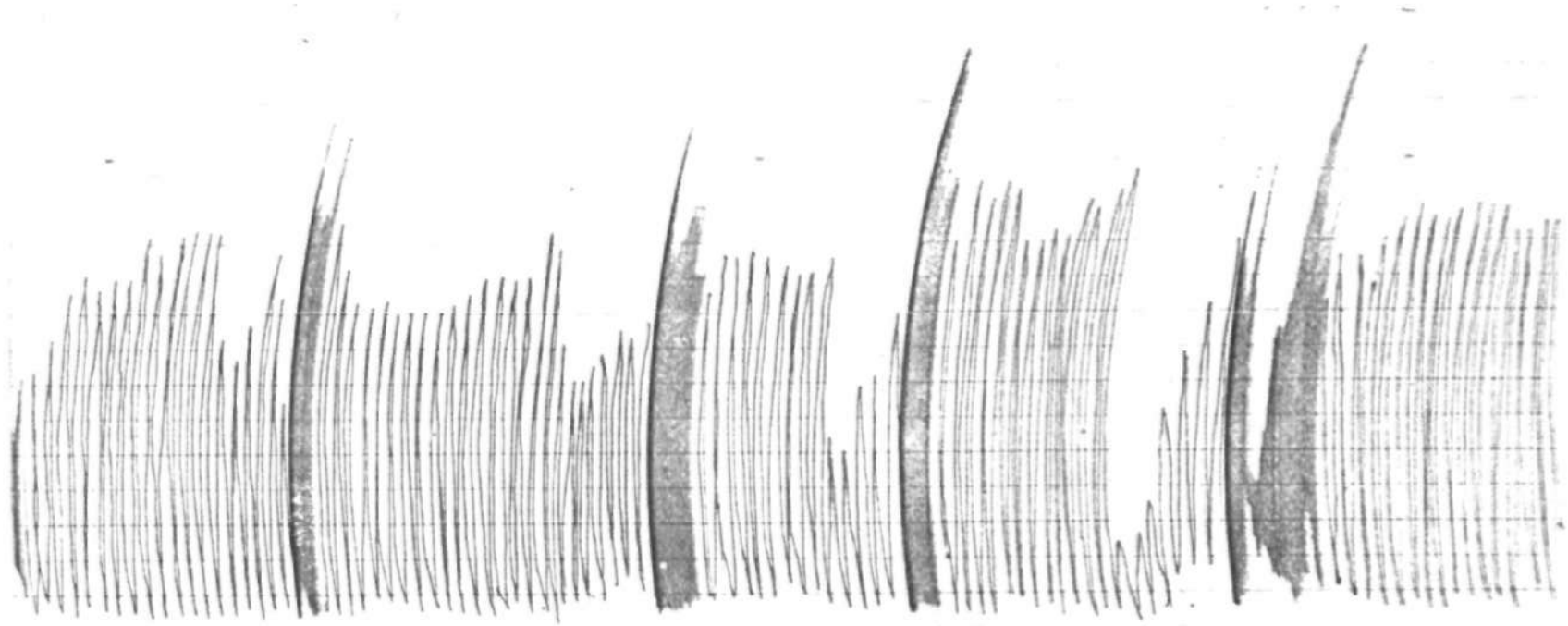


Fig. 3.2 Effect of *Anogessius leiocarpus* extract on rabbit jejunum (100, 200, 400 and 800 µg/ml)

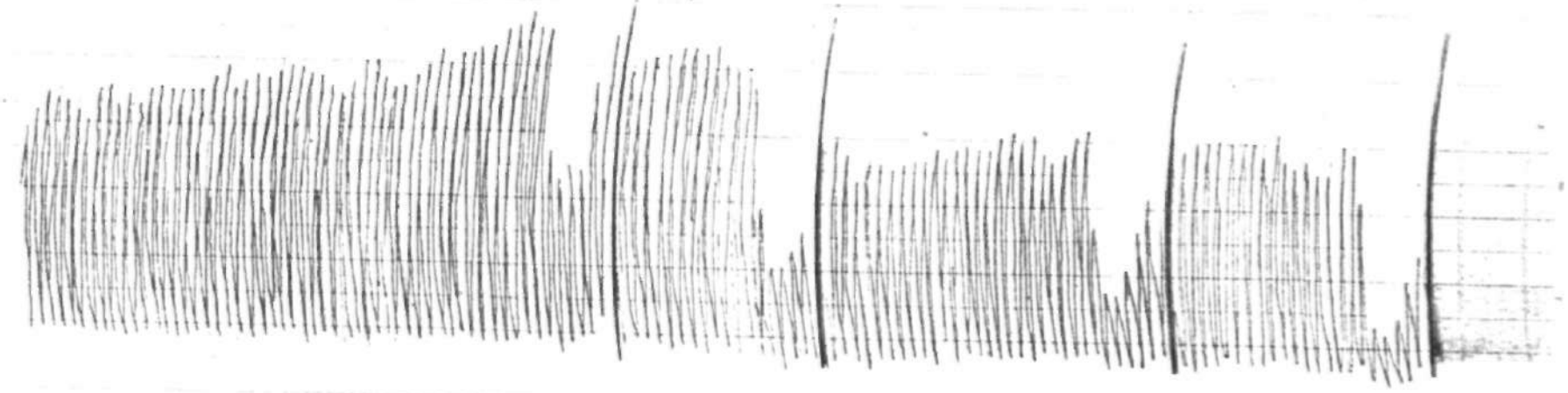


Fig. 3.3 Effect of Combined (*A. leiocarpus* and *P. africana*) extract on rabbit jejunum (100, 200, 400 and 800 μg/ml)

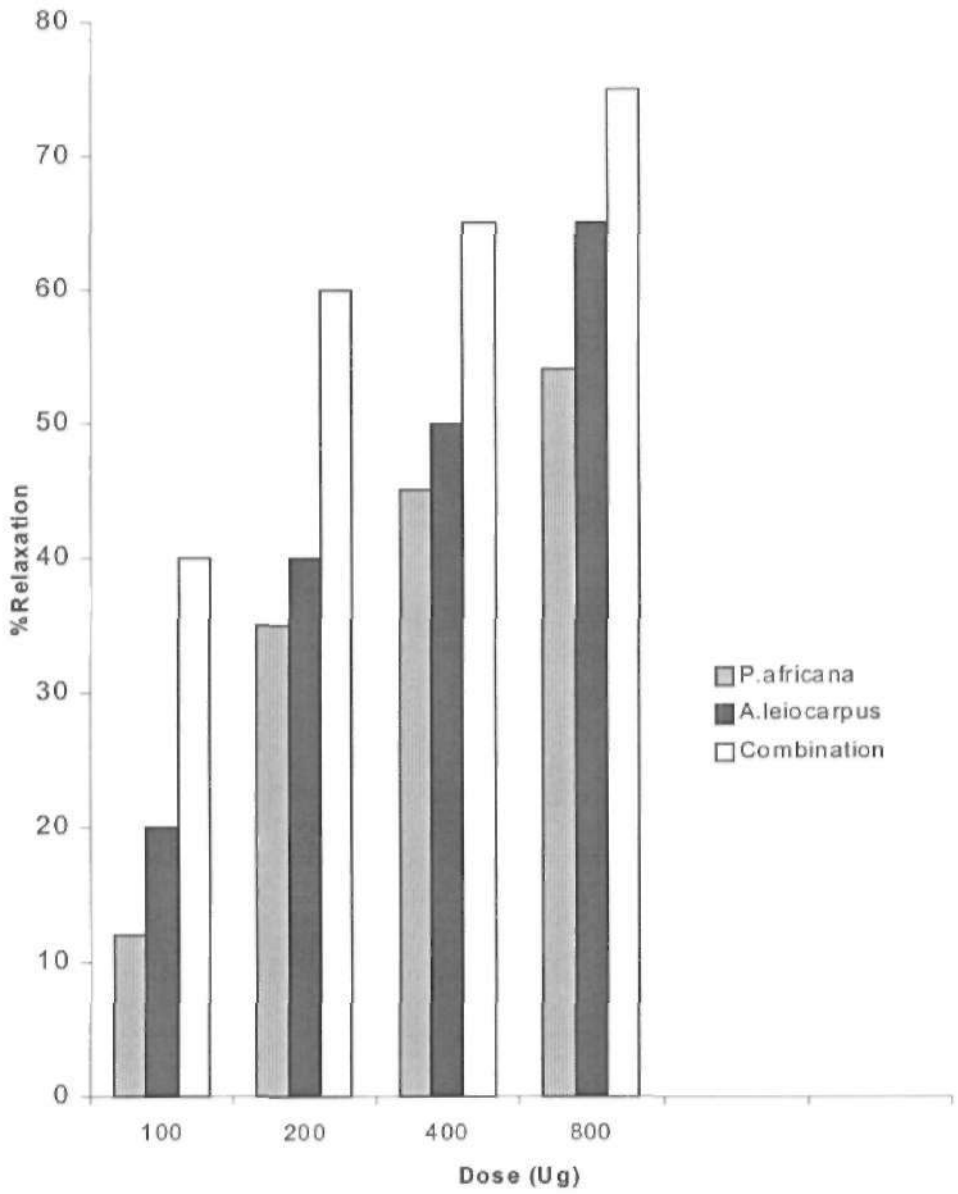


Fig 3.4. % Relaxation / Dose (ug/ml) of pure extracts and their combination on rabbit jejunum

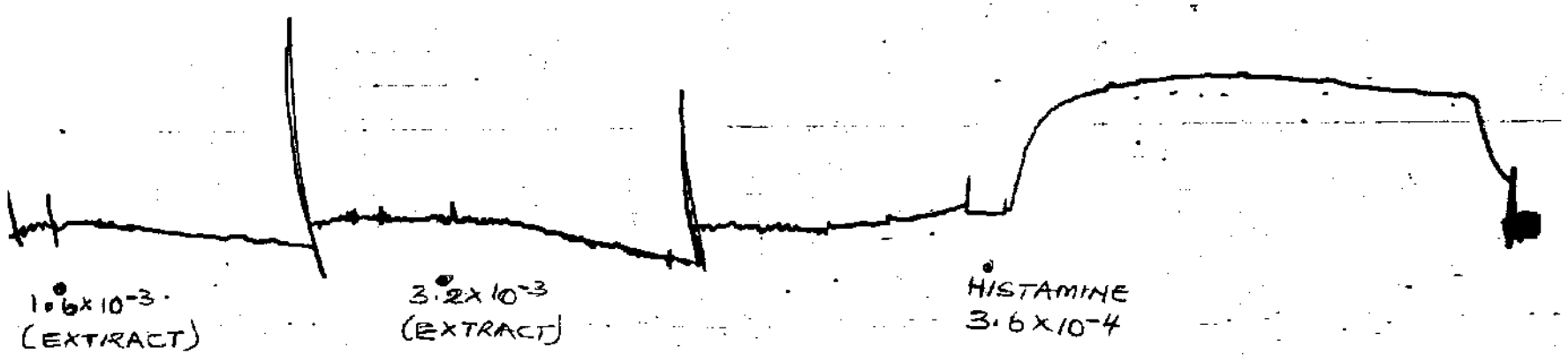


Fig 3.5 Effect of Combined (*A. leiocarpus/ P. africana*) extract on guinea pig tracheal muscle.

. - Extract (1.6 x10-^{3} : 3.2 x 10-^{3}g/ml) X- Histamine (3.6x10-^{4})

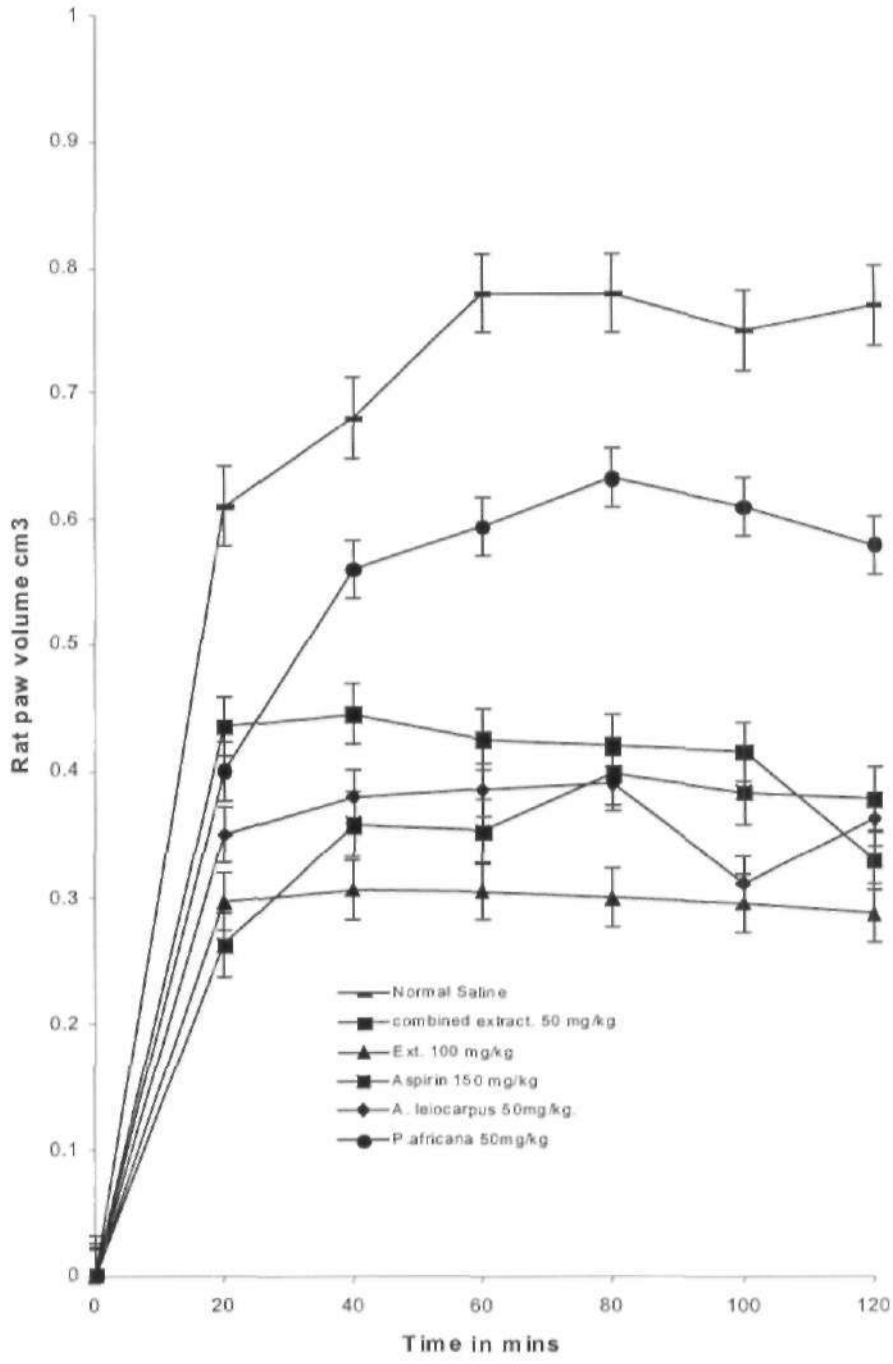


Fig 3.6 Rat paw volume (cm3) / Time(min) following administration of selected doses of crude extract on induced rat paw oedema.

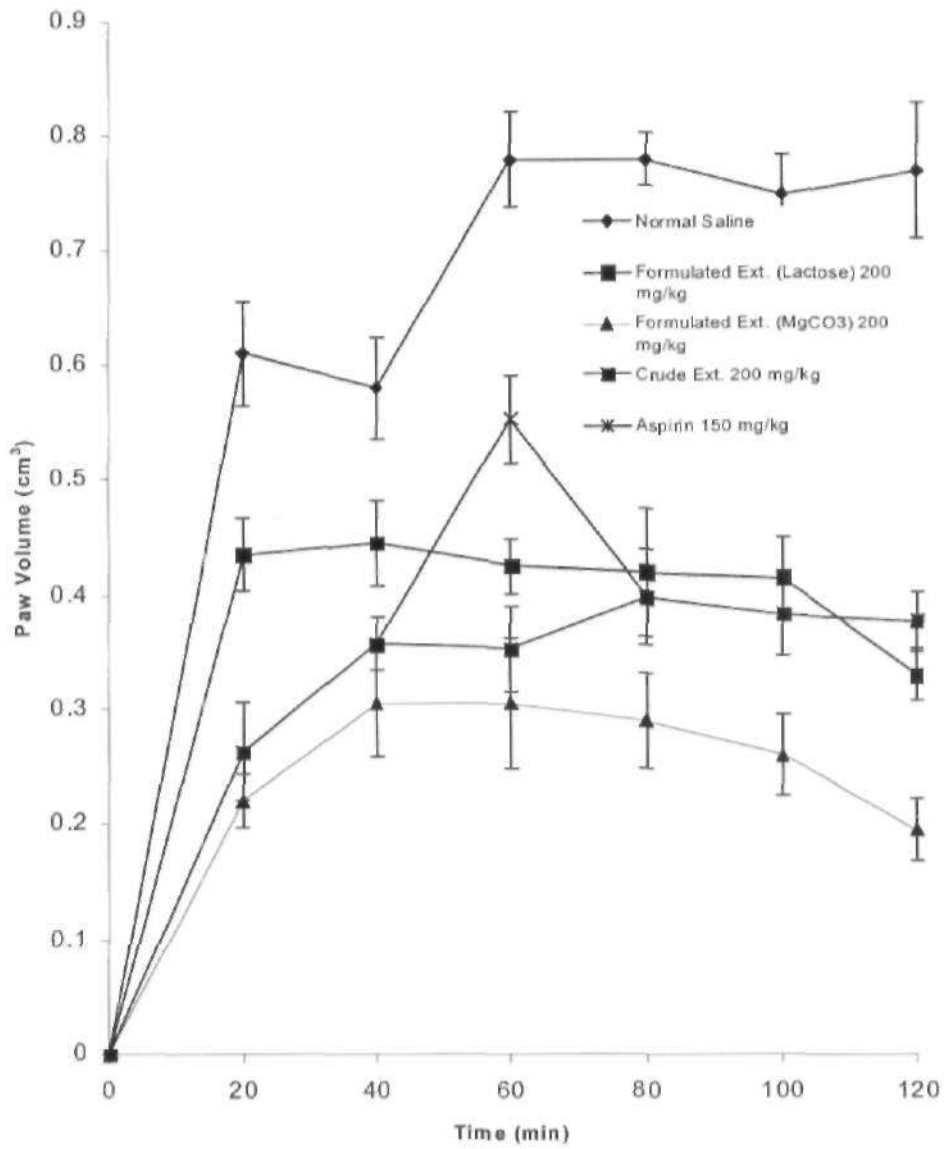


Fig. 3.7 Rat paw volume (cm3) / Time(min) following administration of selected doses of crude and formulated extract on induced rat paw oedema.Effect of formulated extract on induced rat paw oedema

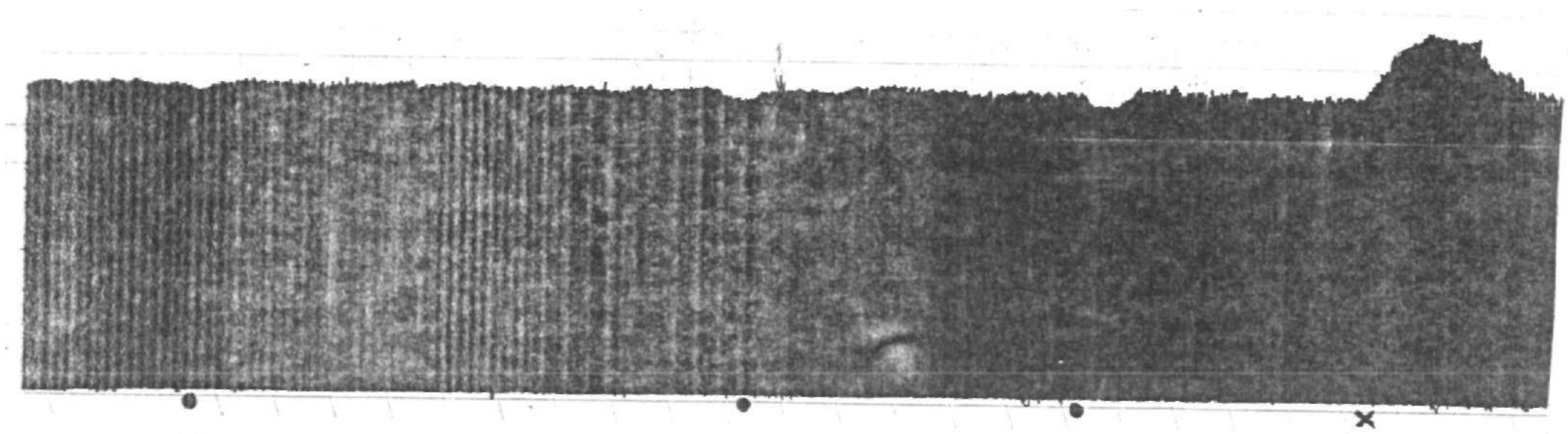


Fig 3.8 Effect of combined (P.africana / A. leiocarpus) extract on guinea pig bronchospasm.

Extract (•)(10mg/kg; 20mg/kg; 60mg/kg) , Acetylcholine (x) 10 μg /kg

observed dose dependant relaxation of the rabbit jejunum might therefore be due to the presence of flavonoids in the extract (Di Carlo *et al*, 1994)

Asthma is considered to be the final manifestation of an underlying inflammation process in the airways (Alastair *et al,* 1993*),* Barnes (1993), further mentioned that asthma has been rediscovered as an inflammatory disease and proved that inflammation is found even in patients with the mildest form of asthma. He further stated that the management of asthma has changed substantially and fundamentally to the early introduction of anti-inflammatory agents rather than reliance on bronchodilators. These facts motivated the investigation into the anti-inflammatory properties of the extracts. The study revealed that *Anogeissus leiocarpus, Prosopis africana* and the combination produced a dose dependant anti-inflammatory activity. Tannins have been reported to exhibit anti-inflammatory activity in acute and chronic inflammatory processes (Kimura and Okuda, 1986). Extracts of *Anogeissus leiocarpus* and *Prosopis africana* at 50mg/kg did not produce a significant ($p< 0.05$) anti-inflammatory effect comparable to Aspirin. The combined extract produced an additive anti-inflammatory activity when compared to the individual plant activity (i.e. % inhibition of combination at 100mg/kg was close to the sum of the individual plant extract's % inhibition)

The anti-inflammatory activity of the formulated extract was similar to that of the crude extract. There was an initial lower paw volume observed with the formulated extract and this observation suggests a possible improvement on the disintegration and /or dissolution properties of the extract leading to an earlier onset of activity.

In asthma the symptoms (paroxysms of expiratory dyspnoea, wheezing, over inflation of the lungs, cough and rhonchi) are due to generalised bronchial airway obstruction, which occur as a result of contraction of bronchial smooth muscles (Norman, 1971). The observed dose dependant relaxation of the guinea pig tracheal chain and bronchiodilatory effect on the guinea pig

bronchiospasm is therefore a scientific indication for the use of the extract in asthma management.

3.6 CONCLUSION

The extract having an LD_{50} > 1.7 g/kg was found to be safe. The pharmacological activity on the anti-asthmatic models i.e. a dose dependent relaxation of the tracheal chain smooth muscle, bronchodialatory effect on guinea pig bronchospasm and the anti-inflammatory activity against the rat paw oedema, all indicate a positive correlation between the effects of the extract and its use in traditional medicine for the management of Asthma.

CHAPTER 4

4.0 FORMULATION PROPERTIES OF HOT WATER EXTRACT.

4.1 INTRODUTION.

Without any iota of doubt and for obvious reasons, tablets represent the most popular dosage form among the contemporary methods of drug administration. In the manufacture of tablets, certain pharmaceutical compounds of diverse origin and chemical activities are usually incorporated with the active ingredient to aid the processing into suitable dosage form. These compounds are generally referred to as tablet excipients, which include diluents, binders, disintegrants, lubricants, etc. They are pharmaceutically important functional component for tablets and therefore represent the framework of the design of tablet formulation.

Several studies have been carried out on the effect of these excipients on the properties of granule and tablets. Levy and Gumtow (1963) studied the effect of certain tablet formulation factors on dissolution rate. Commins *et al* (1968) worked on the influence of starch concentration on disintegration time of tablets. Kassen *et al* (1972) worked on the effect of granule size on physical standards of tablets, while Nasipuri and Akala (1986) and Kunle and Bangudu (1990), studied the effect of binder concentration and type on tablet properties.

This section of the work is aimed at investigating the effect of different excipients on the physical properties of granules and resulting tablets, with a view of selecting the best excipients required to formulate the plant extract into an acceptable tablet dosage form.

4.2 MATERIALS

4.2.1 Chemicals

Hot water extract from section 2.2.2.1

Lactose B.P, Maize Starch B.P (NIPCO Pharmaceuticals, Abuja)

Polyvinyl pyrollidone (PVP) 25-30 (Merck).

Gelatin B.P. (Fisons Scientific, England)

Heavy magnesium Carbonate ,Magnesium Stearate (BDH, U.K)

Xylene (Hopkin and Williams) Essex England.

4.2.2 Equipments

Set of sieves (75, 150, 250, 500, 833 μm).

Ultra X moisture balance

Endecott's test sieve shaker (Endecotts, London, UK)

Erweka (Germany) flow tester

Stampt volumeter model stat 2003, Japan

Pyconometer. (Model 930, Beckman Instrument Ltd).

Single punch power driven tablet press (model THP Shangai)

Monsanto hardness tester (England)

Erweka double drum friabilator (Copley TAR, Germany)

Erweka dissolution apparatus (Germany)

Shimadzu U.V -160A Spectrophotometer (Japan)

4.3 METHODS.

4.3.1 Granulation

Different granule batches were formulated using the wet granulation method. Excipient type/ concentration was varied in the different batches depending on the particular variable being studied. The formula on Table 4.1 below was used for the wet granulation method of massing and screening.

TABLE 4.1: TABLET FORMULA

	Weight per tablet (mg)
Extract	240
Diluent*	360
Binder**	
Disintegrant***	
Lubricant	0.2% w/w
Total wt of Tablet	630

* Lactose; $MgCO_3$

** Starch mucilage: 2.5 and 5.0% w/w
Gelatin: 2.5 and 5.0% w/w
PVP: 2.5 and 5.0% w/w
Water: quantity sufficient

*** Starch 5 and 10% w/w
Cross-linked PVP 2 and 5% w/w
Starch/ 0.2%Na lauryl sulphate 5% w/w

Starch/ 0.2%Na lauryl sulphate – This was prepared by mixing starch BP with 0.2% w/w of Na lauryl sulphate (A surfactant) and used as a disintegrant.

The extract was mixed with other excipients (diluent and disintegrant) for 5 minutes in a mortar using a pestle, after which the binder solution was added in small aliquots. The three binders used were prepared as follows: -

Starch mucilage

Starch powder required to make 2.5% w/v mucilage was suspended in a small quantity of cold water to form a smooth suspension (free from clumps).

Boiling water was then added to the suspension and stirred until mucilage was formed.

Polyvinyl Pyrollidone (PVP) binder

The quantity of PVP powder required to make 2.5% and 5.0 w/v solution of the binder was suspended in cold water and stirred until all the powder went into solution.

Gelatin binder

The required amount of powdered gelatin was suspended in cold water and allowed to hydrate. The suspension was then warmed on a water bath until a flowable material was obtained. To avoid gelling, the binder solution was kept warm during use.

The binders were added to the powder and mixed 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 moistened mass was forced through a 1000 μm screen and the wet granules dried at 60°C for 45 minutes. The dried granules were again forced through the 1000 μm screen in order to break down any lumps.

4.3.2 Granule Properties.

4.3.2.1 Granules Size Distribution

The sieve method as described by Martin *et al*, (1983_a) was employed. 50 g of the granules was used for the analysis. Five (5) sieves of sizes 75, 150, 250, 500 and 833 μm were used. The sieves were arranged in order of decreasing aperture (the largest aperture being on top and the finest at the bottom next to the collector pan). The stack was mounted on an Endecott's test sieve shaker. The granules were placed on the topmost sieve and shaken for 15 minutes. The weights of the granules retained on each sieve including the pan were recorded. The percentage cumulative size was plotted against the sieve

aperture, from which the median particle size was calculated (Marcelo *et al*, 1997).

4.3.2.2 Moisture Content

Moisture content was determined on the Ultra X moisture balance. 10 g of the granules was placed on the moisture balance; the % moisture content was automatically recorded. The average of three of such readings was taken.

4.3.2.3 Flow Rate

This was determined on the Erweka flow tester.10g of the granules was placed in the funnel with the lower orifice closed. The flow rate was automatically calculated on opening the orifice. The average of three readings was taken.

4.3.2.4 Bulk and Tapped Densities

The Stampt volumeter model star 2003 was used. 50 g of the granule was accurately weighed and gently poured into the 100 ml measuring cylinder with the aid of a glass funnel. The powdered volume (Vbp) was read to the nearest 0.5 ml and the bulk density calculated in gm/ml. The cylinder containing the granules was then tapped using the stamp and volumeter until constant volume was obtained. From this, the tapped density was calculated.

4.3.2.5Compressibility Index (Carr 1965).

This was calculated using the equation.

$$C = 1 - \frac{Db}{Dt} \times 100 \quad \text{.....9}$$

Where C is % Compressibility, D_b is bulk density and D_t is tapped density.

4.3.2.6 True Density

The specific gravity bottle method was used (Martin et al, 1983_b). The pycnometer (model 930, Beckman Instrument Ltd) was filled with xylene and

weighed after wiping the spill over liquid. One gram of the granules was weighed and carefully poured into the empty specific gravity bottle, xylene was carefully poured into the pycnometer containing the sample, stirred and allowed to stand for 10 minutes so as to equilibrate with the ambient temperature and ensure release of air bubbles. The pycnometer was thereafter filled to the mark, wiped and the weight of bottle plus content determined. The particle true density D_t was calculated using the equation.

$$Dt = \frac{W}{(a+W)-b} \times SG \quad \text{.....10}$$

where W is weight of granules;

S.G is specific gravity of solvent (xylene);

a is weight of bottle +xylene and

b is weight of bottle + xylene + granules.

4.3.2.7 Angle of Repose

40 g of granules was allowed to flow through a funnel from a fixed height unto a flat surface. The radius (r) and the height (h) were determined. The angle of repose (ϕ) (Martin et al 1983_c) was calculated using equation

$$Tan\Phi = \frac{h}{r}$$

$$\Phi = \arctan\frac{h}{r} \quad \text{.....11}$$

4.3.3 Compression of Granules

The granules were lubricated and compressed using a single punch power driven tablet press (model T.H.P Shangai.) The machine was fitted with a 12 mm concave punch and die set and set at pressure 8 on the machine scale. The speed was set at 15 tablets per minute. The machine settings were arrived at after preliminary investigations.

4.3.4 Evaluation of Tablet Properties.

4.3.4.1 Weight Variation

A total of 10 tablets were used per batch. The tablets were weighed individually and collectively. The average weight, standard deviation and coefficient of variation in each case were respectively determined.

4.3.4.2 Hardness

The crushing strength was determined using the Monsanto hardness tester. The mean of six readings was taken.

4.3.4.3. Friability

Ten tablets were subjected to friabilation in an Erweka double drum friabilator (Copley TAR) at 25 rpm for 4 minutes. The weights of the tablets before and after friabilation were taken. The percentage weight loss was calculated from which percentage friability was determined. The mean of two such determinations was calculated, where capping or fracture of the tablet occurred, friability values were not calculated.

4.3.4.4 Disintegration Tests

The *in-vitro* disintegration time (DT) of the various batches of tablets were determined as recommended in B.P (1993) using an Erweka 4 - station disintegration tester. Distilled water thermostated at $37^{\circ}\pm0.5^{\circ}C$ was used as the disintegration medium. The average of three determinations was taken as the disintegration time.

4.3.4.5 Dissolution Test

Standard solutions of the extract were prepared and filtered through a 0.2 μm filter paper. Using the λmax of 287 nm (Peak from the UV spectra of extract on pg 41), a standard curve (Fig 4.1) was plotted.

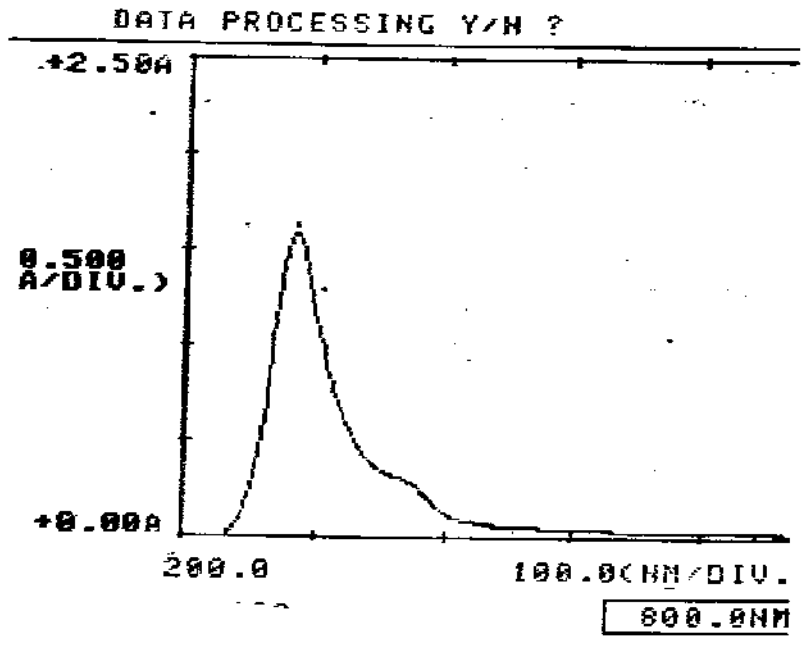


Fig. 4.1(a) U.V Spectra of Hot water combined extract

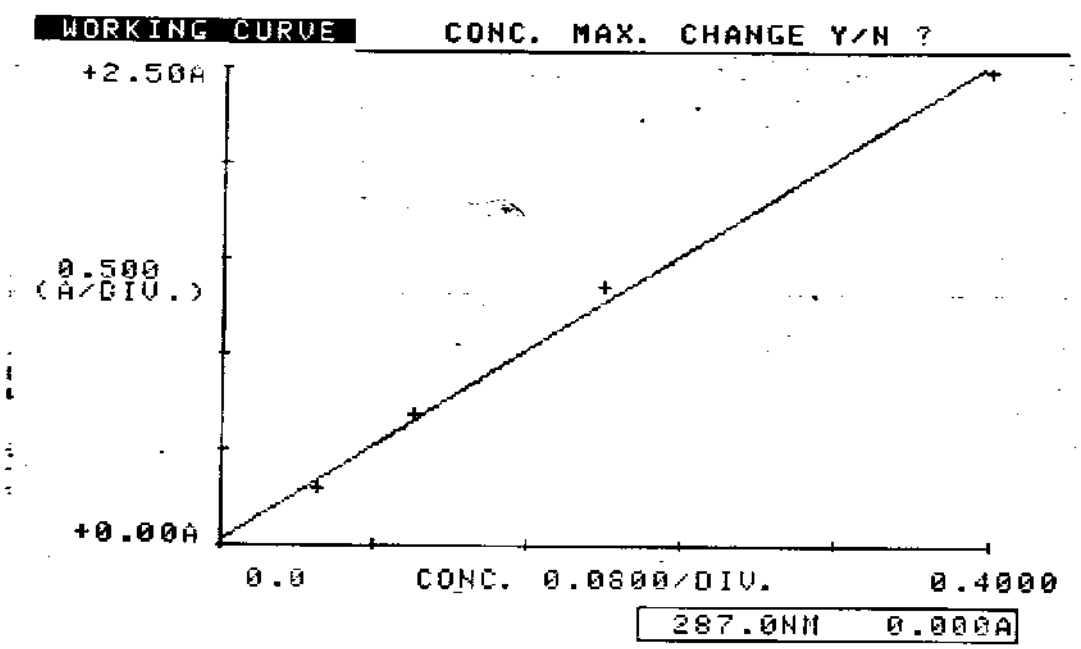


Fig. 4.1(b) Working Curve for dissolution test.

Dissolution test was performed on the tablets using an Erweka dissolution test apparatus; the USP (1990) basket method was followed. The medium used was distilled water thermostatically maintained at 37°±0.5°C using the USP basket method, at a rotational speed of 100rpm (Erweka dissolution test apparatus, model DT). Samples of 2ml were withdrawn at regular time intervals; replaced by distilled water using a syringe and filtered through a 0.2 μm pore filter paper. The samples were suitably diluted with distilled water and analysed using the quantitative mode of the spectrophotometer at a predetermined wave length of 287nm.All dissolution experiments were performed in triplicates and average values calculated.

4.4 RESULTS AND DISCUSSION

4.4.1 Effect Of Variables on Granule Properties

Effect of Diluent's Type on granule properties

Fig. 4.2 shows the cumulative size distribution of granules prepared using lactose and $MgCO_3$ as diluent and starch as binder. Lactose produced bigger granules than $MgCO_3$ having a median granule size of 575 μm as against 390 μm for $MgCO_3$. This and other differences observed such as differences in moisture content, flow rate and densities are explained below.

Table 4.2 Properties of Granules prepared with Starch as Binder

Properties	Diluent type		
	Lactose	$MgCO_3$	Extract
Moisture content (%)	5.9	3.8	7.5
Bulk density (g/ml)	0. 59	0. 47	0.81
Tapped density (g/ml)	0. 63	0. 53	1.136
True density (g/ml)	1.61	1.95	1.76
Angle of repose	28.10	26.90	-
Flowability (g/sec)	7.27	12.31	-
% Compressibility	5.92	9.50	28.32

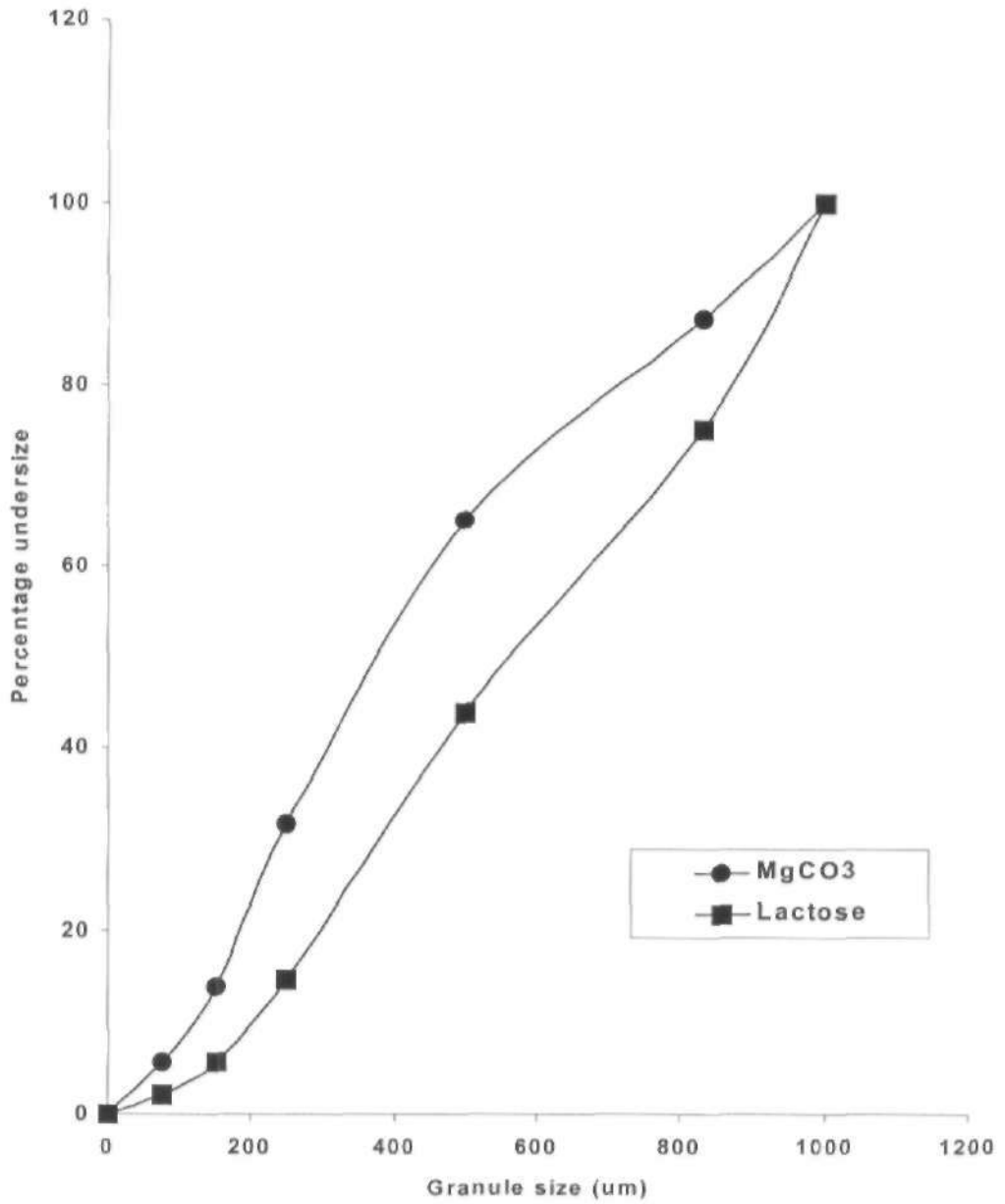


Fig 4.2 Percentage undersize Granule size (um) for granules prepared using Lactose and Magnesium Carbonate as diluents and starch as binder

Results shown in Table 4.2 show that granules produced using $MgCO_3$ as diluent had lower moisture content than those produced using lactose. This difference in moisture content may be attributed to the inherent nature of the diluents as well as differences in the granule size. $MgCO_3$ being only slightly soluble in water would easily loose any water absorbed from the granulating fluid when exposed to drying. Lactose on the other hand is water-soluble and water absorbed from the granulating fluid will not be easily lost during drying. Granules produced using $MgCO_3$ as diluent were smaller in size, resulting to a greater surface area exposed to drying leading to higher loss of moisture.

The true density of granules produced with $MgCO_3$, as diluent was higher than those from lactose. This is probably due to the densities of the diluents. $MgCO_3$ granules, which were smaller, were able to form closer, more intimate packing than the larger lactose granules. This may account for the observed higher bulk and tapped densities for the $MgCO_3$ granules.

Particles size and size distribution has been reported as one of the factors that influence flow of powders. It is generally expected that decrease in particle size will lead to an increase in cohesiveness amongst the fines, and thus constituting an impediment to flow (Martin *et al* 1983_c, Neumann, 1976). This was not observed when the different diluents were used. Granules produced using $MgCO_3$ as diluent of smaller sizes gave better flow properties (lower angle of repose and higher flow rate) than those produced with lactose. This observation may be due to higher moisture content of the latter, which might have made the granules more cohesive thereby, exhibiting poor flow characteristics

Effect of Binder Concentration on Granule Property

The size distributions of granules prepared using lactose and $MgCO_3$ as diluent and starch as binder are shown in Fig 4.3 and 4.4 respectively. The graphs show that granule sizes increased as binder concentration increased from 2.5% to 5.0% irrespective of the diluent used. This was to be expected

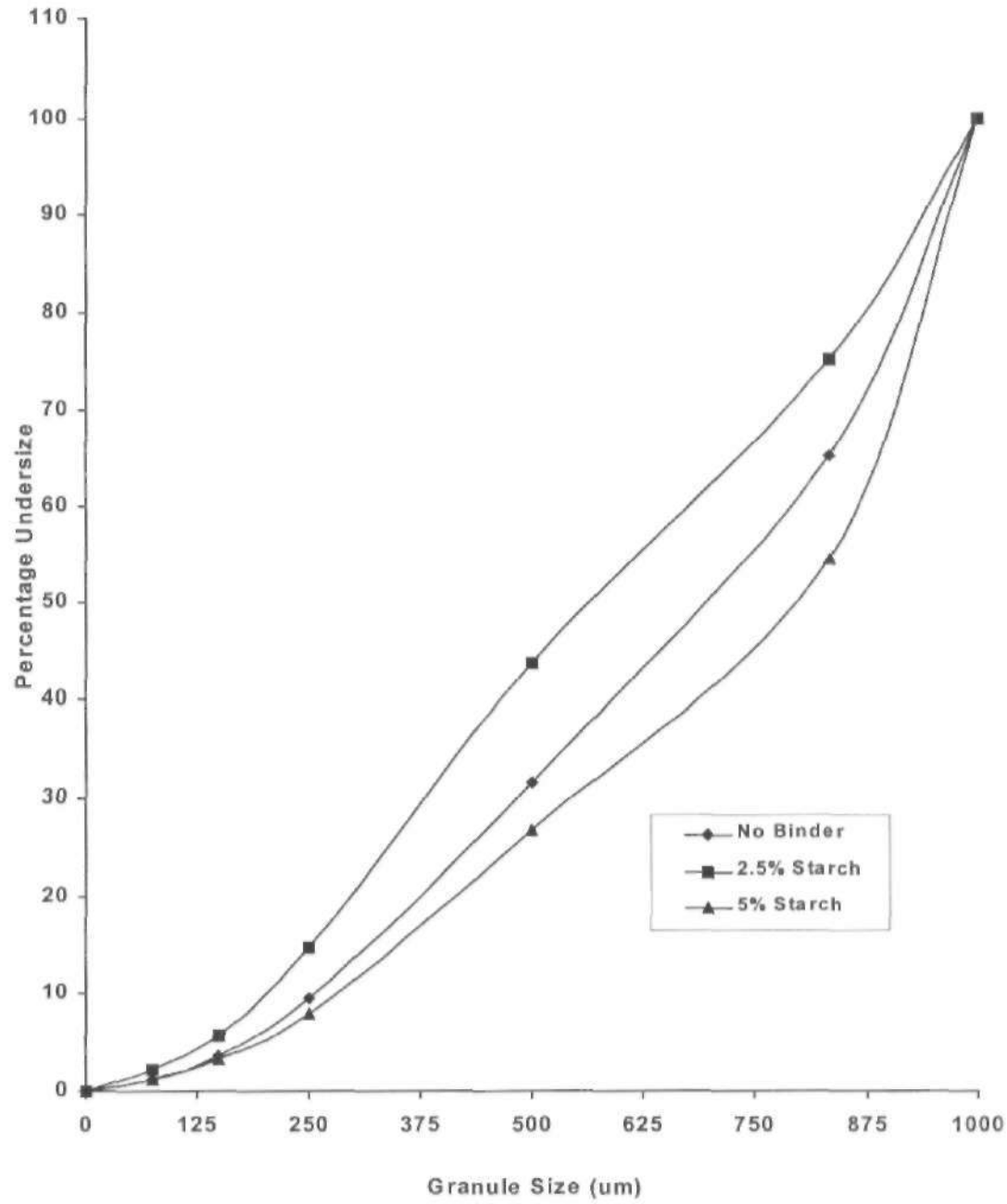


Fig. 4.3 Percentage undersize/ Granule size (um) for granules prepared using Lactose as diluent and selected concentrations of starch as binder.

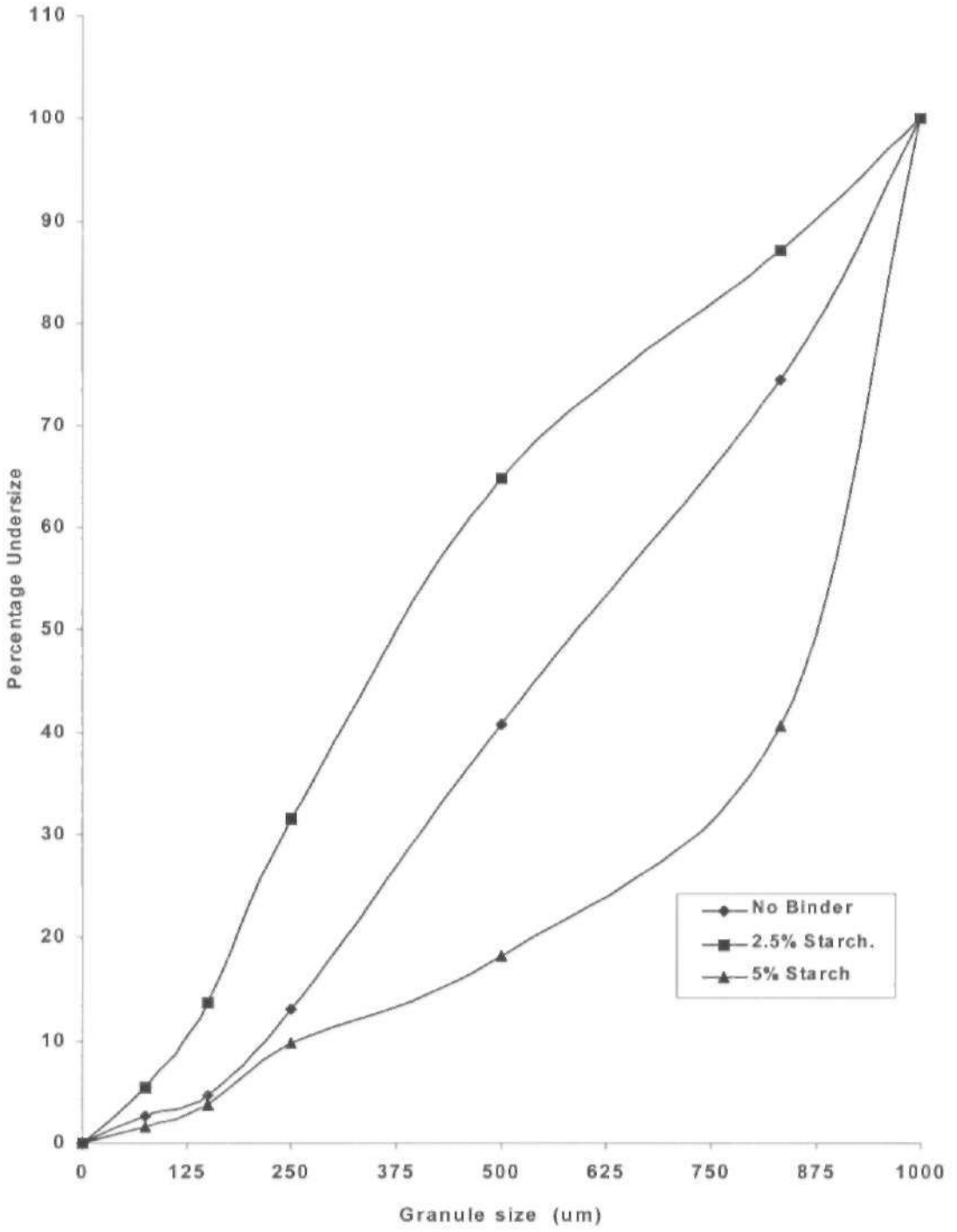


Fig. 4.4 Percentage undersize/ Granule size (um) for granules prepared with $MgCO_3$ as diluent and selected concentrations of Starch as binder

since increase in binder concentration would invariably lead to increased viscosity and stronger bridges between the granules (David and Gloor, 1971, Kunle 1988). The formulation in which only water was used as binder however had average granule size was greater than that of granules formulated with 2.5% binder concentration but less than granules formulated with 5.0% binder concentration. This did not follow the trend expected but may have been due to better penetration, coverage and wetting ability of water due to its low viscosity (Chalmers and Elworthy, 1976).

Tables 4.3 and 4.4 show the effect of different concentrations of starch binder on the properties of granules prepared using lactose and $MgCO_3$ as diluent respectively. There was a general decrease in moisture content with increase in binder concentration.

A decrease in bulk and tapped densities for the granules was observed with increase in binder concentration from 0% to 2.5%. There was however a decrease in tapped and bulk densities as the binder concentration was increased from 2.5% to 5.0%. For granules formulated with gelatin and PVP as binder, there was a decrease in bulk density with increase in binder concentration from 0% to 5.0% while the tapped density decreased with increased binder concentration from 0% to 2.5% and then increased when binder concentrations was further increased from 2.5% to 5.0%.

There was a direct relationship between binder concentration and compressibility. Percentage compressibility increased with increasing binder concentration except for Magnesium Carbonate granules prepared with gelatin as binder (Table 4.3). Here it was observed that there was an initial decrease in % compressibility as binder concentration increased from 0 to 2.5%. Further increase in binder concentration from 2.5 to 5.0% led to an increase in % compressibility.

The effect of different concentrations of binder on the flow properties of resulting granules differs from one diluent to another, with granules formulated

Table 4.3 Properties of Granules Prepared with lactose as diluent *using selected concentration of starch as binder.*

Property	Binder concentration (%w/w)		
	0	2.5	5.0
Moisture content (%)	6.1	5.9	5.7
Bulk density (g/ml)	0.49	0.51	0.53
Tapped density (g/ml)	0.56	0.59	0.56
True density (g/ml)	1.59	1.53	1.71
Compressibility (%)	10.83	13.6	5.83
Flow rate (g/sec)	5.82	5.92	5.11
Angle of repose (θ)	31.21	27.72	31.21

Table 4.4 Properties of Granules prepared with $MgCO_3$ as diluent using different concentrations of starch as binder

Property	Binder concentration (%w/w)		
	0	2.5	5.0
Moisture content (%)	3.2	3.8	4.2
Bulk density (g/ml)	0.78	0.85	0.77
Tapped density (g/ml)	0.91	0.98	0.87
True density (g/ml)	1.91	1.95	2.00
Compressibility (%)	14.22	12.81	11.53
Flow rate (g/sec)	10.66	12.31	9.96
Angle of repose (θ)	29.45	28.99	29.56

with starch as binder, there was an initial increase in flow rate and decrease in angle of repose with increased binder concentration from 0-5% w/w. This was observed for both granules with lactose and magnesium carbonate as diluent (Tables 4.3 and 4.4). For granules formulated with gelatin and PVP as binder, the relationship varied. There was initial decrease in both flow rate and angle of

repose with increased binder concentration from 0 to 2.5% followed by an increase when binder concentration was further increased from 2.5 to 5.0% (Table 4.5).

Table 4.5 Properties of Granules prepared with $MgCO_3$ as diluent using selected concentrations of gelatin as binder.

	Binder concentration (%w/w)		
Granule Property	0	2.5	5.0
Moisture content (%)	3.2	3.1	3.3
Bulk density (g/ml)	0,78	0.77	0.75
Tapped density (g/ml)	0.91	0.87	0.88
True density (g/ml)	1.91	1.96	2.06
Compressibility (%)	14.22	11.53	15.01
Flow rate (g/sec)	10.66	7.74	12.66
Angle of repose (θ)	29.45	28.90	29.14

Effect of binder type on granule properties

The effect of binder type on granule size distribution (mean granule size) was dependant on diluent used. Fig. 4.5 and 4.6 illustrate the cumulative granule size distribution of granules formulated with lactose and $MgC0_3$ respectively. The mean granule size for lactose granules were in the order:

Starch > PVP > water > gelatin;

while for $MgC0_3$ granules, the order was:

Gelatin > water > PVP > starch

The effect of binder type on moisture content in granules formulated with lactose as diluent tend to follow the order of granule size with smaller granules having lower moisture content (Table 4.6). This may have been due to the ability of smaller granules to lose more moisture during drying due to its surface area. This was not observed with granules formulated with Magnesium carbonate as diluent; as granules with starch as binder, that were smaller did

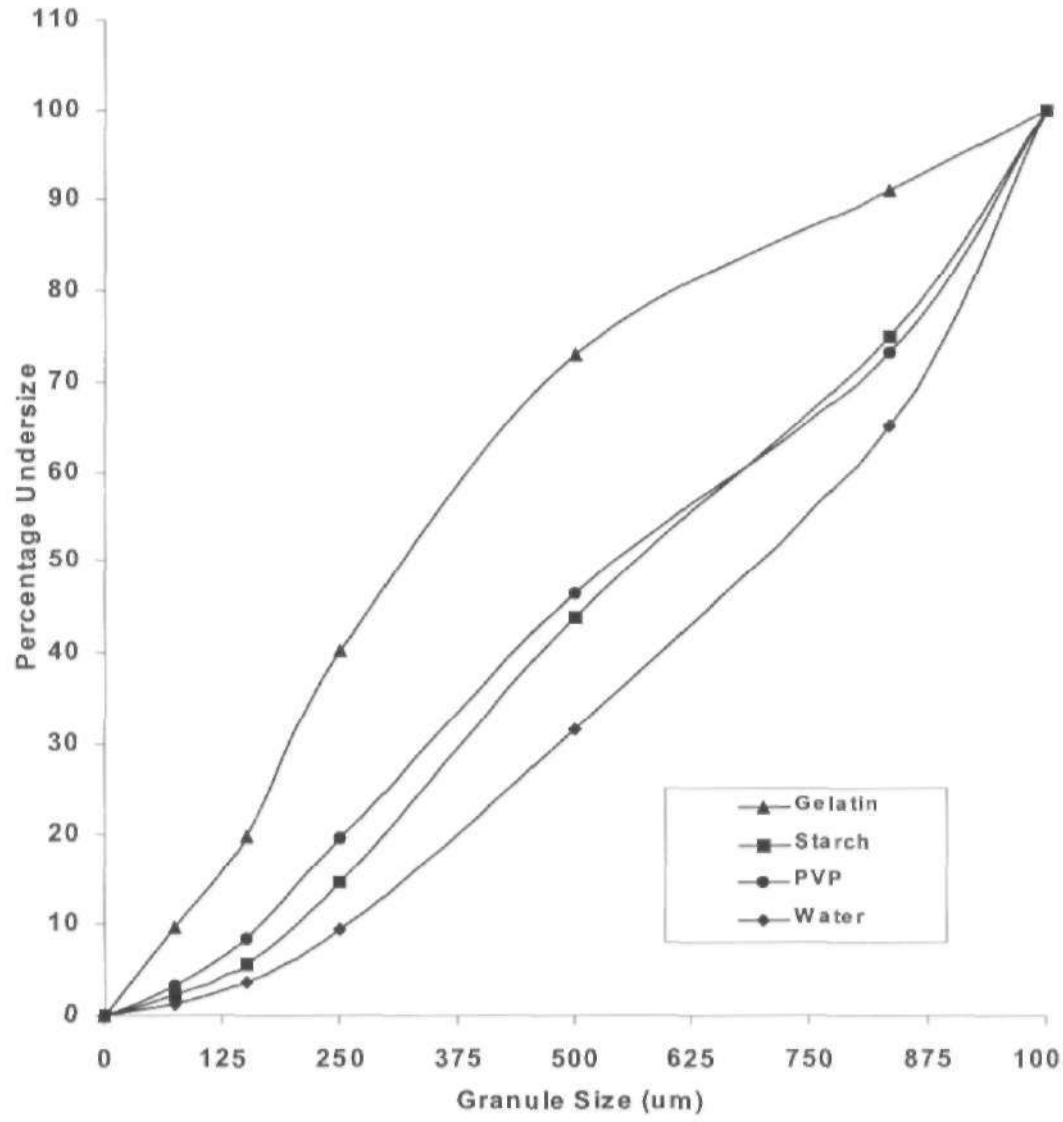


Fig. 4.5 Percentage undersize/ Granule size (um) for lactose granules formulated with the selacted binders.

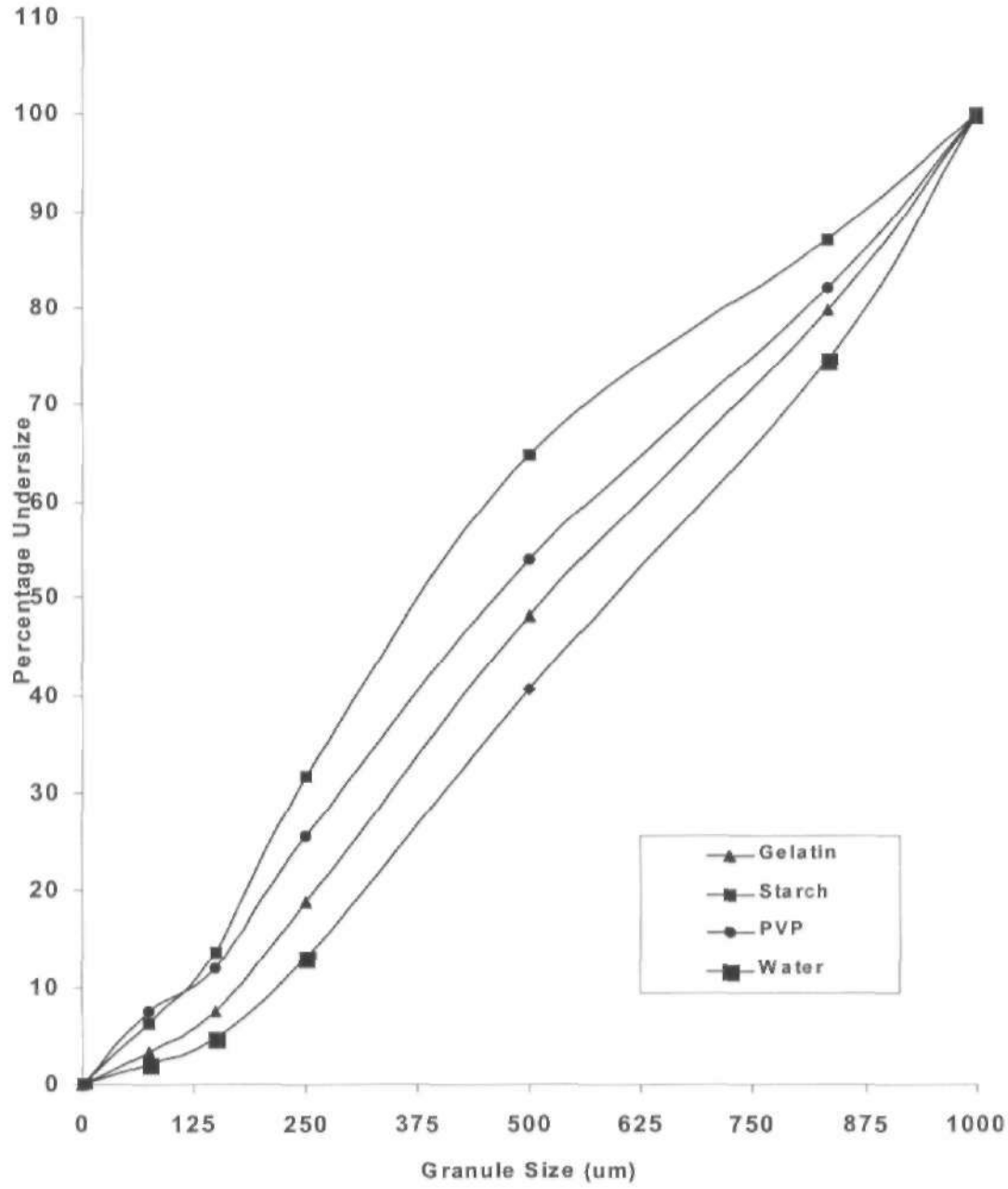


Fig 4.6 **Percentage undersize/ Granule size (um) for granules containing $MgCO_3$ formulated with the selacted binders.**

not have the least moisture content. This suggests that factors other than granule size, like inherent properties of the diluent may have contributed to binder type-moisture relationship.

Tablet 4.6 Properties of Granules prepared with lactose as diluent using selected types of binders.

Granule Property	Binder type			
	Water	Starch	Gelatin	PVP
Moisture content (%)	5.8	5.6	5.2	5.5
Bulk density (g/ml)	0.50	0.59	0.51	0.47
Tapped density (g/ml)	0.56	0.63	0.58	0.54
True density (g/ml)	1.59	1.61	1.53	1.51
Compressibility (%)	10.83	5.92	11.83	11.81
Flow rate (g/sec)	5.82	7.27	8.88	6.49
Angle of repose (θ)	31.55	28.10	28.61	31.65

Tablet 4.7 Properties of Granules prepared with $MgCO_3$ as diluent using selected types of binders

Granule Property	Binder type			
	Water	Starch	Gelatin	PVP
Moisture content (%)	3.2	3.78	3.7	3.9
Bulk density (g/ml)	0.78	0.85	0.77	0.74
Tapped density (g/ml)	0.91	0.97	0.87	0.87
True density (g/ml)	1.90	1.95	1.90	1.87
Compressibility (%)	14.22	12.81	11.53	14.18
Flow rate (g/sec)	10.66	12.31	10.00	12.01
Angle of repose (θ)	29.46	28.99	28.90	29.24

The true densities were in order of starch > water > gelatin > PVP for both diluent used. Binder type / compressibility relationship was affected by diluent type and did not follow any particular order; but the granules formulated with starch as binder and lactose as diluent had the lowest compressibility value, indicating better flow, Carr (1965). The flow properties, such as flow rate and angle of repose were not significantly affected by binder type. The granules formulated with starch as binder and lactose as diluent had best flow properties.

Effect of Disintegrant type and concentration

The moisture content was dependant on the type and concentration of diluent used (Table 4.8). The granules formulated with treated starch gave highest moisture content and this might have been due to the wetting action of the surfactant leading to increase in the rate and extent of water penetration into the powder mix (Kunle, 1997). Moisture content of granules formulated with starch as disintegrant increased with increase disintegrant concentration. PVP (C.L) gave granules of lowest moisture content, and the moisture content decreased with increase in PVP (C.L) concentration.

The true densities increased with increase in disintegrant concentration and granules formulated with starch as disintegrant had lowest true densities followed with granules formed with PVP (C.L) as disintegrant. Highest true density was observed for granules formulated with treated starch (starch/ 0.2% lauryl sulphate).

Addition of sodium lauryl sulphate caused a decrease in both bulk and tapped densities. These results are similar to those reported by Opakunle and Akinpelu (1990). The bulk and tapped densities of granules formulated with PVP (C.L),(a cross-linked polyvinyl pyrollidone) were lower than those formulated with starch as disintegrant and this decreased with increase in disintegrant concentration.

Percentage compressibility was affected by both type and concentration of disintegrant used. There was increase in percentage compressibility with increased disintegrant concentration for granules
formed with starch as diluent. Percentage compressibility was not significantly affected by varying disintegrant concentration with granules formulated with PVP (C.L) as disintegrant. Granules formulated with 5.0% starch as disintegrant gave lowest percentage compressibility, an indication of good flow properties (Carr 1965).

4.8 Properties of Granules Prepared with selected Types and Concentrations of Disintegrant Using lactose as Diluent and Starch as Binder

Granule Properties	Disintegrant type/ concentration				
	Starch 5%	Starch 10%	PVP(CL) 2%	PVP(CL) 5%	Treated Starch (5%)
Moisture content (%)	5.7	5.9	5.6	5.4	6.2
Bulk density (g/ml)	0.53	0.51	0.49	0.44	0.48
Tapped density (g/ml)	0.56	0.58	0.56	0.50	0.53
True density (g/ml)	1.61	1.65	1.71	1.76	1.82
Compressibility (%)	5.84	13.16	11.50	11.20	9.53
Flow rate (g/sec)	8.12	7.12	6.66	5.91	5.71
Angle of repose (θ)	28.21	30.62	29.64	30.46	32.29

Granules formulated with treated starch gave lowest flow rate. This is in agreement with findings of Opakunle and Akinpelu (1976). Increase in disintegrant concentration led to decrease in flow rate. The granules formulated with 5.0% starch as disintegrant had highest flow rate and least angle of repose. There was a general increase in angle of repose with decrease in flow rate.

4.4.2 EFFCT OF VARIABLES ON TABLET PROPERTIES.

Effect of Diluent type on Tablet Properties

Table 4.9 shows the properties of tablets produced with lactose and $MgCO_3$ as diluent and starch as binder. The table shows that tablets produced with lactose as diluent produced harder tablets. This could be due to the higher moisture content of the granules (Table 4.2), which will strengthen the solid bridges between the granules under pressure.

Table 4.9 Properties of Tablets formulated with Lactose and MgCO3 as Diluents and Starch as Binder

	Diluent type	
Tablet properties	Lactose	$MgCO_3$
Tablet weight (mg)	634.70±9.43	619.60±23.60
Hardness (Kgf)	5.50	3.0
Friability (%)	0.63	1.74
Disintegration time (min)	12.25	12.50
Dissolution time (min)	31	40

Tablets produced with $MgCO_3$ failed the friability test and this could also be due to lower moisture contents of the granules (Table 4.2). Though, the disintegration times for the tablets produced using lactose and $MgCO_3$ were very close there was faster release of the active drug from tablets produced using lactose. This is an indication of better dissolution profile of the lactose granules, which may also be attributed to the water solubility of the lactose diluent.

Effect of Binder Concentration on Tablet Properties

The effect of binder concentration on tablet properties using lactose and magnesium carbonate as diluent is tabulated on Tables 4.10 and 4.11

Table 4.10 Properties of Tablets Formulated with lactose as diluent using selected concentrations of starch as binder

	Binder concentration (w/w)		
Tablet properties	0	2.5	5.0
Tablet weight (mg)	632.60±6.32	634.70±9.43	630.90±9.36
Hardness (Kgf)	6.80	6.50	7.20
Friability (%)	1.89	0.63	1.05
Disintegration time (min)	10.70	12.50	13.50
Dissolution time (min)	21	23	31

Table 4.11 Properties of Tablets Formulated with $MgC0_3$ as diluent using selected concentrations of starch as binder

	Binder concentration (w/w)		
Tablet properties	0	2.5	5.0
Tablet weight (mg)	622.43±9.38	633.50±8.02	628.74±8.56
Hardness (Kgf)	3.9	3.0	4.0
Friability (%)	1.38	1.74	1.07
Disintegration time (min)	16.50	12.10	20.50
Dissolution time (min)	30.	28	45

There was general increase in tablet hardness when binder concentration was increased from 2.5 - 5.0%. This trend has been reported with other drug materials (Esezobo and Ambujam, 1982). The interacting forces and bonds among the particles and the binder present are responsible for the strength of the tablets (York and Pilpel, 1973). There was however a decrease in tablet hardness between 0 - 2.5% binder concentration. This may have been due to

the higher moisture content of granules formulated with 0% binder concentration (Table 4.2), which would enhance formation of more solid bonds.

The relationship between tablet friability and binder concentration varied with the type of binder used. For tablets formulated with starch as binder, 2.5% binder gave lowest friability. Tablets formulated with gelatin and PVP as binder produced tablets that were highly friable, indicating formation of very weak bonds between the granules.

Disintegration time increased with increase in binder concentration for all the binders used when lactose was used as diluent. This is in conformity with observations of Esezobo, (1986). This was also true for tablets formulated with magnesium carbonate as diluent at binder concentration of 2.5 - 5.0%. Tablets formulated with 0% binder concentration and magnesium carbonate as diluent however had higher disintegration time than the tablets formulated with 2.5% binder concentration. This lower granule size and higher moisture content of granules formulated with 0% binder concentration may have contributed to this observation.

Dissolution time increased with increase in binder concentration. This may have been due to the formation of binder films around the powder particles or granules. This forms a mucilaginous viscous barrier on the granules when the tablets break-up and make contact with the dissolution medium, preventing drug contact with water, and leading to delay in dissolution (Esezobo and Pilpel, 1977). Disintegration time also generally increased with increased (from 2.5-5%) binder concentration, irrespective of the diluent used.

Effect of Binder Type on Tablet Properties

Properties of tablets formulated using different binders are depicted in Table 4.12 and 4.13. As shown the type of binder used affected the tablet hardness. The hardness values for tablets formulated with lactose as diluent, was in order:

water > starch > gelatin = PVP.

The increase in hardness from starch to PVP can be attributed to increase in viscosity of the binder solutions, which would lead to increase bond formation and result in increased hardness (Kunle, O.O 1988)

Table 4.12 Properties of Tablets Formulated with Lactose as Diluent using selected Binders.

Tablet properties	Binder Type			
	Water	Starch	Gelatin	PVP
Tablet weight (mg)	622.43±10.4	634.70±9.4	633.50±8.0	622.83±8.3
Hardness (Kgf)	6.8	6.5	4.5	4.5
Friability (%)	1.9	0.6	1.8	4.2
Disintegration time (min)	10.2	12.5	14.1	10.1
Dissolution time (min)	21.0	31.0	29.5	35.0

Water, though less, viscous gave tablets with the highest hardness and the slightly higher moisture content of the granules (Table 4.6) may have been responsible for this observation (Kurup and Pilpel, 1984).

Tablets formulated with starch as binder though not the hardest had lowest friability regardless of diluent type. Friability ranking for tablets formulated with lactose is:

PVP>water>gelatin=starch

Tablets formulated with PVP as binder had least disintegration time for both diluents used. This might be due to the low tablet strength of the tablets formulated with PVP as binder (Table 4.13). For other binders there was no direct relationship between the disintegration time and tablet hardness. Tablets formulated using lactose as diluent and water as binder, though had the highest tablet hardness (6.8 kgf), gave lower disintegration time than tablets formulated

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Table 4.13 Properties of Tablets Formulated with $MgCO_3$ as Diluent using selected Binders.

Tablet properties	Binder Type			
	Water	Starch	Gelatin	PVP
Tablet weight (mg)	638.68±8.6	626.43±10.7	624.37±8.9	621.84±10.7
Hardness (Kgf)	3.2	3.50	3.0	3.0
Friability (%)	1.3	1.1	1.2	1.9
Disintegration time (min)	16.3	12.5	13.5	10.1
Dissolution time (min)	*30.0*	28.0	35.0	35.0

with gelatin as binder that had a hardness of 4.5 kgf. The longest dissolution time (at T_{75}) was observed with tablets formulated with PVP as binder. This was not expected, going by the low disintegration time of the tablets (Table 4.13). This suggests that hardness may be used to explain intergranular bonds but might not necessarily account for the intragranular bonds, which have to be broken before dissolution takes place. Generally tablets formulated with water or starch as binder gave good dissolution as observed from the dissolution times 28 minutes or 30minutes, (tables 4.12 and 4.13) which are within acceptable BP (1990) limits

Effect of Disintegrant Concentration and Type on Tablet Properties

Table 4.14 shows the effect of disintegrant type/concentration. on tablet properties. The tablet formulated with treated starch as disintegrant gave lowest hardness and highest friability. Nasipuri and Omotosho (1985) made similar observations. Generally tablets formulated with PVP (C.L) as disintegrant gave lower hardness than those formulated with untreated starch as

Table 4.14 Properties of Tablets Formulated with Lactose as Diluent Using selected Disintegrants.

Tablet properties	Disintegrant Type/ concentration				
	Starch 5%	Starch 10%	PVP (CL) 2%	PVP (CL) 5%	Treated Starch (5%)
Hardness (Kgf)	6.50	6.70	6.00	5.70	5.20
Friability (%)	0.64	1.06	0.91	1.13	1.52
Disintegration time (min)	13.50	10.50	7.12	6.00	9.75
Dissolution time (min)	31.0	25.0	20.3	18.0	36.5

disintegrant. Friability increased with increase in disintegrant concentration for both starch and PVP (C.L), with granules formulated with 5.0% starch as disintegrant giving lowest friability

Increase in disintegrant concentration led to decrease disintegration time for both starch and PVP (C.L). Treated starch gave tablets with disintegration time lower than tablets formulated with starch as disintegrant, but higher than those for tablets formulated with PVP (C.L) as disintegrant. Nasipuri and Omotosho (1985) also observed decrease in disintegration time with addition of surfactant. The disintegrant action of PVP (C.L) has been attributed to its ability to swell as well as take-up water (Kornblum and Stoopak, 1973)

Dissolution time (T_{75}) was found to decrease with decrease disintegration time for tablets formulated with starch and PVP (C.L) as disintegrant. Increased dissolution time (T_{75}) was however found with tablets formulated with treated starch (starch/ Na lauryl sulphate) as disintegrant. This did not conform to findings of Nasipuri and Omotosho (1985), and Esezobo (1985) who observed increased dissolution rates with surfactant treatment. The increase in dissolution time observed with surfactant (treated starch) may have been due to interaction between the extract (drug) and surfactant (Kurosaki *et*

al, 1989) .The interaction between drug and surfactant was thought to be due to formation of micellar complexes whereby the hydrophilic potion of the micelle is shielded away from the dissolution medium. (Miyamoto *et al*, 1983).

CHAPTER 5

5.0 COMPRESSION AND COMPACTION CHARACTERISTICS OF EXTRACT FORMULATIONS.

5.1 INTRODUTION.

Particle sizes and shapes affect the compression and compaction characteristics of pharmaceutical powders and granules. (Pasonen and Paronen, 1990) Particle sizes of powders & granules influence the compaction characteristics of tablets, e.g the hardness. Several attempts have been made to predict how these compacts are formed and modifying rate of the size and shape of the particles. (Heckel, 1961a&b) was able to derive an equation for predicting the mechanism of consolidation of powders and the effect of particle size on it. The nature of the plot obtained from the equation:

$$\ln\left[\frac{1}{1-D}\right] = KP + A \quad \text{.....6}$$

is an indication of the consolidation characteristics of the powder mass.

The effect of particle size, binder concentration, binder type and diluent type on the compaction characteristics of the extract formulations will be studied in this section.

5.2 MATERIALS AND METHODS.

5.2.1 Materials

Chemicals

Hot water Extract (Using extraction method 2.2.2.1)

Maize starch, Lactose B.P (NIPCO Pharmaceuticals Abuja)

Magnesium carbonate (BDH Chemicals- England)

Gelatin B.P (Fisons Scientific, England)

Polyvinyl Pyrollidone (PVP) 25-30 (Merck)

Magnesium stearate (British Drug House U.K)

Ethanol (BDH Chemicals Ltd, England)

Equipments

Carver hydraulic hand press (model C, Carver Inc., U.S.A)

Erweka handness tester (model MT, Germany)

Mituoyo model IDC 1012EB (Mitutoyo corporation, Japan)

5.2.2 Method

The wet granulation method of massing and screening was used as described under section 4.3.1. The granules were separated into different granule size ranges using a set of sieves (150, 250, 500 and 833 μm) on an Endecott's test Sieve Shaker. Dried granules were weighed and 10 compacts from each selected granule size were made at different compression pressure levels (28.294, 56.588, 84.882, 113.176, 169.764 and 226.352 MNm^{-2}), with the Carver hydraulic hand press using flat-faced punch of 10.5mm diameter (the punches were lubricated with 1% w/v dispersion of magnesium stearate in ethanol before each compression). After ejection, the tablets were stored over silica gel in a dessicator for 24 hours to allow for elastic recovery and hardening. The diameter and thickness of the compacts were determined using a Mitutoyo digimatic indicator; an Erweka hardness tester was used to determine compact hardness. Tensile strength was calculated using the following equation:-

$$Ts = \frac{2P}{\Pi Dt} \quad \text{.....12}$$

Where T_s is the tensile strength of tablets, P is the load necessary to cause fracture (diametrically), t is the thickness and D is diameter of the tablet; t and D are in mm.

Using the Heckel equation (Heckel, 1961a & 1961b), a graph of *ln (1/ 1-D)* versus compression pressure (*P*) was plotted. The yield pressure P*y*, which is a measure of the ability of the material to consolidate by plastic flow, was determined from the slope of the linear region of the graph. *A*, (intercept) was determined by regression analysis using the prisms graph pad programme. From the value of A the relative density D_A that describes the densification of the material due to the filling and rearrangement was obtained (Roberts and Rowe, 1986).

5.3 RESULTS AND DISCUSSION.

5.3.1 Effect of Diluent Type on Heckel plots.

Fig. 5.1, 5.2 and 5.3, shows the Heckel plots of the effect of different binders on granules formulated using lactose and $MgCO_3$ as diluents. As depicted in these graphs, formulations containing lactose as diluent gave approximately a straight line (i:e there is a linear relationship). This implies that granules containing the extract of the plant and lactose deformed principally by plastic deformation. Previous studies had indicated that lactose when subjected to compaction forces usually undergoes first fragmentation, followed by plastic deformation (Armstrong and Haines-Nutt, 1972). This intrinsic deformation characteristic of lactose was modified by the hot water extract of the plants.

On the other hand, granules prepared using $MgCO_3$ as diluent exhibited two stages of deformation – an initial fragmentation followed by plastic flow, a property exhibited also by $MgCO_3$ alone. This implies that the hot water extract did not alter the deformation characteristics of $MgCO_3$ when used as diluent

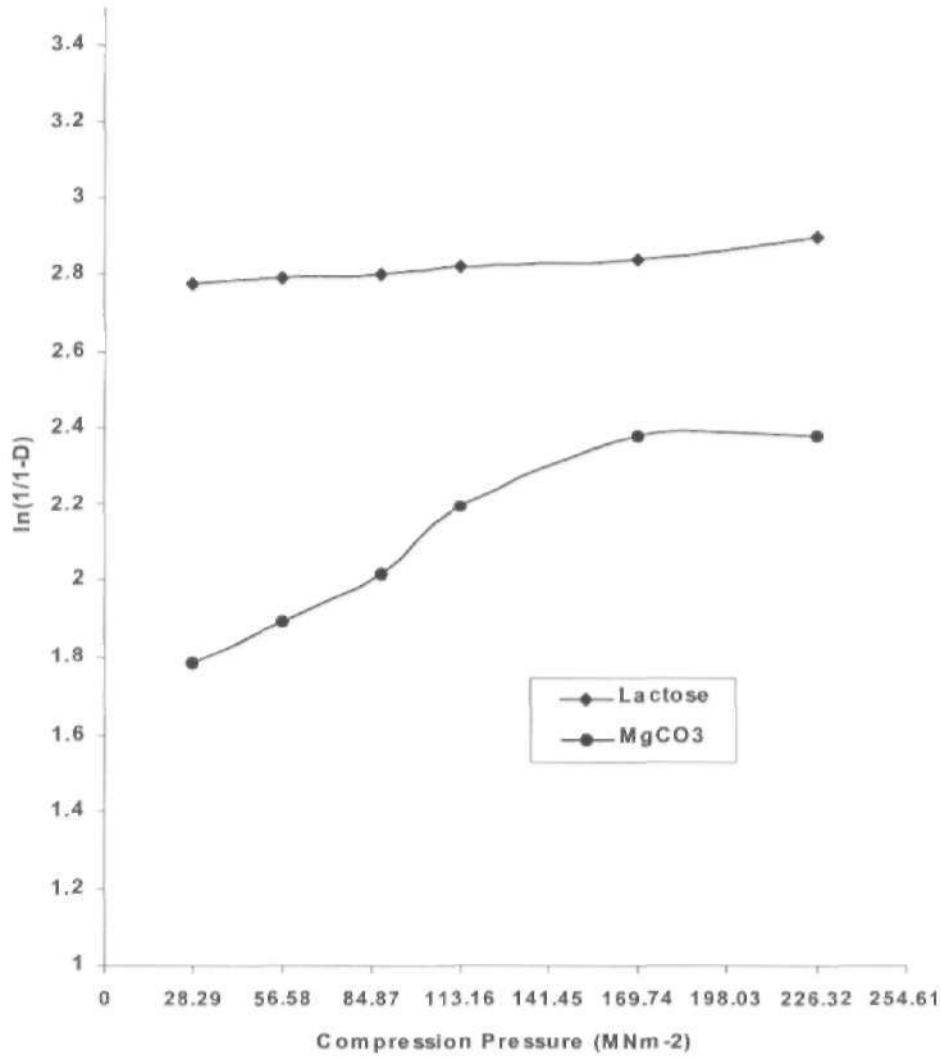


Fig 5.1 Heckel plots of Granules containing starch as binder

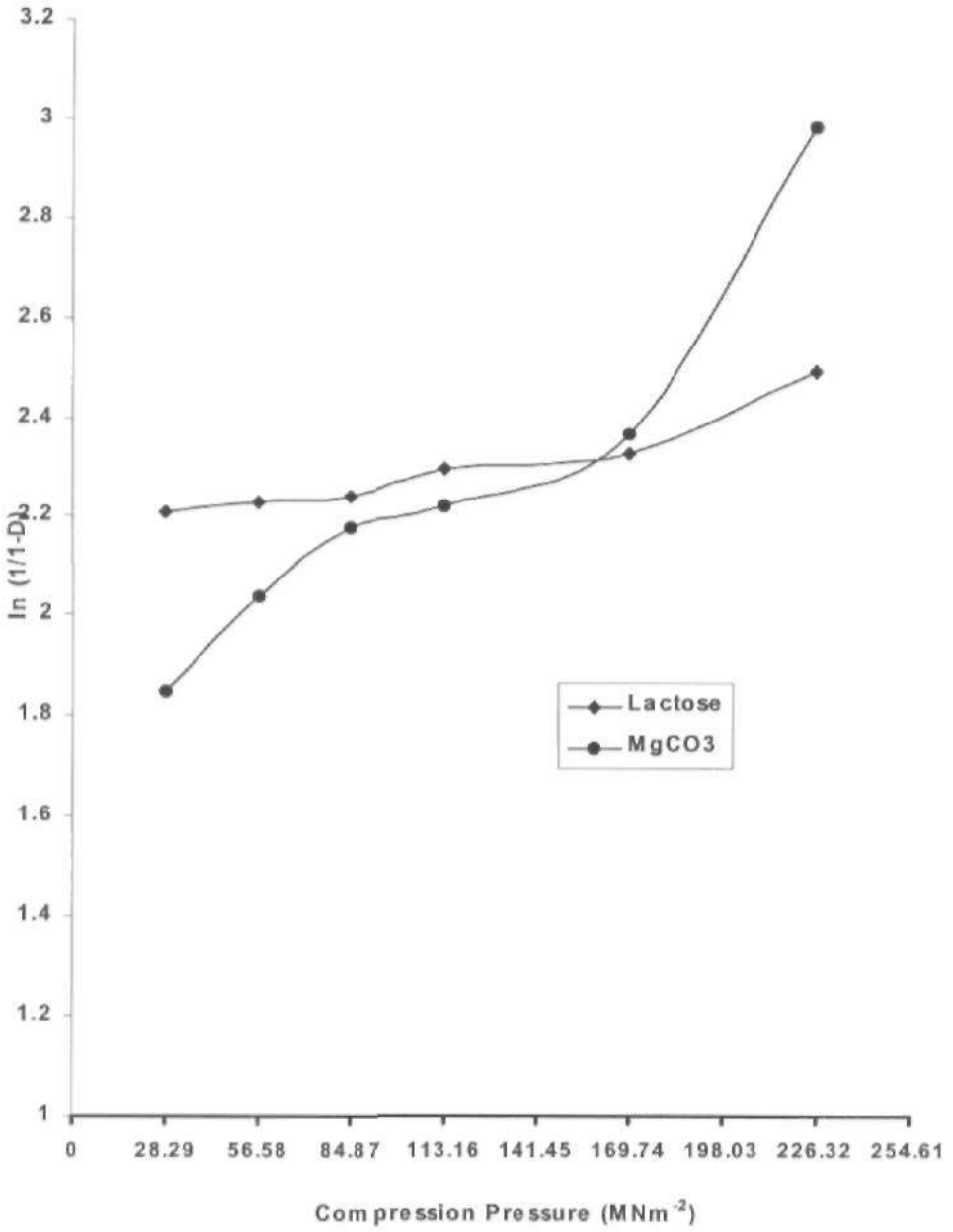


Fig 5.2 Heckel plots for Granules containing gelatin as binder

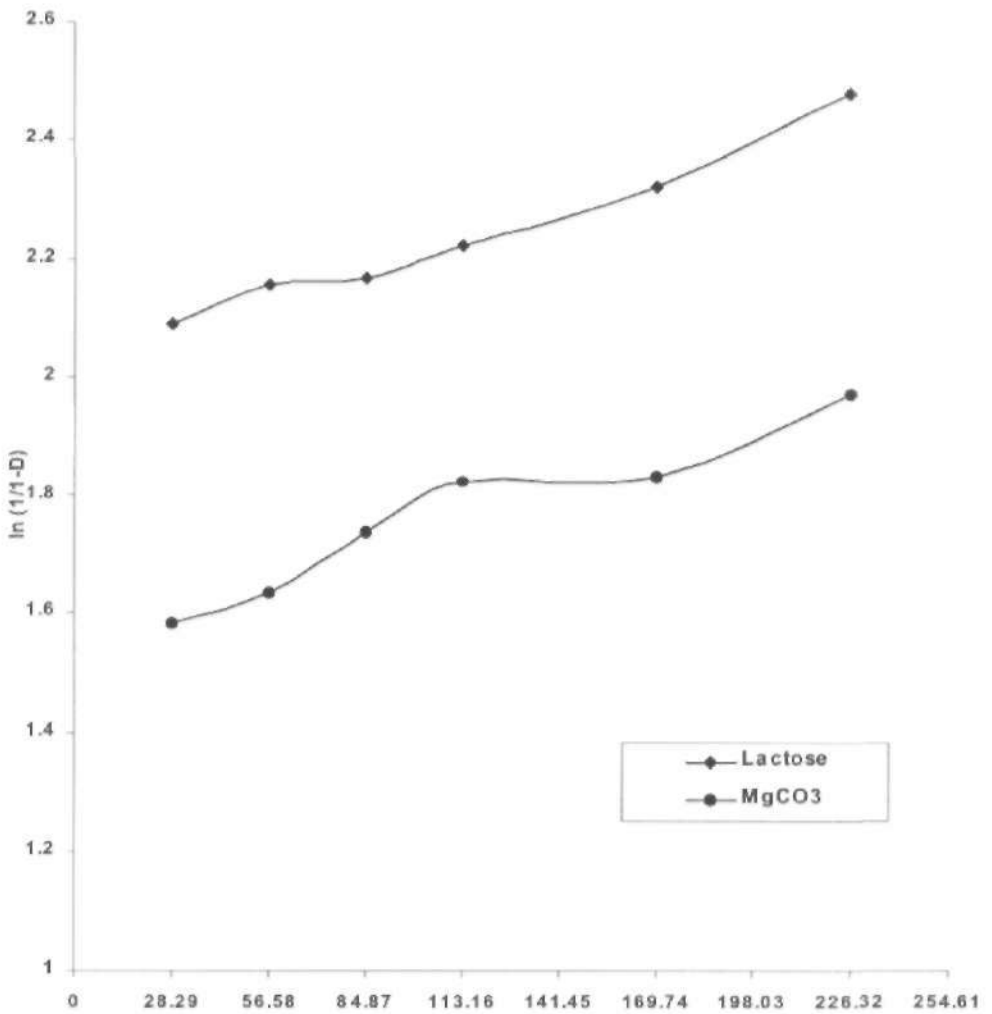


Fig 5.3 Heckel plots for Granules formulated with PVP as binder

Table 5.1 Heckel Constants for Granules Prepared with selected Diluents and Starch as Binder.

Diluent Type	Py (MNm^{-2})	A	e^{-A}	D_A $(1- e^{-A})$	D_O	D_B (D_A-D_O)
Lactose	1712	2.757	0.0634	0.9366	0.3484	0.5882
$MgCO_3$	309.1	1.742	0.1751	0.8247	0.4553	0.3694

Table. 5.2 Heckel Constants for Granules Prepared with selected Diluents and Gelatin as Binder.

Diluent type	Py (MNm^{-2})	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B (D_A-D_O)
Lactose	734.2	2.144	0.1171	0.8829	0.3348	0.5481
$MgCO_3$	197.9	1.699	0.1828	0.8172	0.4346	0.3826

Table 5.3 Heckel Constants of Granules Prepared with selected Diluents and PVP as Binder.

Diluent type	Py (MNm^{-2})	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B (D_A-D_O)
Lactose	529.0	2.026	0.1318	0.8681	0.3146	0.5535
$MgCO_3$	533.6	1.55	0.2122	0.7878	0.4429	0.3449

The Heckel constants obtained from the linear regression plots of *ln (1/1-D)* versus compression pressure for various formulations are listed in Tables 5.1, 5.2, and 5.3. The yield pressure Py; which is the reciprocal of the slope, (K) 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 Justin, 1983). Higher value of yield pressure indicates the on-set of plastic deformation at relatively low pressure. Lactose granules gave higher Py (yield pressure) values indicating that granules

formulated with lactose as diluent deformed plastically at relatively lower pressures compared to granules formulated with magnesium carbonate as diluent. This conforms to earlier observation: that the two consolidation stages of lactose were modified by the extract.

The results in Tables 5.1 –5.3 also show that granules formulated with magnesium carbonate as diluent had lower D_A, compared with those of lactose, indicating that it was denser in the precompression phase, especially during the die filling and early stages of downwards movement of granules from the upper punches into the die. This may be attributed to differences in particle size and shape (Itiola, 1993). Granules formulated with lactose as diluent, being larger sized would not tend to pack as closely as the granules formulated with magnesium carbonate as diluent. Granules formulated with $MgCO_3$ were of smaller sizes, and thus are characterized by compact (close) packing, lower porosity and hence greater densification compared with the loosely packed lactose granules that allow for intergranular pores (Vromans *et al*, 1988)

D_0, describes the density of the granules in the die at zero pressure. The values are higher for granules formulated with magnesium carbonate. The smaller granule sizes of $MgCO_3$ may also be responsible for this.

The densification due to rearrangement of particles during the initial stage of compaction (D_B) was lower for granules formulated with magnesium carbonate as diluent. This is in line with the findings of York (1978), and Paronen and Juslin (1983), who found that the rearrangement of particles occur more with smaller sized particles and least with larger particles.

5.3.2 Effect of Binder Concentration on Heckel plots.

The Heckel plots of Fig 5.4 and 5.5 show the effects of binder concentration on compaction properties of the granules prepared with lactose as diluent. As depicted granules prepared with lower concentrations (2.5%) of starch, deformed mainly by plastic deformation while at higher concentration, both initial fragmentation and plastic deformation occurred. The two different

binder concentrations of gelatin and PVP (2.5 &5.0%) produced granules that deformed by fragmentation and plastic flow.

Heckel plots of effect of binder concentration on granules formulated using magnesium carbonate as diluent, are shown in Fig 5.6 and 5.7. All the plots showed an initial linear region followed by a portion of decreasing slope as compression pressure increased. These two portions represent an initial fragmentation and rearrangement of the granules, followed by plastic deformation.

Table 5.4 Heckel Constants for Granules Prepared with Lactose as Diluent and Starch as Binder.

Binder concentration	Py (MNm^{-2})	A	e^{-A}	D_A $(1- e^{-A})$	D_O	D_B (D_A-D_O)
0%	572.3	2.088	0.1239	0.8761	0.333	0.543
2.5%	1302	2.547	0.0783	0.9217	0.2788	0.6429
5.0%	257.9	2.530	0.07965	0.9203	0.2674	0.6529

The Heckel constants obtained from the linear regression plots are represented on Tables 5.4 and 5.5 for granules formulated with Lactose as diluent, starch and gelatin as binder at different concentration levels respectively. The Heckel constants were affected by binder concentration and the effect varied with type of binder used. The yield pressure, Py which is an indication of granules ability to deform plastically was highest for granules formulated with 2.5% starch binder, and lowest with 5.0% starch as binder, but when gelatin was used as binder, Py was highest for granules formulated with

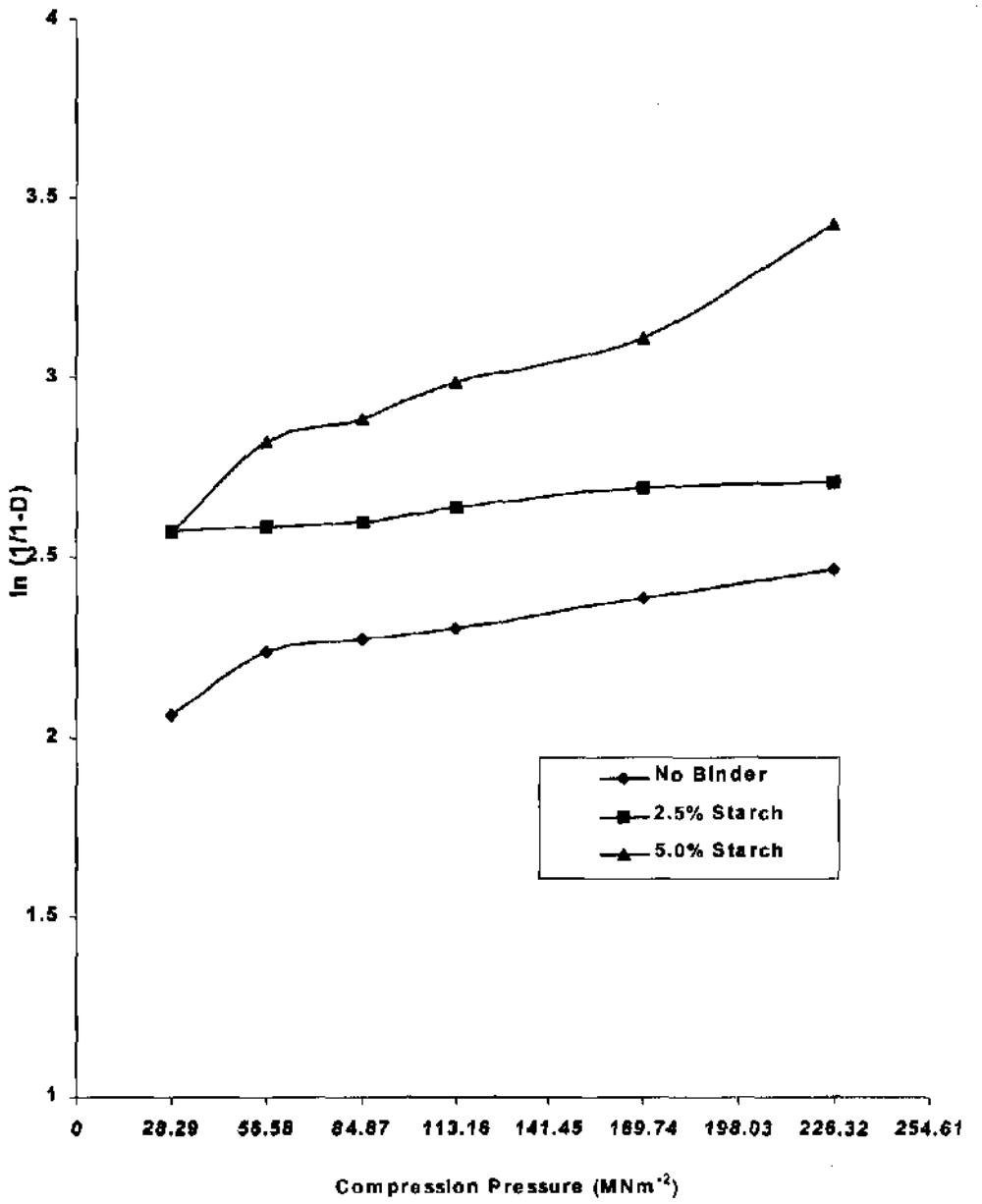


Fig 5.4 Heckel plot of Granules prepared with Lactose as diluent and selected conconcentrations of Starch as binder

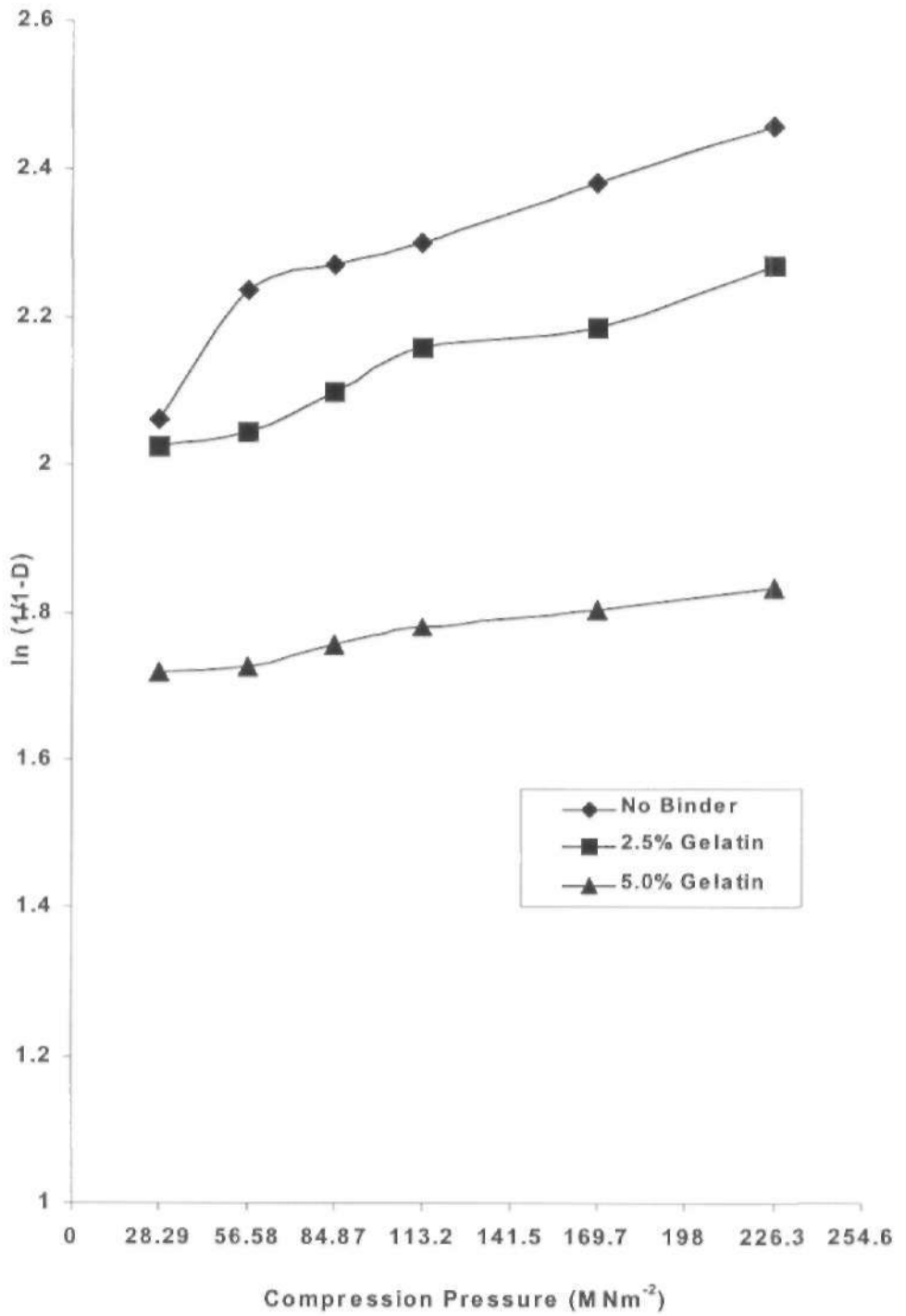


Fig. 5.5 Heckel plot of Granules prepared with Lactose as diluent and selected concentrations of Gelatin as binder

Table

5.5 Heckel Constants for Granules Prepared with Lactose as Diluent and Gelatin as Binder

Binder concentration	Py (MNm^{-2})	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B (D_A-D_O)
0%	572.3	2.088	0.1239	0.8761	0.333	0.5431
2.5%	809.3	1.992	0.1364	0.8636	0.285	0.5777
5.0%	1537	1.694	0.1837	0.8163	0.270	0.0546

5.0% gelatin as binder and lowest for granules formulated with 0% binder. Relative density, D_A, was higher for granules formulated with 2.5% starch as binder and lowest for granules formulated with 0% binder concentration. Based on granule size alone the ranking order of D_A values should have been D_A for 2.5% > D_A for 0% > D_A for 5%. Therefore other factors, like shape of the granules might have been responsible for the observed higher D_A for granules formulated with 0% binder concentration (Itiola, 1993). D_O which describes the die filling stage decreased with increased binder concentration between 2.5% and 5.0% (Tables 5.4 and 5.5) and this was as expected since granules formulated with 2.5% binder concentration were probably smaller than those formulated with 5.0% binder concentration and would be expected to pack more closely (Vromans *et. al*, 1989). D_O for granules formulated with 0% binder concentration however did not follow this trend. It gave highest D_O despite the fact that its granule size was greater than that of 2.5% binder concentration. This observation points to the fact that particle size alone might not be enough to explain the die filling stage and that particle shape could have contributed to the observation.

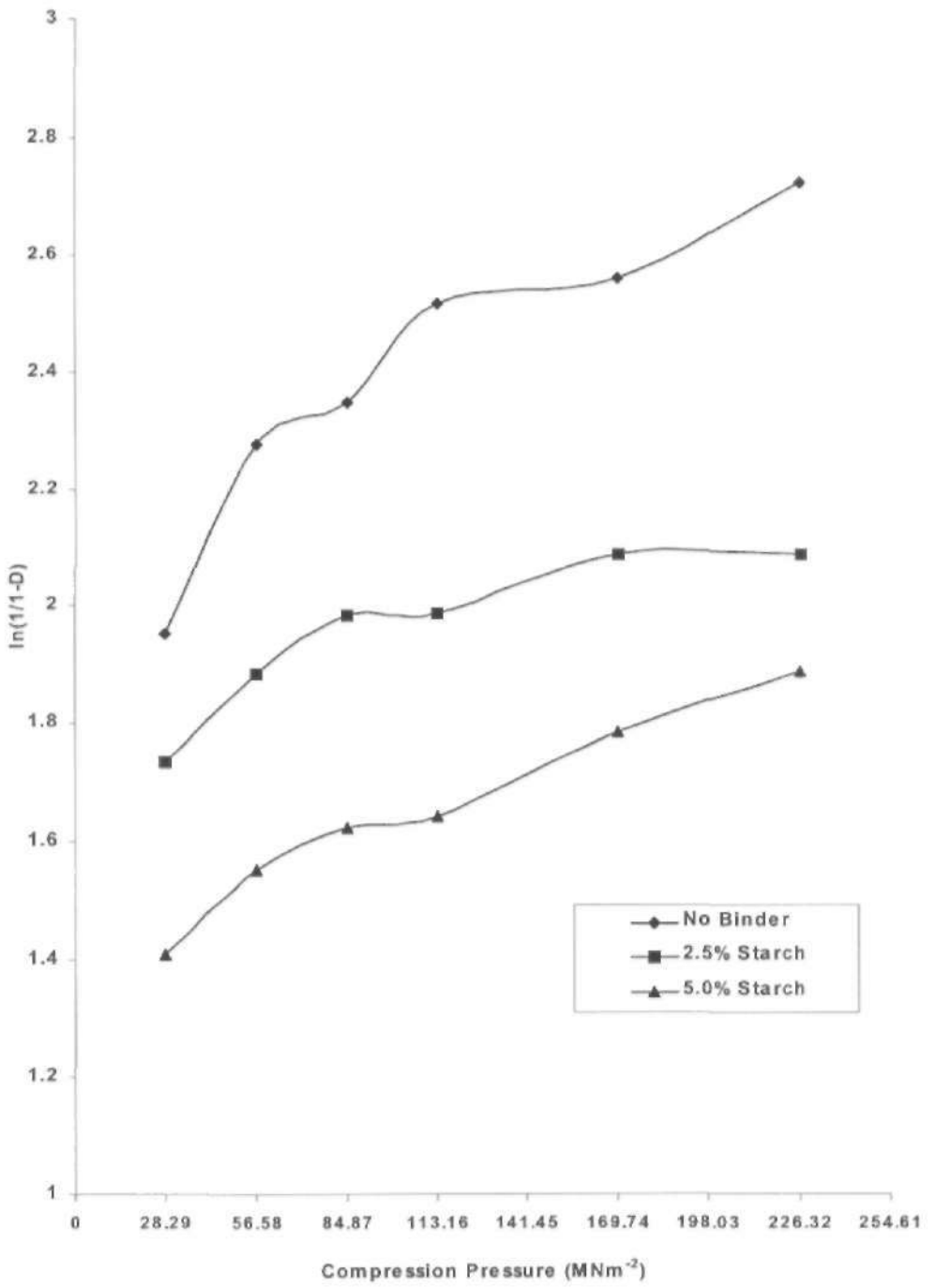


Fig 5.6 Heckel plot of Granules prepared with $MgCO_3$ as diluent and selected concentrations of Starch as binder

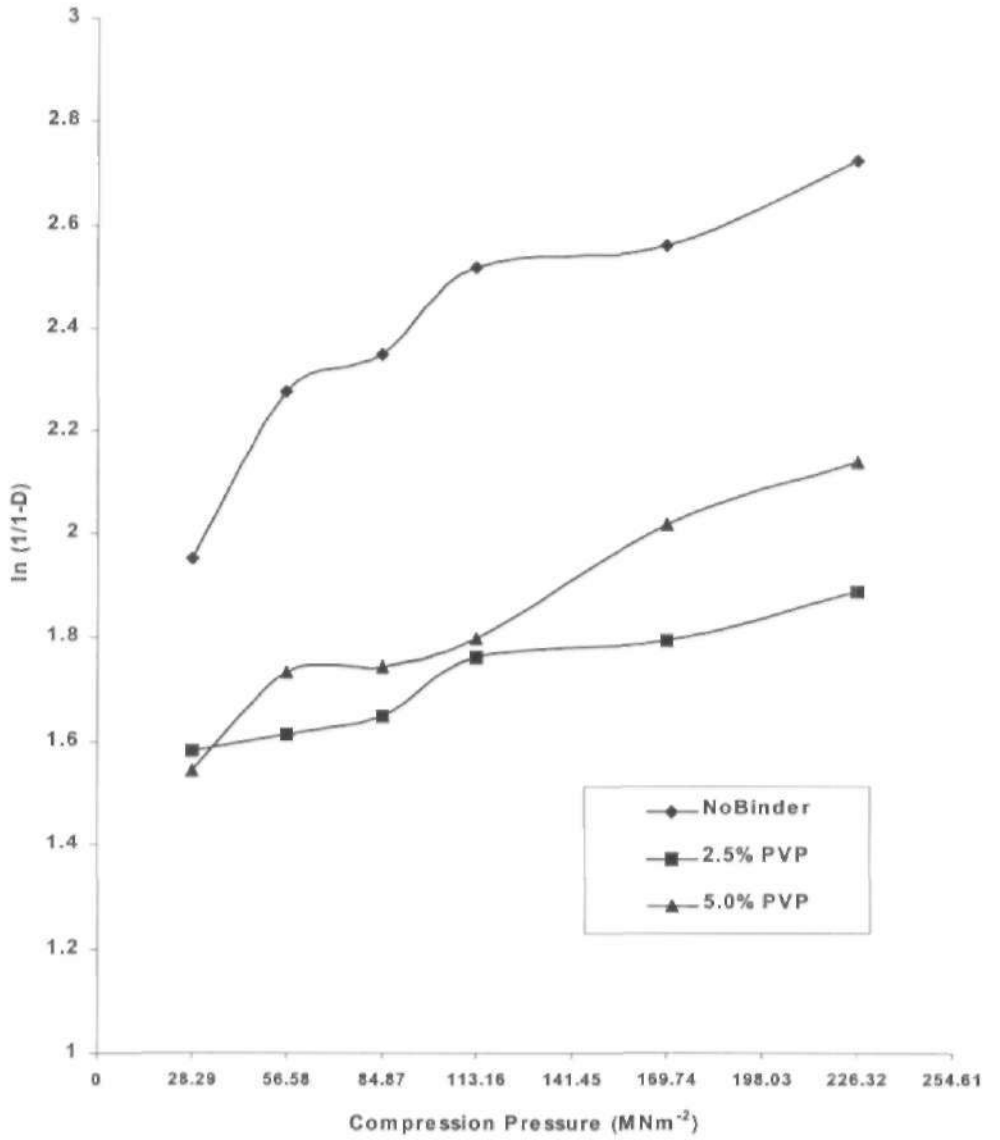


Fig 5.7 Heckel plot of Granules prepared with MgCO3 as diluent and selected concentrations of PVP as binder

The values of D_B were found to increase with binder concentration for granules formulated with lactose as diluent and starch as binder (Table 5.4). For granules formulated with gelatin as binder (Table 5.5), there was no relationship between binder concentration and D_B as there was a decrease in D_B between 2.5% and 5.0% binder concentration.

The Heckel constants for granules formulated with magnesium carbonate as diluent with starch and PVP as binder at different concentration levels is shown on Tables 5.6 and 5.7. The Py was highest for granules formulated with 2.5% binder concentration and lowest for granules formulated with 0% binder concentration. The order of ability of granule to deform plastically (*agdp*) was therefore:

2.5% >5.0% > 0%.

D_A, which describes the stage of deformation due to die filling and rearrangement decreased with increase in binder concentration, with smaller having higher D_A. D_O and D_B also decreased with increase in binder concentration for granules formulated with magnesium carbonate.

Table 5.6 Heckel Constants of Granules Prepared with $MgCO_3$ as Diluent and Starch as Binder.

Binder concentration	Py (MNm^{-2})	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B (D_A-D_O)
0%	294.7	2.013	0.1335	0.8665	0.2407	0.6258
2.5%	610.4	1.776	0.1693	0.8307	0.2336	0.5971
5.0%	444.7	1.395	0.2478	0.7522	0.2151	0.5371

Table 5.7 Heckel Constants of Granules Prepared with $MgCO_3$ as Diluent and PVP as Binder .

Binder concentration	Py (MNm^{-2})	A	e^{-A}	D_A $(1- e^{-A})$	D_O	D_B (D_A-Do)
0%	278.1	1.998	0.1356	0.8644	0.2407	0.6237
2.5%	611.6	1.525	0.2176	0.7823	0.2233	0.559
5.0%	363.3	1.525	0.2176	0.7823	0.2260	0.5563

5.3.3 Effect of Binder Type on Heckel Plots.

The effect of Binder Type on Heckel Plots for granules formulated with lactose and magnesium carbonate as diluent are represented on Figs. 5.8 and 5.9 respectively. The binder type affected the deformation characteristics of the granules. Fig. 5.8 shows that granules formulated with gelatin and starch as binder gave linear plots at all compression pressures indicating probable total plastic deformation, while those formulated with no binder (water) and with PVP as binder had two distinct segments corresponding to an initial fragmentation, followed by plastic deformation.

For granules formulated with magnesium carbonate as diluent, there was no distinct pattern of deformation. The plots tend more towards that of initial fragmentation followed by plastic deformation. The Heckel constants as presented on Table 5.8 for granules formulated with lactose as diluent show that Py values which is the yield pressure is in ranking order of:

Starch > PVP > Gelatin > Water

This indicates that granules formulated with starch as binder deform plastically at relatively lower pressure compared to granules formulated with the other binders. For granules formulated with magnesium carbonate the ranking order was:

PVP > Starch > Gelatin > water

D_A, which describes the densitification of the material, due to die filling and rearrangement for granules formulated with lactose (Table 5.8) was in order of:

starch > water > PVP > gelatin

This resembles the ranking order of the average granule size (*ags*) (Fig, 4.2) where the average granule size were in ranking order:

water > starch > PVP > gelatin

Table 5.8 Heckel Constants of Granules Prepared with selected Binders and lactose as Diluent.

Binder Type	Py (MNm^{-2})	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B (D_A-D_O)
Water	572.3	2.088	0.1239	0.8761	0.333	0.5431
Starch	1302	2.547	0.0783	0.9217	0.2788	0.6429
Gelatin	809.3	1.992	0.1364	0.8636	0.2859	0.5777
PVP	1145	2.021	0.1325	0.8675	0.3180	0.5495

Table 5.9 Heckel Constants for Granules Prepared with selected Binders and $MgCO_3$ as Diluent.

Binder Type	Py (MNm^{-2})	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B (D_A-D_O)
Water	294.6	2.012	0.13372	0.8662	0.2407	0.6258
Starch	610.4	1.776	0.1693	0.8307	0.2336	0.5971
Gelatin	344.8	1.564	0.2092	0.7908	0.2331	0.5577
PVP	643.8	1.538	0.2148	0.7852	0.2242	0.5610

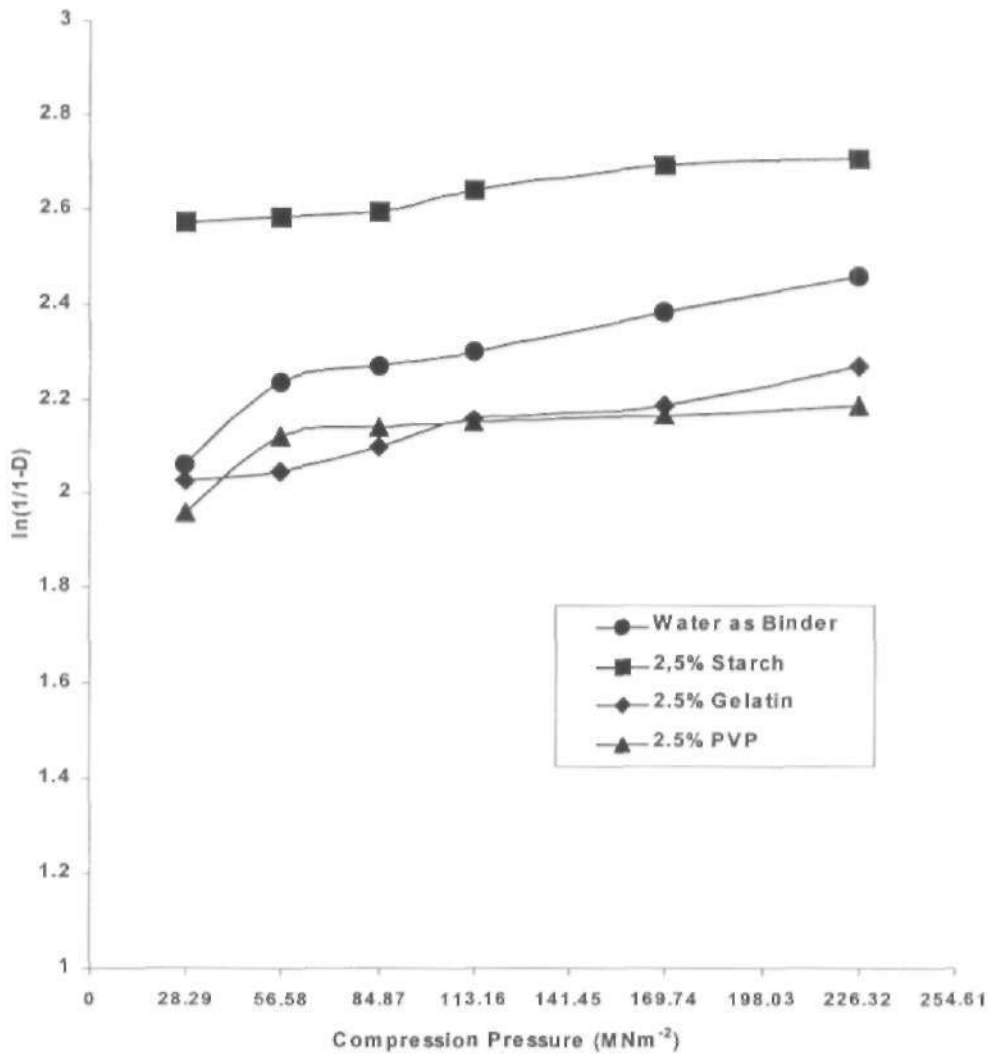


Fig 5.8 Heckel plot of the Granules prepared using selected binders and Lactose as diluent

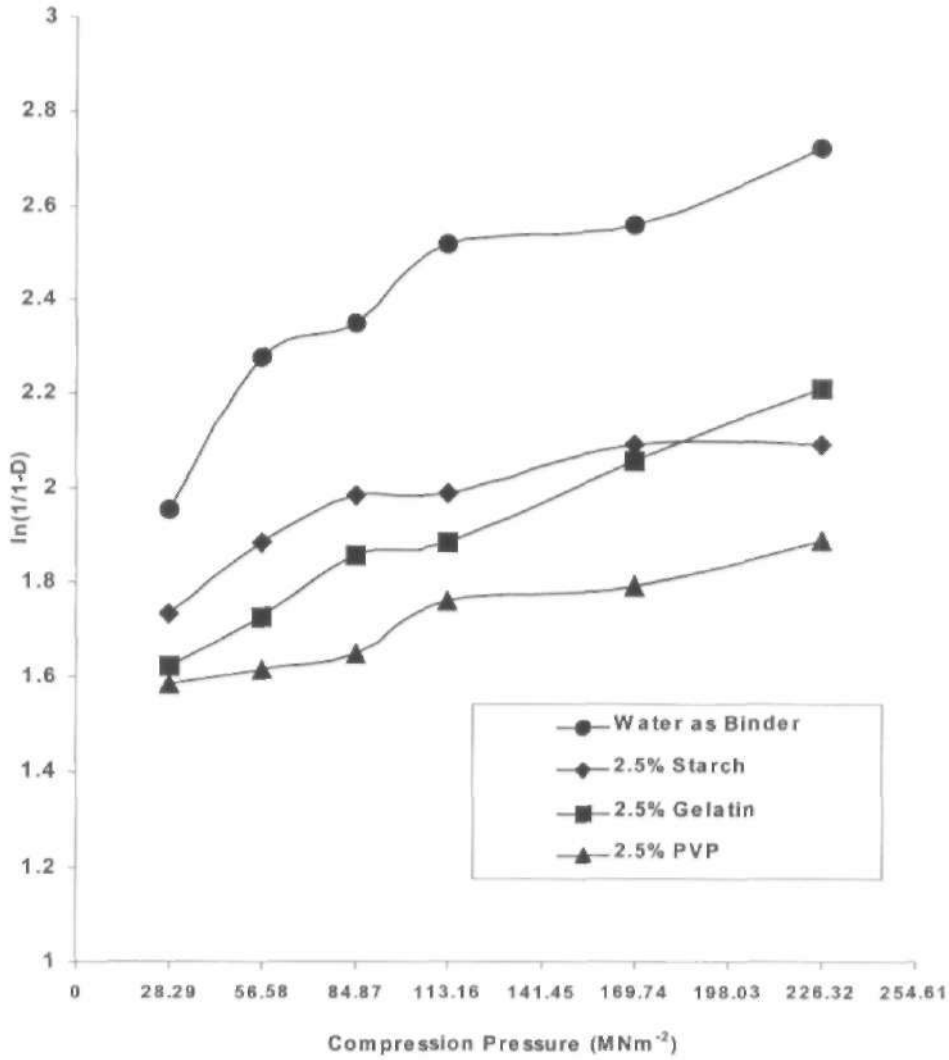


Fig 5.9 Heckel plot of the Granules prepared using selected binders and $MgCO_3$ as diluent

When magnesium carbonate was used as diluent the ranking order of D_A was:

water > starch > gelatin > PVP

This did not follow the average granule size trend, suggesting that factor other than granule size like granule shape might play important role in determining D_A values (Itiola 1993). Do, which describes the die filling or the density of the powder in the die at zero pressure varied with binder type. For granules formulated with Lactose as diluent, the ranking order was:

water > PVP > gelatin > starch.

This order may probably be due to differences in binder viscosity. Davies and Gloor (1972) proposed that binders form a coat around the dry mixed particles and that the thickness of this coat increases with binder concentration (viscosity). This coat would possibly cause resistance to particle-particle attraction and therefore reduce densification of the granules in the die. The values of D_B were:

starch > gelatin > PVP > water

These values agree with the increase in viscosity for granules formulated with lactose as diluent.

The Heckel constants for granules formulated with magnesium carbonate as diluent with different binder types are represented on Table 5.9. It is seen that granules formulated with PVP as binder had the highest yield pressure indicating that these granules deform plastically at a lower pressure compared to granules formulated with other binder types. The order of the Py values was:

PVP > starch > gelatin > water

D_A, which describes the densification of the material due to filling and rearrangement, was in order:

water > starch > gelatin > PVP,

when magnesium carbonate was used as diluent.

5.3.4 Effect of granule size on Heckel plots.

Figs. 5.10 and 5.11 show the Heckel plots of different granule sizes of formulation using lactose as diluent, gelatin and starch as binders.The plots show very close to linearity relationship between *ln (1/1-D)* and compression pressure for all pressure levels except for granule size >500<833 μm when Gelatin was used as binder (Fig. 5.10). The linearity of the plots suggests that the granules deform mainly by plastic deformation.

D_A, which describes the densification and rearrangement stage increased with increase in granule size. It would be expected that smaller granules would pack more closely leading to a lower D_A. Do, the density of the granules in the die at zero pressure decreases with increase in granule size. The larger granules did not pack as closely as the smaller granules and this will allow formation of intergranular pores (Vromans *et al*, 1985). The densification due to rearrangement of particles during the initial stages of compression increased with increasein granule size. This findings is in line with those of Huffine and Bonilla (1962), Fell and Newton (1971) and Paronen and Juslin (1983) who observed that the rearrangement of particles occur more with smaller sized particles.

Effect of granule size on Heckel plots for formulations with magnesium carbonate as diluent, starch and PVP as binders are represented in Figs. 5.12 and 5.13 respectively. The plots show two segments indicating an initial fragmentation followed by plastic deformation for both plots.

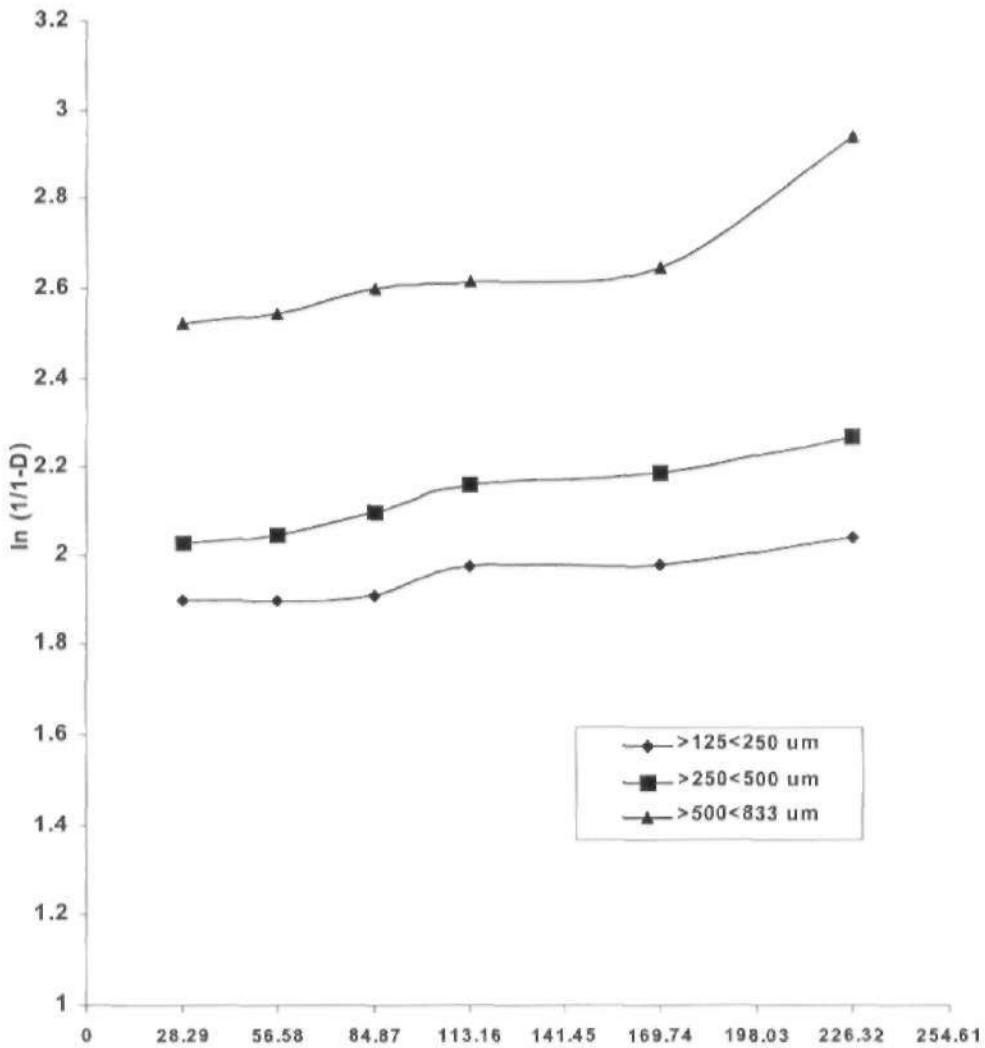


Fig. 5.10 Heckel plot of different sizes of Granules prepared using Lactose as diluent and Gelatin as binder

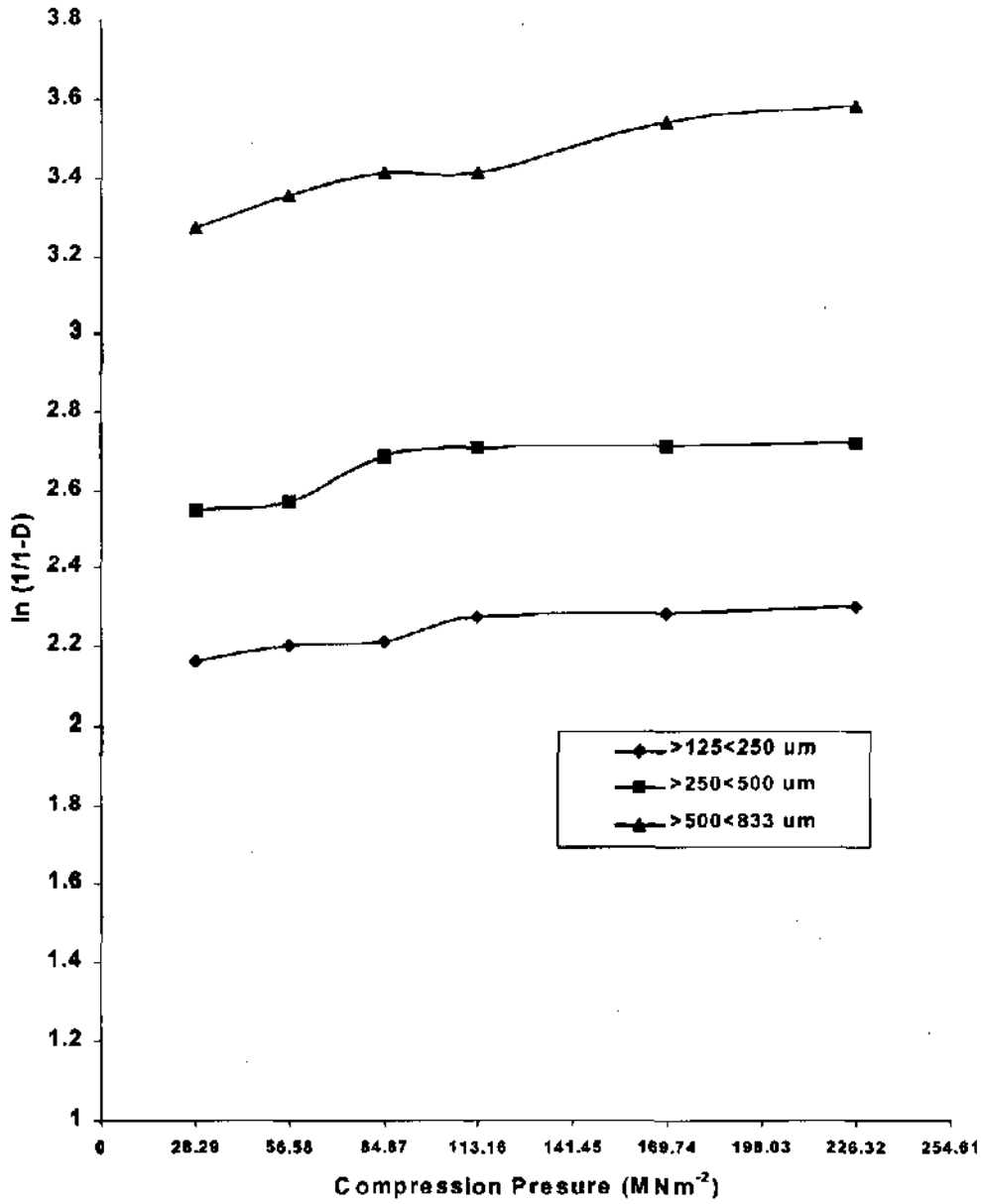


Fig. 5.11 Heckel plot of different sizes of Granules prepared using Lactose as diluent and Starch as binder

Table 5.10 Heckel Constants for Different sizes of Granule prepared using Lactose as diluent and Gelatin as binder.

Granule Size (μm)	Py (MNm^{-2})	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B (D_A-D_O)
>125 < 250	1334	1.865	0.1548	0.8452	0.3287	0.5165
>250 < 500	810.8	1.992	0.1364	0.8636	0.3115	0.5521
>500 < 833	541.2	2.435	0.08759	0.9141	0.3120	0.6021

The relationship between granule size and the Heckel constants were not consistent when magnesium carbonate was used as diluent (Table 5.12 and 5.13). With Starch as binder the Py values were in ascending order:

(>125<250) > (>250<500) > (>500<833) μm,

while Py values for granules using PVP as binder it were in ascending order:

(>125<250) > (>250<500) > (>500<833) μm,

The D_A, values increased with increase granules size (>125<250) and (>250<500) μm, and decreased thereafter. The irregularity in trend may have been due to granule shape. The granule shape might also have been responsible for the trend observed in D_O, and D_B values; an initial decrease followed by increase in D_O and an initial increase followed by decrease in D_B with increasing granule size.

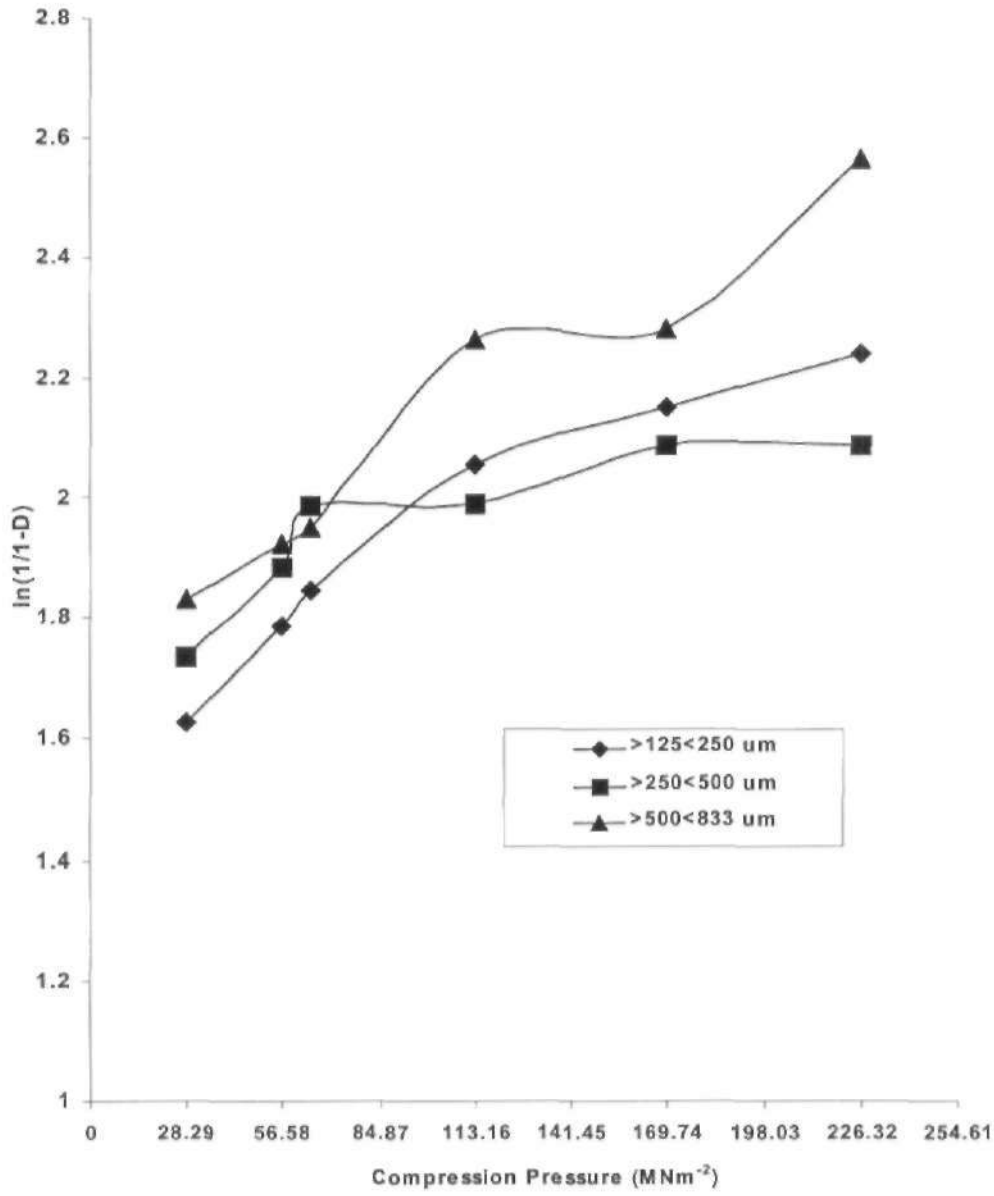


Fig. 5.12 Heckel plot of different sizes of Granules prepared with $MgCO_3$ as diluent and Starch as binder

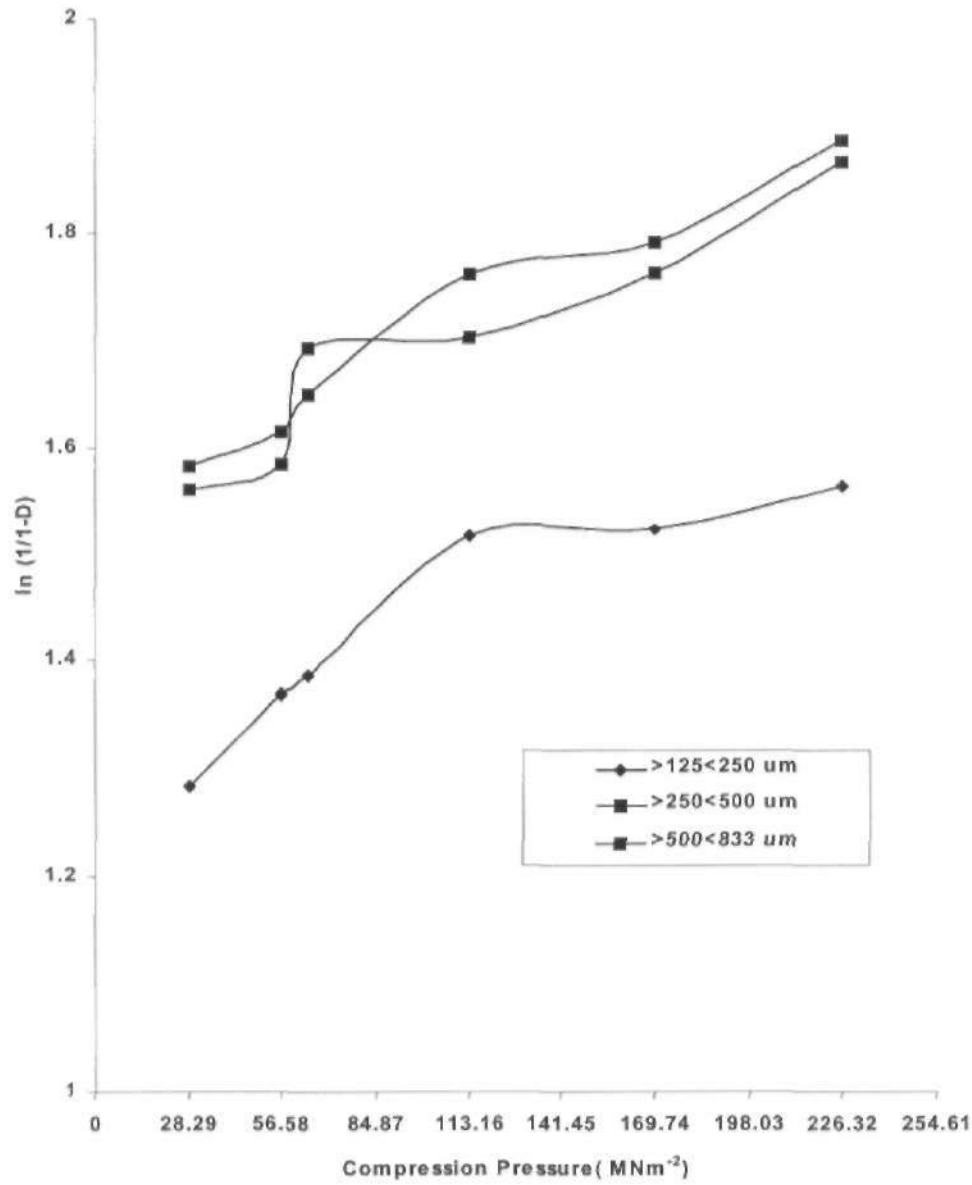


Fig. 5.13 Heckel plot of different sizes of Granules prepared with $MgCO_3$ as diluent and PVP as binder

Table 5.11 Heckel Constants for Different Sizes of Granules Prepared using Lactose as diluent and Starch as binder.

Granule Size (μm)	Py (MNm^{-2})	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B (D_A-D_O)
>125 < 250	1441	2.158	0.1155	0.8845	0.3079	0.5766
>250 < 500	1149	2.576	0.0773	0.9227	0.3006	0.6211
>500 < 833	653.1	3.255	0.0385	0.9615	0.2993	0.6622

Table 5.12 Heckel Constants for Different Sizes of Granules Prepared using $MgCO_3$ as diluent and Starch as binder.

Granule Size (μm)	Py (MNm^2)	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B $D_A-D_O)$
>125 < 250	324.3	1.602	0.2014	0.7986	0.249	0.549
>250 < 500	610.4	1.776	0.1693	0.8307	0.229	0.601
>500 < 833	271.2	1.718	0.1794	0.8206	0.233	0.587

Table 5.13 Heckel Constants for Different Sizes of Granules Prepared using $MgCO_3$ as diluent and PVP as binder.

Granule Size (μm)	Py (MNm^{-2})	A	e^{-A}	D_A $(1-e^{-A})$	D_O	D_B (D_A-D_O)
>125 < 250	726.5	1.284	0.2769	0.7231	0.2202	0.5129
>250 < 500	641.3	1.538	0.2148	0.7852	0.2244	0.5608
>500 < 833	662.9	1.524	0.2178	0.7822	0.2233	0.5589

5.3.5. Compressibility Profiles of Extract Formulations.

The tensile strength profiles of compacts formulated with lactose and magnesium carbonate as diluents are represented in Fig 5.14 and 5.15.The tensile strength for compacts formulated with Lactose as diluent decreased with increased granule size (Fig. 5.14). There was however an initial increase of tensile strength between 56.59 and 84.768 MNm^{-2} pressure before being followed by a decrease. This is in line with findings of Mackenna and Mcattety (1982) who found that the tensile strength of lactose and Starch compacts increased with decrease in particle size. This observation suggests that an optimal compression pressure of 84.768 Mnm^{-2} would be required to form a compact with highest tensile strength when lactose is to be used as diluent.

For compacts formulated with magnesium carbonate as diluent on the other hand there was an initial decrease in tensile strength with increase in granule size from (>125<250μm) to (>250<500μm) followed by an increased when granule size increased to (>500<833μm). The shape of the granules (>500<833μm) may have contributed to this observation as most of the granules had irregular shapes (increased surface irregularity), which may have led to increased number of binding surface area (Alderborn *et al*, 1988). There was an increase in tensile strength with increase in compression pressure for all the granule size. The increase in tensile strength with increase compression pressure further confirms that granules formulated with magnesium carbonate as diluent consolidated by fragmentation as well as by plastic deformation. As deformed particles fragment into a number of smaller discrete parts during compression (Ritter and Sucker, 1980) resulting in formation of new clean surfaces that serve as potential bonding areas (Parrott *et al*, 1990).

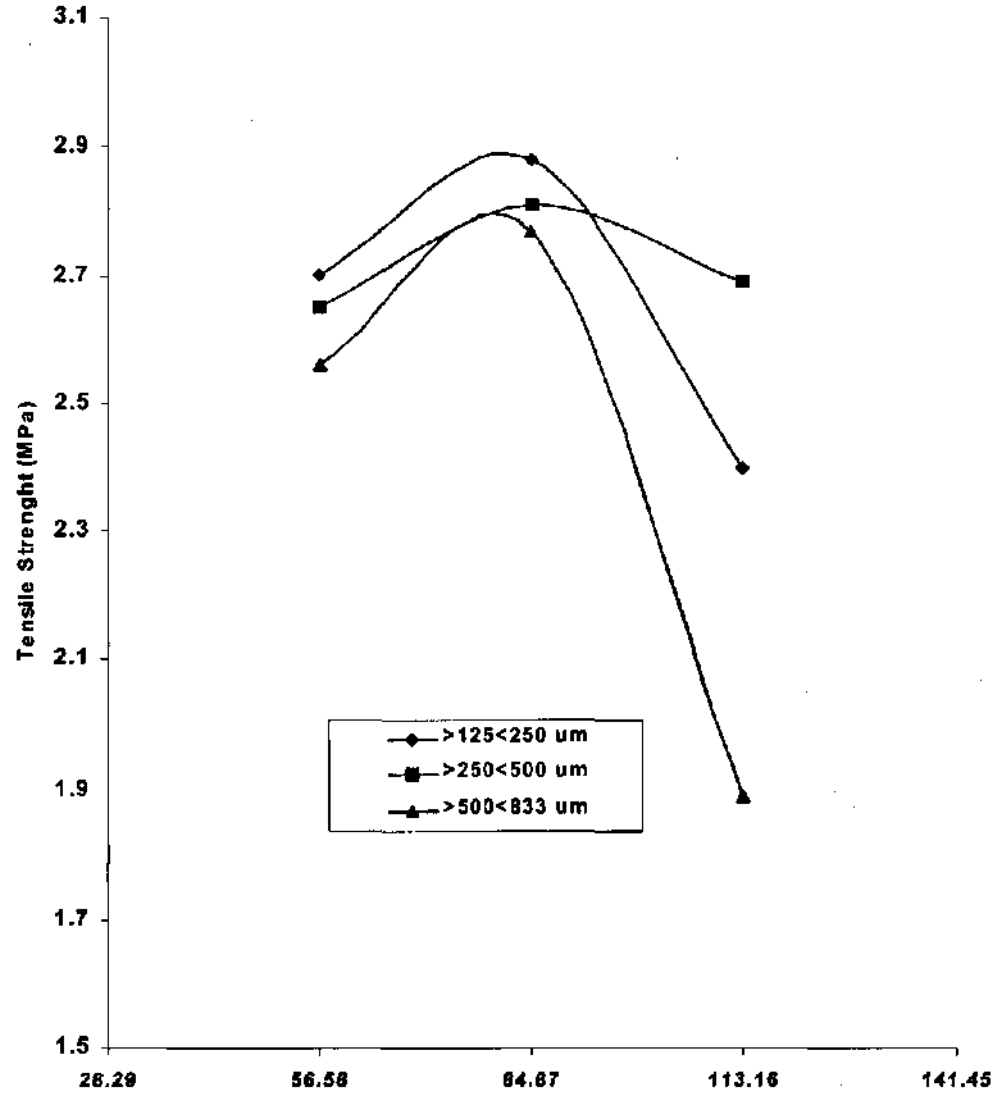


Fig. 5.14 Tensile strength (MPa) / Compression Pressure (MN m^{-2}) for tablets produced with lactose as diluent and Starch as binder

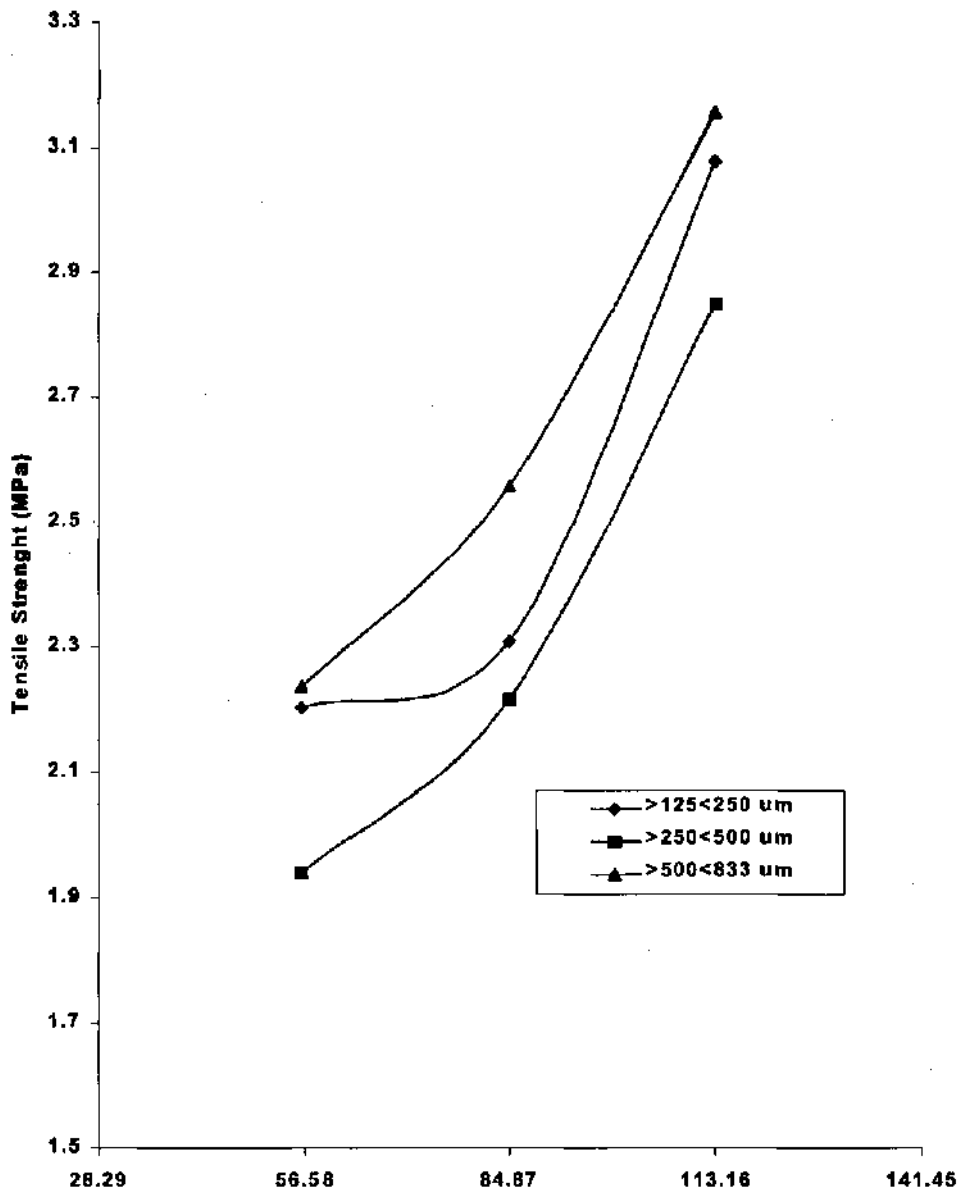


Fig. 5.15 Tensile strength (MPa) / Compression Pressure (MNm-2) for tablets produced with $MgCO_3$ as diluent and Starch as binder

CHAPTER SIX

6.0 CONCLUSION

The stem barks of *Anogeissus leiocarpus* and *Prosopis africana* were extracted using cold (maceration) and hot water extraction methods. Results of the phytochemical studies showed that *Anogeissus leiocarpus* contained saponins, glycosides, tannins, and flavonoids as indicated by previous workers. Similarly, *Prosopis africana* was found to contain alkaloids, saponins, tannins, glycosides and flavonoids. The secondary metabolites of the combination agreed with these findings.

Pharmacological evaluation studies showed that these plants possess pharmacological actions are indicative of their antiasthmatic activity. The combination was additive / synergistic in its antiasthmatic activities (effect on the rabbit jejunum and anti-inflammatory effect on the induced rat paw oedema), and generally less toxic than the individual components as evident in the LD_{50}'s.

The diluent used was found to markedly affect the quality of the tablets produced from the two plants. For example, tablets produced using lactose (a water soluble) as diluent were of more superior quality compared with those formulated with $MgCO_3$ (water insoluble) as diluent. Binder type and concentration were also found to modify the properties of the resulting tablets. Of the four binders used starch gave the best quality tablets especially when used at a concentration of 2.5%. Tablets formulated with starch (5.0%) as disintegrant were pharmaceutically more acceptable than those formulated with C.L (PVP) and treated-starch.

Compaction studies using the Heckel equation showed that formulations prepared with lactose consolidated mainly by plastic deformation, characteristic of a type A material, while those formulated with $MgCO_3$ as diluent consolidated by an initial fragmentation followed by plastic

deformation; which is characteristic of a type B material. This finding suggested that the extract modified the consolidation characteristics of lactose, which is a known type B material. The tensile strength of the tablets formulated with $MgCO_3$ increased as the compression pressure increased from 56.58 to 113.16 MNm^{-2} while tensile strength of tablets formulated with lactose was highest at the compression force of 84.87 MNm^{-2}.

The results of this work showed that good quality tablets of *Anogeissus leiocarpus* and *Prosopis africana* can be produced when the following excipents are combined: lactose, 60% diluent, starch 2.5%w/v (q.s) as binder and starch 5% as disintegrant.

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APPENDIX

APPENDIX I

Effect of extracts on induced rat paw oedema measured 120 minutes after induction.

Extract	**Dose mg/kg**	**Mean paw volume ± S.E**	**% Inhibition**
Control	Normal saline	0.754± 0.025	-
Prosopis africana	50	0.602± 0.018	20.15
Anogeissus leiocarpus	50	0.371 ± 0.058*	50.79
Combination	100	0.276 ± 0.016**	63.52
Aspirin	150	0.374 ± 0.056*	56.39

* P< 0.05 ** P< 0.005

APPENDIX 11

Size distribution of granules produced using lactose as diluent and different binders

Granule size	Percentage undersized			
(μm)	Gelatin	Starch	P.V.P	Water
0	0	0	0	0
75	9.63	2.25	3.28	1.26
150	19.65	5.65	8.38	3.61
250	40.24	14.68	19.56	9.55
500	73.07	43.75	46.38	31.57
833	91.10	75.04	73.15	65.15
1000	100	100	100	100

APPENDIX 111

Size distribution of granules produced using $MgCO_3$ as diluent and different binders

Granule size	Percentage undersized			
(μm)	Gelatin	Starch	P.V.P	Water
0	0	0	0	0
75	3.26	6.34	7.49	2.16
150	7.48	13.68	11.99	4.72
250	18.81	31.65	25.67	13.06
500	48.10	64.92	53.82	40.70
833	79.81	87.13	82.17	74.53
1000	100	100	100	100

APPENDIX 1V

Heckel plots for granules formulated using lactose as diluent

Compression	In(1/1-D)			
Pressure (MNm^{-2})	Water	Starch	Gelatin	P.V.P
28.294	2.062	2.573	2.026	1.959
56.588	2.237	2.584	2.046	2.120
84.882	2.271	2.598	2.100	2.140
113.176	2.301	2.643	2.160	1.146
169.764	2.384	2.696	2.187	2.166
226.352	2.461	2.708	2.271	2.190

APPENDIX V

Heckel plots for granules formulated using $MgCO_3$ as diluent

Compression	In (1/1-D)			
Pressure (MNm^{-2})	Water	Starch	Gelatin	P.V.P
28.294	1.950	1.735	1.627	1.584
56.588	2.276	1.883	1.725	1.615
84.882	2.349	1.983	1.855	1.648
113.176	2.517	1.986	1.883	1.761
169.764	2.561	2.088	2.054	1.790
226.352	2.724	2.089	2.213	1.886