PREPARATION, DISSOLUTION RATE AND AGING STUDIES OF HYDROCHLOROTHIAZIDE

BY

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APPROVAL

This thesis submitted by Luka Baba Panya meets the regulations governing the award of the degree of Master of Science (Pharmaceutics) of the Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, and it is approved for its contribution to Science and literacy presentation.

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DECLARATION

I hereby declare that this thesis has been composed by myself and that it is record of my own research work. It has not been accepted in any previous application for a higher degree. All quotation marks and the sources of information are specifically acknowledged by means of references.

Luka Baba PANYA

Date: 8th August 1985

D E D I C A T I O N

MY GOD FOR HIS GUIDANCE

AND

MY PARENTS FOR THEIR LOVE AND CARE.

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ABSTRACT

The influence of polyvinylpyrrolidone (PVP) 10,000, 44,000 and urea on the solubility and dissolution rate of hydrochlorothiazide have been investigated. Physical mixtures and coprecipitates of drug and carriers, of various compositions, were prepared. It was established by the ultraviolet spectrophotometric and thin layer chromatographic methods, that hydrochlorothiazide is stable in dispersion with all the carriers employed. There was a general increase in the dissolution rate of hydrochlorothiazide from the physical mixtures and coprecipitates when compared to the pure drug alone. Polyvinylpyrrolidone 10,000 was superior to PVP 44,000 while the least increase in dissolution rate was observed with urea coprecipitates. Local solubilization effects of the carriers at the microenvironment of the drug particle was proposed as the probable mechanism of dissolution rate increases from the physical mixtures. This is supported by increase in the aqueous solubility of hydrochlorothiazide in the presence of the carriers. The infrared spectra of the coprecipitates of hydrochlorothiazide with the carriers, when compared to those of the pure drug and carriers, did not show any shift in the major peaks particularly between frequencies 1300 cm^{-1} and 3600 cm^{-1}. This precludes the possibility of solid-solid interaction between the drug and carriers.

Dissolution rate data for compressed tablets prepared from the pure drug and 30 % coprecipitates with urea and PVP 10,000 showed that PVP 10,000 is superior to urea in enhancing the dissolution rate of hydrochlorothiazide; a trend similar to that observed with the powder samples. While definite increases in dissolution rates were observed for tablets prepared from hydrochlorothiazide-urea coprecipitates, those from hydrochlorothiazide-PVP 10,000 coprecipitates showed significant decreases after storage at various relative humidity (RH) conditions for about 105 days. However, tablets prepared from the pure drug did not show signifcant changes in dissolution profile. While the high water absorption capacity of urea accounts for increases in the dissolution rates, the unique hardening characteristic of PVP 10,000 with age, may account for the decreases in dissolution rate of hydrochlorothiazide from aged tablets. Possible changes in the physical nature of the drug on aging may be a contributory factor to changes in the dissolution rate profile observed.

While the solid dispersion technique has been demonstrated to be of biopharmaceutical signifcance, the choice of carriers is critical in attaining reasonable increase in dissolution rates of poorly soluble drugs.

C O N T E N T S

CHAPTER ONE - INTRODUCTION		Page
1.1	General Introduction	1
1.2	Factors affecting solubility and dissolution rate	6
1.3	Dispersion technique	11
1.3.1	Definition of solid dispersion	11
1.3.2	Methods of preparation of solid dispersion	11
1.3.3	Classification and characterization of dispersions	14
1.3.4	Aging effects of solid dispersions ...	27
1.4	Literature review	28
1.5	Research problem and objectives	39
CHAPTER TWO - PRELIMINARY INVESTIGATIONS ...		42
2.1	Drugs and carriers used and the criteria for their selection	42
2.1.1	Criteria for drug and carrier selection ...	42
2.1.2	Drug and carriers employed	45
2.2	Determination of the wavelength of maximum absorption (λ max) for hydrochlorothiazide	48
2.2.1	Method	48
2.2.2	Results and discussion	49
2.3	Plotting the standard curve	52
2.3.1	Method	52
2.3.2	Results and discussion	52
2.4	Determination of the solubility of hydrochlorothiazide in water at 37°C ...	55
2.4.1	Method	55

C O N T E N T S (Contd')

		Page
2.4.2	Results and discussion	55
2.5	Aqueous solubility of hydrochlorothiazide as a function of carrier concentration at 37°C	55
2.5.1	Method	56
2.5.2	Results and discussion	56
CHAPTER THREE -	PREPARATION AND DISSOLUTION STUDIES OF THE COPRECIPITATES OF HYDROCHLOROTHIAZIDE WITH THE VARIOUS CARRIERS	60
3.1	Method of sample preparation	60
3.1.1	Solvent method	60
3.1.2	Physical mixture	61
3.1.3	Hydrochlorothiazide powder	61
3.2	Determination of the stability of hydrochlorothiazide in the coprecipitates	61
3.2.1	Ultra-violet spectrophotometry	62
3.2.1.1	Method	62
3.2.1.2	Results and discussion	63
3.2.2	Thin layer Chromatography	65
3.2.2.1	Preparation of plates	66
3.2.2.2	Method	66
3.2.2.3	Results and discussion	67
3.3	Infrared studies	69
3.3.1	Method	69
3.3.2	Results and discussion	70
3.4	Evaluating the Uniformity of hydrochlorothiazide in the coprecipitates and physical mixtures	76

C O N T E N T S (Contd')

		Page
3.4.1	Method	76
3.4.2	Results and discussion	77
3.5	In-Vitro dissolution rate studies of the powder samples	82
3.5.1	Apparatus	82
3.5.2	Method	84
3.5.3	Problems associated with the tape method of dissolution rate testing and the precautionary measures necessary	87
3.5.4	Results and discussion	90
CHPATER FOUR - FORMULATIONS STUDIES	... ...	134
4.1	Introduction	134
4.2	The direct compression vehicle: microcrystalline cellulose	138
4.3	Working formula and calculations ...	138
4.4	Method of tablet formulation	141
4.5	Physical tests on tablets	141
4.5.1	Weight variation	142
4.5.1.1	Method	142
4.5.1.2	Results and discussion	142
4.5.2	Uniformity of diameter of tablets ...	147
4.5.2.1	Method	147
4.5.2.2	Results and discussion	147
4.5.3	Friability test	150
4.5.3.1	Method	150
4.5.3.2	Results and discussion	151
4.5.4	Hardness test	152

C O N T E N T S (Contd')

		Page
4.5.4.1	Method	152
4.5.4.2	Results and discussion	152
4.5.5	Uniformity of contents	153
4.5.5.1	Method	153
4.5.5.2	Results and discussion	153
4.5.6	Disintegration test	157
4.5.6.1	Method	157
4.5.6.2	Results and discussion	157
4.5.7	Dissolution rate studies	158
4.5.7.1	Method	158
4.5.7.2	Results and discussion	159
CHAPTER FIVE - AGING STUDIES	... ...	164
5.1	Storage conditions	165
5.2	Evaluation of aged tablets	165
5.2.1	Dissolution rate tests	165
5.2.1.1	Method	165
5.2.2	Disintegration tests	166
5.2.2.1	Method	166
5.3	Results and discussion	166
	References	187

List of tables

2.1 Determination of wavelength of maximum absorption of hydrochlorothiazide in 10 % methanol solution in distilled water

2.2 Plotting the Standard Curve

2.3 Solubility of hydrochlorothiazide in solutions of PVP 10,000 of various concentrations in distilled water at 37°C.

2.4 Solubility of hydrochlorothiazide in solutions of PVP 44,000 of various concentrations in distilled water at 37°C.

2.5 Solubility of hydrochlorothiazide in solutions of urea of various concentrations in distilled water at 37°C.

3.1 Stability of hydrochlorothiazide in its coprecipitate with PVP 10,000.

3.2 Stability of hydrochlorothiazide in its coprecipitate with PVP 44,000.

3.3 Stability of hydrochlorothiazide in its coprecipitate with urea

3.4 Uniformity of hydrochlorothiazide in hydrochlorothiazide -PVP 10,000 coprecipitates.

3.5 Uniformity of hydrochlorothiazide in hydrochlorothiazide - PVP 10,000 physical mixtures.

3.6 Uniformity of hydrochlorothiazide in hydrochlorothiazide-PVP 44,000 coprecipitates.

3.7 Uniformity of hydrochlorothiazide in hydrochlorothiazide - PVP 44,000 physical mixtures.

3.8 Uniformity of hydrochlorothiazide in hydrochlorothiazide - urea coprecipitates.

3.9 Dissolution rate test data for pure hydrochlorothiazide in distilled water at 37°C.

3.10 Dissolution rate test data for 10 % hydrochlorothiazide-PVP 10,000 physical mixtures in distilled water at 37°C

3.11 Dissolution rate test data for 10 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water at 37°C.

3.12 Dissolution rate test data for 10 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C.

3.13 Dissolution rate test data for 10 % hydrochlorothiazide - PVP 44,000 coprecipitates in distilled water at 37°C.

3.14 Dissolution rate test data for 10 % hydrochlorothiazide - urea coprecipitates in distilled water at 37°C.

3.15 Dissolution rate test data for 20 % hydrochlorothiazide - PVP 10,000 physical mixtures in distilled water at 37°C.

3.16 Dissolution rate test data for 20 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water at 37°C.

3.17 Dissolution rate test data for 20 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C.

3.18 Dissolution rate test data for 20 % hydrochlorothiazide - PVP 44,000 coprecipitates in distilled water at 37°C.

3.19 Dissolution rate test data for 20 % hydrochlorothiazide - urea coprecipitates in distilled water at 37°C.

3.20 Dissolution rate test data for 30 % hydrochlorothiazide - PVP 10,000 physical mixtures in distilled water at 37°C.

3.21 Dissolution rate test data for 30 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water at 37°C.

3.22 Dissolution rate test data for 30 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C.

3.23 Dissolution rate test data for 30 % hydrochlorothiazide - PVP 44,000 coprecipitates in distilled water at 37°C.

3.24 Dissolution rate test data for 30 % hydrochlorothiazide - urea coprecipitates in distilled water at 37°C.

3.25 Dissolution rate test data for 40 % hydrochlorothiazide - PVP 10,000 physical mixtures in distilled water at 37°C.

3.26 Dissolution rate test data for 40 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water 37°C.

3.27 Dissolution rate test data for 40 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C.

3.28 Dissolution rate test data for 40 % hydrochlorothiazide - PVP 44,000 coprecipitates in distilled water at 37°C.

3.29 Dissolution rate test data for 40 % hydrochlorothiazide - coprecipitates in distilled water at 37°C.

3.30 Dissolution rate test data for 50 % hydrochlorothiazide - PVP 10,000 physical mixtures in distilled water at 37°C.

3.31 Dissolution rate test data for 50 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water at 37°C.

3.32 Dissolution rate test data for 50 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C.

3.33 Dissolution rate test data for 50 % hydrochlorothiazide - PVP 44,000 coprecipitates in distilled water at 37°C.

3.34 Dissolution rate test data for 50 % hydrochlorothiazide - urea coprecipitates in distilled water at 37°C.

3.35 Times taken for 60 %, 75 %, 90 % (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution from its dispersion with urea.

3.36 Times taken for 60 %, 75 %, 90 %, (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution from its dispersions with PVP 10,000.

3.37 Times taken for 60 %, 75 %, 90 % (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution from its dispersions with PVP 44,000.

4.1 Working formula for tablet manufacture employing pure hydrochlorothiazide.

4.2 Working formula for tablet manufacture employing coprecipitates of hydrochlorothiazie with either urea or PVP 10,000.

4.3 Weight varaition of tablets prepared from pure hydrochlorothiazide.

4.4 Weight variation of tablets prepared from 30 % hydrochlorothiazide - urea coprecipitate.

4.5 Weight variation of tablets prepared from 30 % hydrochlorothiazide - PVP 10,000 coprecipitate.

4.6 Uniformity of diameter of tablets prepared from pure hydrochlorothiazide.

4.7 Uniformity of diameter of tablets prepared from hydrochlorothiazide - urea coprecipitate.

4.8 Uniformity of diameter of tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate.

4.9 Friability test on tablets prepared from pure hydrochlorothiazide and its coprecipitate with urea and PVP 10,000.

4.10 Hardness test on tablets prepared from pure hydrochlorothiazide and its coprecipitates with urea and PVP 10,000.

4.11 Uniformity of contents of tablets prepared from pure hydrochlorothiazide.

4.12 Uniformity of contents of tablets prepared from hydrochlorothiazide - urea coprecipitate.

4.13 Uniformity of contents of tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate.

4.14 Disintegration times of tablets prepared from pure hydrochlorothiazide and its coprecipitates with urea and PVP 10,000 in distilled water at 37°C.

4.15 Dissolution rate data for tablets prepared from pure hydrochlorothiazide in distilled water at 37°C.

4.16 Dissolution rate data for tablets prepared from hydrochlorothiazide - urea coprecipitate in distilled water at 37°C.

4.17 Dissolution rate data for tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate in distilled water at 37°C.

5.1 Dissolution rate data for aged tablets prepared from pure hydrochlorothiazide in distilled water at 37°C after storage for 40 days under a R.H. of 6 to 30%.

5.2 Dissolution rate data for aged tablets prepared from pure hydrochlorothiazide in distilled water at 37°C after storage for 105 days under a R.H. of 6 to 30 %.

5.3 Dissolution rate data of aged tablets prepared from pure hydrochlorothiazide in distilled water at 37°C after storage for 40 days under a R.H. of 75 %.

5.4 Dissolution rate data for aged tablets prepared from pure hydrochlorothiazide in distilled water at 37°C after storage for 105 days under a R.H. of 75 %.

5.5 Dissolution rate data for aged tablets prepared from hydrochlorothiazide - urea coprecipitate in distilled water at 37°C after storage for 40 days under R.H. of 6 to 30 %.

5.6 Dissolution rate data for aged tablets prepared from hydrochlorothiazide - urea coprecipitate in distilled water at 37°C after storage for 40 days under a R.H. of 75 %.

5.7 Dissolution rate data for aged tablets prepared from hydrochlorothiazide - urea in distilled water at 37°C after storage for 105 days under a R.H. of 6 to 30 %.

5.8 Dissolution rate data for aged tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate in distilled water at 37°C after storage for 40 days under a RH of 6 to 30 %.

5.9 Dissolution rate data for aged tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate in distilled water at 37°C after storage for 105 days under a RH of 6 to 30 %.

5.10 Dissolution rate data for aged tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate in distilled water at 37°C after storage for 40 days under a R.H. of 75 %.

5.11 Dissolution rate data for aged tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate in distilled water at 37°C after storage for 105 days under a R.H. of 75 %.

5.12 Average disintegration times for aged tablets prepared from pure hydrochlorothiazide and it's coprecipitates with urea and PVP 10,000 in distilled water at 37°C.

List of figures

1.1 Simple phase diagram of a system showing eutectic formation between two compounds A and B.

1.2 Simple phase diagram of a system showing solid solution formation between two compounds A and B.

1.3 Schematic illustration of substitutional solid solution.

1.4 Schematic illustration of interstitial solid solution.

2.1 Wavelength of maximum absorption for hydrochlorthiazide in 10 % methanol solution in distilled water.

2.2 Standard Beer's plot for hydrochlorothiazide in 10 % methanol solution in distilled water.

2.3 Aqueous solubility of hydrochlorothiazide as a function of carrier concentration at 37°C.

3.1 Developed thin layer chromatogram of pure hydrochlorothiazide and its 30 % coprecipitates with urea and PVP 10,000.

3.2 Infrared spectrum of pure hydrochlorothiazide in KBr.

3.3 Infrared spectrum of pure PVP 10,000 in KBr.

3.4 Infrared spectrum of 30 % hydrochlorothiazide - PVP 10,000 coprecipitate in KBr.

3.5 Infrared spectrum of pure urea in KBr.

3.6 Infrared spectrum of 30 % hydrochlorothiazide - urea coprecipitate in KBr.

3.7 Dissolution profile of pure hydrochlorothiazide in distilled water at 37°C.

3.8 Dissolution profiles of pure hydrochlorothiazide and its 10 % dispersions in PVP 10,000, 44,000 and urea, in distilled water at 37°C.

3.9 Dissolution profiles of pure hydrochlorothiazide and its 20 % dispersions in PVP 10,000, 44,000 and urea, in distilled water at 37°C.

3.10 Dissolution profiles of pure hydrochlorothiazide and its 30 % dispersions in PVP 10,000, 44,000 and urea, in distilled water at 37°C.

3.11 Dissolution profiles of pure hydrochlorothiazide and its 40 % dispersions in PVP 10,000, 44,000 and urea, in distilled water at 37°C.

3.12 Dissolution profile of pure hydrochlorothiazide and its 50 % dispersions in PVP 10,000, 44,000 and urea, in distilled water at 37°C.

3.13 Times required for 60 %, 75 %, 90 % (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution, from hydrochlorothiazide - urea coprecipitates of various compositions.

3.14 Times required for 60 %, 75 %, 90 % (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution from hydrochlorothiazide - PVP 10,000 coprecipitates of various compositions.

3.15 Times required for 60 %, 75 %, 90 % (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution from hydrochlorothiazide - PVP 44,000 coprecipitates of various compositions.

4.1 Dissolution profiles of tablets prepared from pure hydrochlorothiazide and its 30 % coprecipitates in urea and PVP 10,000, in distilled water at 37°C.

5.1 Dissolution profiles of fresh and aged tablets prepared from pure hydrochlorothiazide in distilled water at 37°C.

5.2 Dissolution profiles of fresh and aged tablets prepared from 30 % hydrochlorothiazide - urea coprecipitate, in distilled water at 37°C.

5.3 Dissolution profiles of fresh and aged tablets prepared from 30 % hydrochlorothiazide - PVP 10,000 coprecipitate, in distilled water at 37°C.

List of Plates

3.1 The tape method dissolution rate test apparatus.

CHPATER ONE

1.1 INTRODUCTION

The objective of any product development is to control the stated behaviour of that product when in clinical use. This can be achieved by controlling various factors, one of which may be the dissolution pattern which consequently influences the absorption characteristics.

Dissolution has been defined by Wagner, (1971) as the act of dissolving while dissolution rate is the rate of dissolving of a chemical or medicament from a solid. Biopharmaceutics conceives dissolution rate as the rate at which medicamentsdissolve from intact dosage forms or from fragments or particles formed from the dosage form under test.

The importance of dissolution rate tests on a drug product stems from the fact that drug absorption and its physiologic availability depends largely upon having the drug in solution. Infact, before any drug material is absorbed from the site of administration into the systemic circulation, it must be in solution; that is to say that it must undergo the process of dissolution.

It has been well established (Wagner 1961; Lees, 1963; Dare, 1964) that where a drug is readily absorbed from solution, dissolution is frequently the rate limiting step in the gastrointestinal absorption of the drug from a solid dosage form. This relationship becomes more distinct when considering poorly water soluble drugs.

Many of the modern therapeutic agents are poorly soluble in water and in the aqueous luminal fluid of the gastrointestinal tract, as such the in-vivo dissolution rate of these compounds is low and their absorption is often incomplete and erratic (Levy, 1963 a). It is therefore mandatory that the dissolution characteristics of such substances be established in order to ensure physiologic availability and hence the in-vivo activity.

A good knowledge of the in-vitro dissolution profile of a drug coupled with the knowledge of certain physico-chemical properties inherent to the drug material for example, the pKa and partition coefficient and also the solvent properties of the gastrointestinal fluid, can give an insight into the in-vivo absorption characteristics and physiologic availability of orally administered dosage forms. Dissolution test data is therefore an important

property of a satisfactory drug product; consequently the need for dissolution rate tests in the design, evaluation and quality control of pharmaceutical dosage forms, more especially solid dosage forms, is clearly seen.

There are various approaches to improving the dissolution rate of poorly soluble drug materials, the fundamental one being through particle size reduction by various ways and means.

The role of particle size becomes most significant when one is considering poorly water soluble drugs. Review articles which specifically concern the effect of particle size on the dissolution, absorption and biological activity of medicaments are available (Lees, 1963; Levy, 1963 b; Dare, 1964; Fincher, 1968).

Brunner and Tolloczko, (1900) had earlier established that the dissolution rate of a drug substance bear direct proportionality with the surface area exposed to the dissolution medium. On this basis Levy, (1963 b) noted that, "in those instances where the intrinsic dissolution rate of a drug is so low that the drug is ordinarily not completely absorbed when administered in a solid dosage form, the more rapid absorption attained by increasing the

specific surface area will also cause an increase in the total amount of drug absorbed from a given dose". That is to say that the dissolution rate and bioavailability of a poorly soluble drug material could be enhanced by decreasing the particle size which consequently increases the specific surface area of the drug material. Similar observations were made by Wagner, (1961); Lees, (1963) and Dare, (1964).

Some of the conventional methods that have been employed to achieve particle size reduction include:

(a) Trituration and other mechanical methods such as ball milling, hammer milling etc.

(b) Controlled precipitation by change in solvent, temperature, pH of the medium and by application of ultrasonic waves (Scheikh, et al., 1966; Hem, et al., 1967; Skauen, 1967).

However, these methods have their limitations. For instance, mechanical trituration and milling is not always applicable to all drugs due to differences in their physico-chemical properties. Sometimes the

resultant fine particles acquire static charges and tend to aggregate or agglomerate into larger particles thereby disallowing the expected increase in the dissolution and absorption rate of the drug (Lin, et al., 1968).

Controlled precipitation by solvent change poses the problem of selecting a non-toxic solvent and is always limited to drugs of low doses. Drug precipitation from solution in the gastrointestinal tract has the preliminary problem of getting the drug into solution; particularly poorly soluble drugs. These problems have made it necessary for more effective means of achieving particle size reduction to be sought.

The unique approach of solid dispersion technique to reduce particle size and increase the rate of dissolution and absorption of poorly soluble drugs was first demonstrated by Sekiguchi and Obi, (1961). On exposing a eutectic mixture of sulfathiazole and urea prepared by 'fusion' method to aqueous media, the soluble 'carrier' (urea) dissolved rapidly leaving the insoluble drug in an extremely fine state of subdivision, thereby increasing the effective surface area of the drug exposed to the medium.

Levy, (1963 b); Kanig, (1964) and later Goldberg, et al., (1966 a, b, c) further promulgated the possibility of increasing the dissolution rate and absorption through the 'solid solution' approach where unlike the eutectic, the drug is dispersed in the carrier at molecular level.

This project is aimed at utilizing the solid dispersion technique to improve the dissolution characteristics and hence the absorption and bioavailability of a poorly soluble drug; hydrochlorothiazide.

1.2 FACTORS AFFECTING SOLUBILITY AND DISSOLUTION RATE

It has been recognised that the release of active drug from pharmaceutical drug products may be influenced greatly by physico-chemical factors inherent to the drug, such as the pKa and the partition coefficient and by the method of formulation. Many factors, together with particle size (already discussed in 1.1) have been proved to influence, either directly or indirectly, the dissolution characteristics of a drug material both in-vitro and in-vivo.

A sound knowledge of these factors will not only help in achieving desirable and useful dissolution test data, but may also create an opportunity for modifying and improving the solubilities, dissolution rate, absorption and hence clinical effectiveness of drugs.

These factors include:-

(i) Polymorphism

Certain drug substances are capable of existing in more than on crystal form. Polymorphic forms of a drug usually exhibit different physico-chemical properties including melting point and solubility characteristics. With such drugs, the metastable forms usually have greater aqueous solubility because they are thermodynamically less stable.

(ii) Amorphous state and solvation

Certain substances do not exist in any crystalline form and are said to be amorphous. Such amorphous forms are usually less stable than the crystalline forms and are often more soluble too.

Some drug molecules sometimes have solvent molecules associated with them to form solvates. In cases where water is the solvent, they are known as hydrates. The existence of solvation and also the degree of solvation may cause differences in the solubilities of drugs in these forms as compared to the non-solvated drug molecules.

(iii) Salt formation by acidic and basic drugs

The alkaline metal salts of weak acids for example, the sodium, postassium and calcium salts and the mineral acid salts of weak bases for example the hydrochlorides and sulphates are usually more soluble than the corresponding weak acids and bases. It is worth noting however that increased solubility is not the only trend observed with salt formation of weak acids and bases.

(iv) Complexation, a form of molecular association is known to influence the solubility of a drug in a solvent. This does not apply to liquid solutions only but could be observed also with solid solutions. The formation of molecular compounds (complexes) through the solid dispersion technique may increase the solubility of poorly soluble drugs.

(v) Static electrification of solid drug particles

Conventional mixing, blending, micronization and coating processes could introduce static charges on the drug particles causing them to aggregate thus reducing the specific surface area of the particles. This could lead to a decrease in the dissolution rate of the drug.

(vi) Surfactants

When a drug formulation incorporates a surfactant, it causes a decrease in the surface and interfacial tension thereby allowing for a more intimate contact between the drug and the solvent (dissolution medium). This improves wettability and consequently the solubility and dissolution rate of the drug is increased.

(vii) Miscellaneous factors

Other formulation factors such as amount and type(s) of diluent and disintegrant; granular size and size distribution, compressional force and speed of compression, pressure applied during the filling of capsules, type and amount

of lubricant used are known to variously affect the dissolution rate of pharmaceutical drug products. Others include the humidity of the manufacturing environment, storage conditions for dosage forms and the age of the dosage forms under consideration.

1.3 DISPERSION TECHNIQUE

1.3.1 DEFINITION OF SOLID DISPERSION

Solid dispersions have been defined by Mayersohn and Gibaldi, (1966) as, "dispersions of one or more active ingredients in an innert water soluble carrier or matrix at solid state prepared by melting (fusion), solvent or melting-solvent method". Similarly, the term coprecipitate refers to solid dispersion prepared by the solvent method (Simonelli, et al., 1969). These definitions exclude dispersions of a drug in a solid diluent achieved by mechanical mixing.

1.3.2 METHODS OF PREPARATION OF SOLID DISPERSION

Three methods have variously been employed in the preparation of solid dispersions. These include

(i) Melting (Fusion) method

This method was first demonstrated by Sekiguchi and Obi, (1961). Here the physical mixture of the drug and the water soluble carrier is heated directly under controlled temperature until it melts. The melted mixture is then rapidly cooled to solidify, preferably

in an ice bath, under rigorous stirring. Rapid cooling can also be achieved by pouring the hot melt on a stainless steel plate accompanied by a stream of cold air blowing over the melt or a current of cold water running at the opposite side of the plate as was done by Goldberg, et al., (1966 a, b, c) and Chiou and Riegelman, (1969). Further hardening could be achieved by storing the coprecipitates in a desiccator at ambient temperatures.

It is essential that complete melting and uniform mixing of the melt be achieved. Rapid cooling is advantageous because the drug or solute molecules are trapped in the solvent matrix by the instantaneous solidification process (Moore, 1963). This act allows for superstaturation of the drug in the carrier (polymer) matrix. Other advantages associated with this method are its simplicity and economy.

The fusion method, however, has disadvantages since it is limited to only thermostable materials. Thermolabile and volatile drugs and carriers cannot be employed

here as they may evaporate or even decompose during the fusion process. Oxidative decomposition can be prevented or minimised by heating the mixture over a blanket of an inert gas, in vacuum or in closed containers.

(ii) Solvent method

It involves dissolving the physical mixture of the drug and carrier in a common solvent, either alone or in a mixture of solvents followed by evaporation of the solvent. The solid residue (coprecipitate) is further dried in a desiccator at ambient temperatures to achieve complete solvent evaporation and hardening which allows for easy pulverization.

Major advantages associated with this method are that, thermal decomposition of the drug and carrier is minimised or completely prevented, at such low temperatures required to evaporate the solvent.

The disadvantages associated with this method are its high cost, the difficulty in achieving complete removal of the solvent and in reproducing crystal forms, possible adverse effects of trace amounts of solvent on the stability of the drug and carrier and the

difficulty in achieving supersaturation of the drug in the carrier as compared to quenching (rapid cooling) in the fusion method. The possibility of achieving dispersions in a solvent using water soluble polymers was demonstrated by Tachibana and Nakamura, (1965) and later by Mayersohn and Gibaldi, (1966).

(iii) Melting-solvent method

This involves dissolving the drug first in a suitable solvent and then incorporating the drug solution into the melt of the carrier. It may, however, be difficult or impossible to achieve a uniform dispersion if the liquid solvent is immiscible with the melt of the carrier. Furthermore, this method is limited to easily melted carriers.

1.3.3. CLASSIFICATION AND CHARACTERISATION OF SOLID DISPERSIONS

Solid dispersions have been classified into various categories based on their drug release patterns (Chiou and Riegelman, 1971 a; Hajratwala, 1974). These include:-

(a) Simple eutectic mixtures

(b) Solid solutions

(c) Glass solutions and glass suspensions

(d) Amorphous precipitation in a crystalline carrier

(e) Complex or compound formation between the drug and carrier

a) Simple eutectic mixtures (Illustrated in Fig. 1.1)

When a solution of A and B is cooled from a point f to g (Fig. 1.1) then some solid A is crystalized out from the solution. Further cooling to point h causes more solid A to be crystallized out. This causes a change in the composition of the solution (in respect of A and B) corresponding to a point i. As the temperature falls, the composition of the remaining liquid moves along the cooling curve CE. A limit is reached when the liquid is saturated with both A and B which on further cooling, the two solids crystallize out in the same ratio in which they exist in the saturated solution. The solid mixture consisting of X % A and Y % B is the eutectic mixture and U is the eutectic temperature.

These are obtained by rapid solidification of the fused mixture of two components that show complete liquid miscibility and mone or negligible solid-solid solubility. Goldberg, et al., (1965 a) described

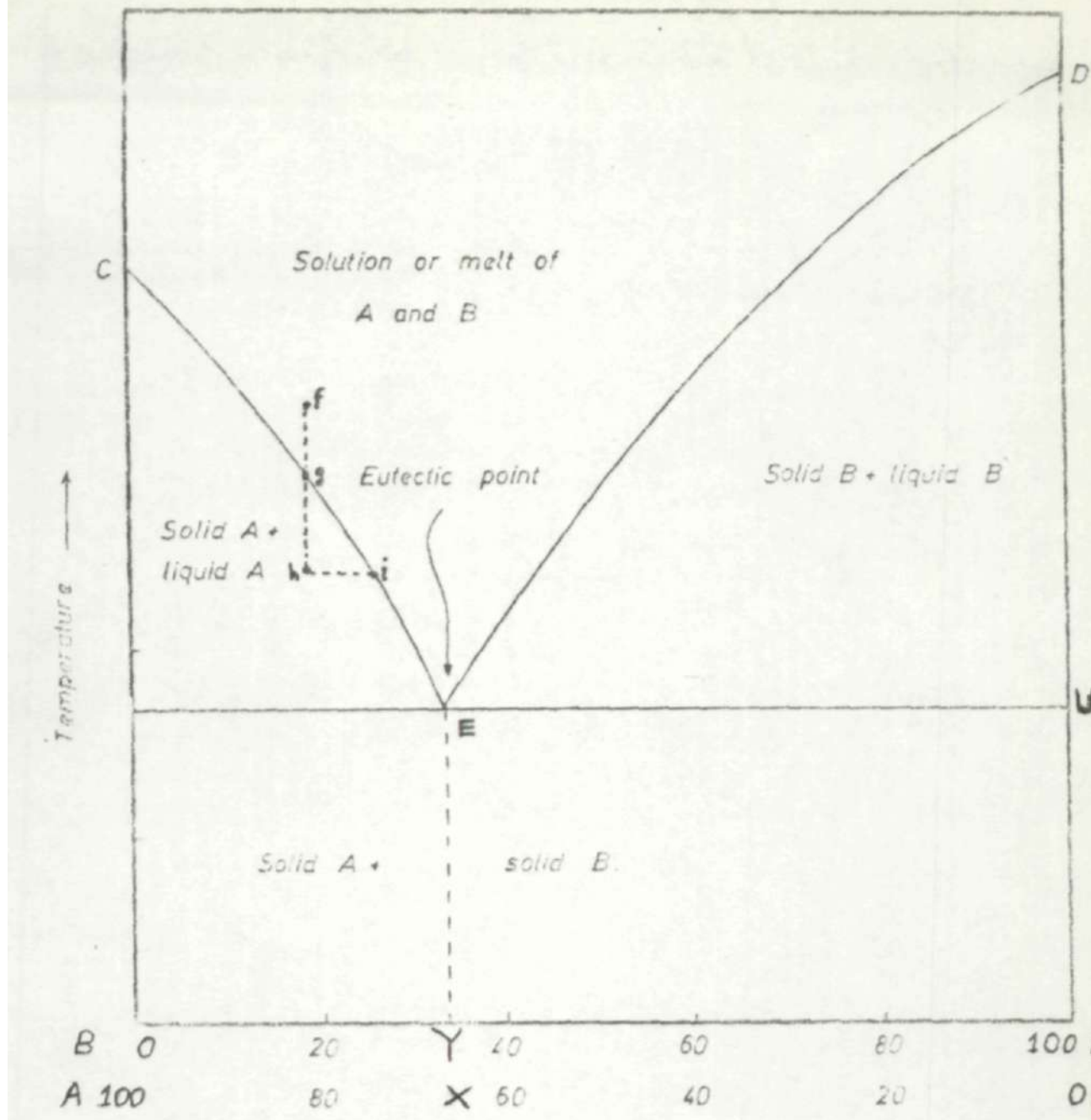


FIG 1.1 Simple phase diagram of a system showing eutectic formation between compounds A and B. Points C and D are the melting points of pure A and B respectively. Eutectic composition is x% A and Y% B.

simple eutectic mixtures as an intimately blended physical mixture of crystalline components of the drug and carrier.

When eutectic mixtures of a two component system, consisting of a poorly soluble drug and a readily water soluble carrier, is exposed to an aqueous medium, the drug material is released as very fine crystalline particles, thus increasing the effective surface area of the drug with a consequent increase in the dissolution rate and probably the gastrointestinal absorption of that drug (Sekiguchi and Obi, 1961). This has been one of the commonest explanations to observed increases in the dissolution rates and absorption of many drugs from solid dispersions with various carriers. Such increases could also be due to:

(i) (a) An increase in drug solubility when the majority of its crystallites are extremely small (Martin, et al., 1969).

(ii) Solubilization of the drug particles around its microenvironment by the rapidly dissolving carrier. This was demonstrated by Goldberg, et al., (1966 a) for the physical mixture of acetaminophen and urea.

(iii) Absence of aggregation or agglomeration of fine particles of the hydrophobic drug that may occur due to the presence of electrostatic charges developed during handling and processing operations, which result into formation of larger particles with reduced effective surface area.

(iv) Excellent wettability and dispersibility of the drug from a eutectic mixture or other solid dispersion systems of a drug and a water soluble carrier. The water soluble carrier sorrounding each drug particle dissolves rapidly allowing easy wetting of the particles by the medium.

(v) Crystallization of the drug material as a high energy polymorphic form which, most often, have higher solubilities and will therefore dissolve faster from solid dispersions. This is the rational explanation to the increased dissolution rate of hydroflumethiazide from its dispersion with PVP (Corrigan and Timoney, 1975).

While dissolution of simple eutectic mixtures result in microfine particles, it is worth appreciating that the crystal sizes of these particles depend largely on the relative proportion of the drug to the carrier.

Chiou and Riegelman, (1971 a) have expressed that dispersions having a low drug content have finer particles than those with higher drug content.

(b) Solid solutions.

From Figure 1.2, it may be noted that solid B dissolves in solid A to form a solid solution (α region) which contains X % of B at saturation. Similarly solid A dissolves in solid B to form a second solution (β region) containing Y % of A at saturation. At the eutectic composition, crystals of saturated solid solutions α and β precipitate by alternative crystallization in a fixed ratio (40 % α and 60 % β). No pure crystals of A or B crystallize in the system. In the regions labelled α and β, there exist solid solutions of continuously variable composition up to X % of B and Y % of A respectively.

Solid solutions are being defined by Findlay, (1951) as systems that consist of a solid solute dissolved in a solid solvent, with the solute and solvent crystals crystallizing together in a single homogeneous phase. That is to say that the drug and the carrier molecules take up

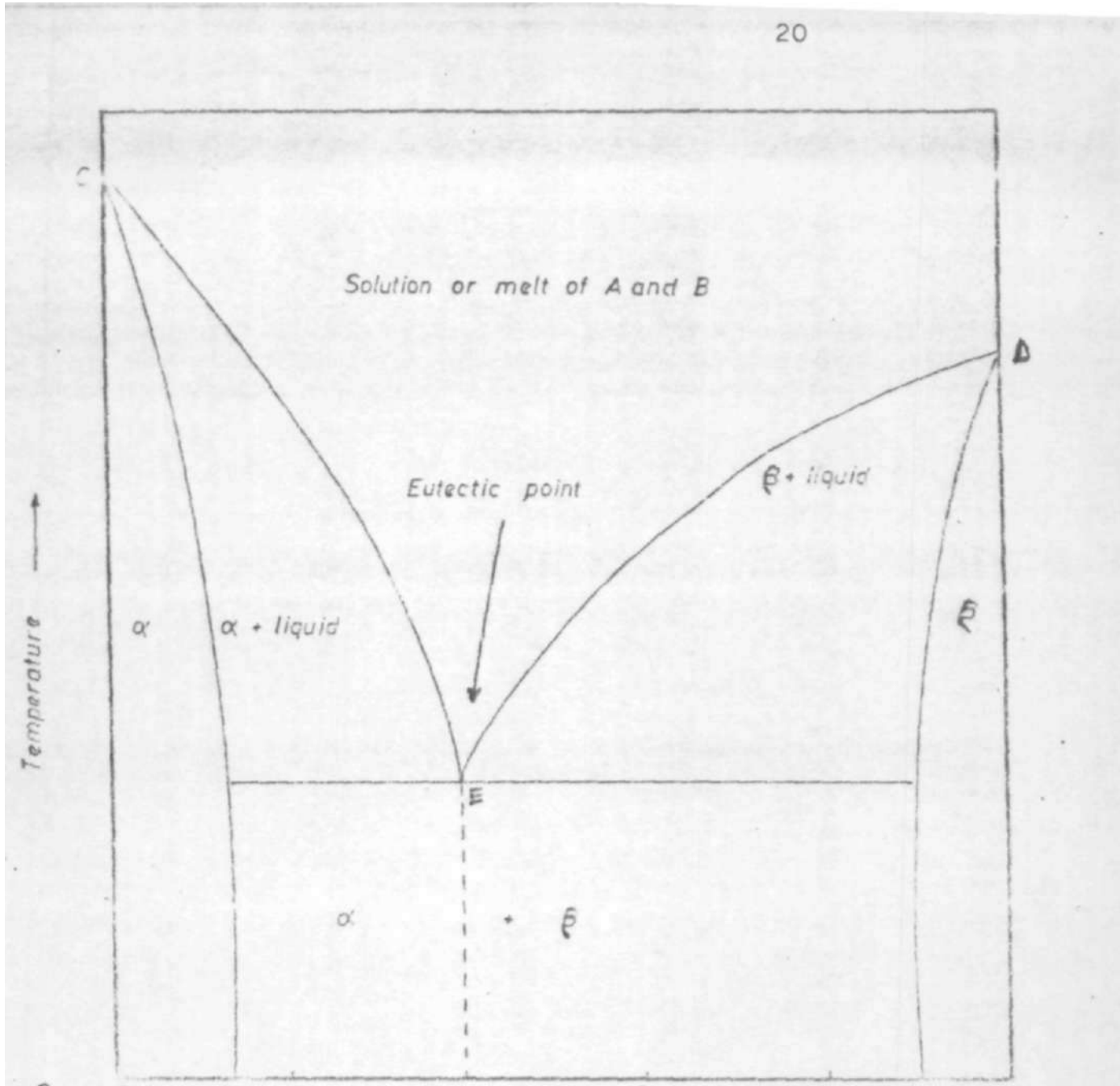


FIG. 1:2 Simple phase diagram of a system showing solid solution formation between compounds A and B. The eutectic mixture consist of the saturated solid solution of B in A (α) and saturated solution of A in B (β) at a fixed ratio. C and D are the melting points of pure A and B respectively.

positions in the same crystal lattice forming a single phase. This definition therefore conceives the drug in solid solutions, unlike the eutectics, to be distributed at molecular level throughout the carrier. This means that dissolution of the drug molecules takes place in the solid phase prior to exposure of the solid solution to the dissolution medium (Goldberg, et al., 1965 a). This and many other factors under simple eutectics (1.3.3. a) explain the drug release mechanisms and increased dissolution rates through solid solutions.

Chiou and Riegelman, (1971 a) have classified solid solutions into two main groups based either on the extent of miscibility of the drug and carrier or the crystalline nature of the solid solution.

Classification based on the degree of miscibility features:

(i) Continuous solid solutions, where two components (drug and carrier) are soluble in one another at the solid state in all proportions. It can be clearly understood that with such systems, increased dissolution rate of the drug will be expected only when the relative composition of the drug to the carrier is low.

(ii) Discontinuous solid solutions, where there is only a limited solubility of the solute in the solvent.

Classification based on the crystal nature of the solid solution features:-

(i) Substitutional solid solutions: (Illustrated in Figure 1.3)

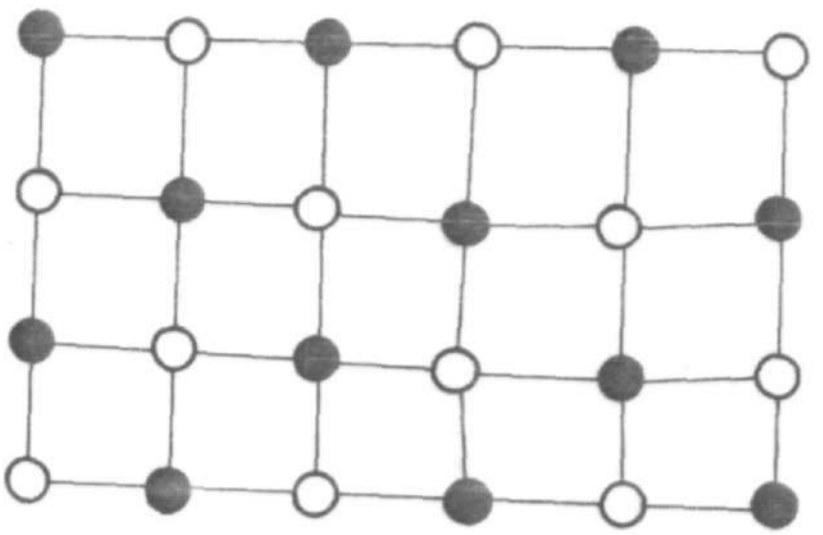
Here the molecules of the solute (drug) enters the space lattice of the solid carrier in a substitutional manner.

(ii) Interstitial solid solutions: (Illustrated in Figure 1.4)

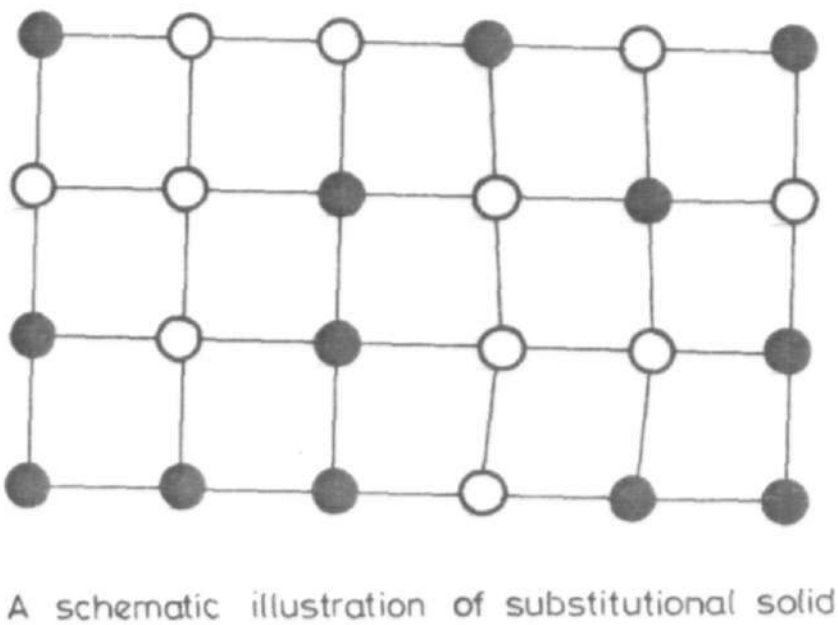
Here the molecules of the solute lie between the interstitial spaces of the crystal lattice of the solid solvent.

The limiting factor to the formation of either of these solid solution types is the relative molecular size of the drug and the carrier. For interstitial solid solutions of a drug in the carrier, the solute molecules must be small compared to the solvent molecules; while an almost equal molecular size of the two components is the condition for substitutional solid solutions to be formed.

a



b



FIG· 1:3 A schematic illustration of substitutional solid solution. ● - solid solute and ○ - solid solvent.

a = ordered substitution.

b = Random substitution.

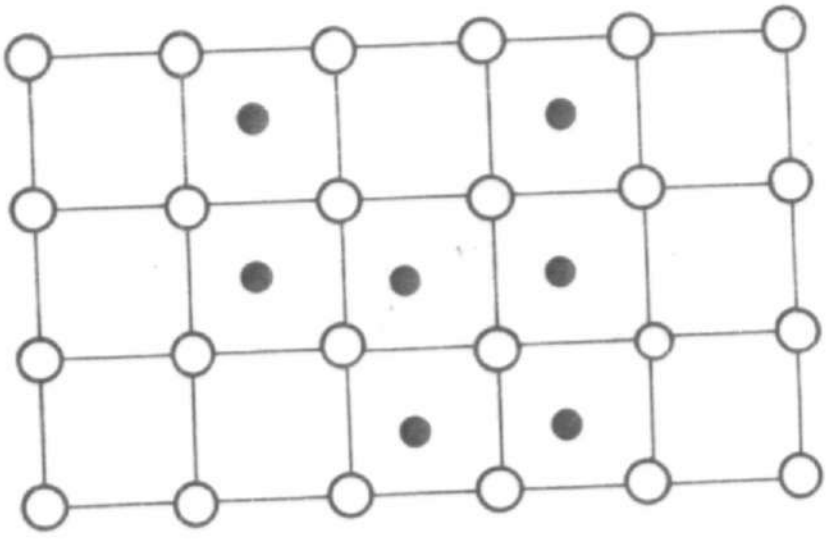


FIG. 1:4 A schematic illustration of an interstitial solid solution. ● - solid solute and ○ - solid solvent.

C. Glass solutions and glass suspensions

Chiou and Riegelman, (1971 a) in their review article defined glass solutions as a homogeneous glassy system in which a solute dissolves in a glassy solvent. Similarly a glass suspension is a system in which precipitated particles are suspended in a glassy solvent. A glass solution of a poorly soluble drug in a rapidly water soluble glass forming carrier, on exposure to water, releases the in-situ dissolved drug rapidly because the carrier dissolves quickly (Chiou and Riegelman, 1969). Glass solutions are advantageous over solid solutions in that, at drug concentrations in the carrier exceeding its solid solubility, the particle size of crystallized solute is much smaller than it would be in a solid solution. Additionally, because of the viscous nature of glass solutions, crystal growth is less likely to occur as compared to solid solutions. On this basis, glass solutions of a drug is expected to have a higher dissolution rate than its corresponding solid solution. Citric acid and urea have been found to exhibit glassy characteristics (Chiou and Riegelman, 1969; Ford and Rubinstein, 1977). However the formation of a glass solution is a function of the cooling rate of the melt. Quenching (sudden cooling) is best for achieving supersaturation of glass solutions.

D. Amorphous precipitation in a crystalline carrier

Here instead of the drug and carrier crystallizing simultaneously from a melting or a solvent method of preparation and forming a eutectic mixture, it may precipitate out as an amorphous form in the crystalline carrier. Since the amorphous form of a drug is the highest energy form, it should have better dissolution rates than the crystals, whether or not, the crystals are dispersed in the carrier. Such a dispersion of an amorphous sulfathiazole in a crystalline urea was thought to be the primary contributory factor in increasing it's oral absorption in man (Sekiguchi and Obi, 1961). Chiou and Riegelman, (1971 a) postulated that a drug of high supercooling property has more tendency of solidifying as amorphous form in the presence of a carrier. Similar observations were made for hydroflumethiazide-PVP systems (Corrigan and Timoney, 1975).

E. Complex or compound formation between drug and carrier

At high concentrations of a drug dispersed in a carrier, possibilities are that the two remain as individual components or as a drug-carrier complex with the drug existing either in the

crystalline or amorphous form. Such a drug-carrier complex may show increased dissolution rates of the drug.

1.3.4 AGING EFFECTS OF SOLID DISPERSIONS

Precipitation of the solute along with changes in the physico-chemical characteristics is the most important aging effect associated with glass solutions and solid solutions. Precipitation may occur on storage of solid dispersions if the concentration of the solute exceeds it's equilibrium solubility in the solvent.

With eutectic mixtures, aging properties are manifested as coarsening of the dispersed drug molecules thus reducing their effective surface area.

Other aging effects frequently observed are the hardening of the dispersions. All these have been found to be variously dependant on the storage time, temperature, humidity and the relative composition of drug to carrier in the dispersion (Allen and Kwan, 1969; Chiou and Niazi, 1971; Ford and Rubinstein, 1977; 1980).

For purposes of completeness in evaluating the practical utility of solid dispersion technique to improve pharmaceutical drug products, it is necessary to investigate the aging effects on the dissolution

characteristics of solid dispersions. This is because increased particle size and the rate of precipitation have a critical influence on the dissolution characteristics of dispersed systems.

1.4 LITERATURE REVIEW

Following the findings of Sekiguchi and Obi, (1961) many researchers have investigated the effectiveness and the potentials of solid dispersion technique as a means of promoting the dissolution rate, absorption and bioavailability of poorly water soluble drugs. Many results obtained showed this technique to be of potential use in the development of better drug products that can yield a more clinically significant drug level in the blood.

Goldberg, et al., (1966 a, b, c) examined the increased dissolution rate and produced phase diagrams for paracetamol-urea, griseofulvin-succinic acid and chloramphenicol-urea solid dispersions. They attributed the increased dissolution rate to the formation of solid solutions.

Subsequently Chiou, (1971) and Chiou and Niazi, (1973) found little evidence for the formation of solid solutions in the griseofulvin and chloramphenicol

systems. These authors believed that the increased dissolution was probably a surface area phenomenon.

In another development Chiou and Riegelman, (1969) prepared solid dispersions of griseofulvin in polyethylene glycol of various molecular weight grades and of pentaerythritol in citric acid by the melt or solvent method. They observed that due to the viscous and supercooling effects of polyethylene glycol, nucleation and crystal growth of griseofulvin in the solid dispersion was retarded leading to increased dissolution rate of the drug. Similarly increased dissolution of griseofulvin in citric acid was attributed to the formation of glass solutions of the drug in the glassy citric acid.

Summers and Enever, (1976) made similar observations when they investigated the properties of solid dispersions of primidone and citric acid. Glass solution of primidone in citric acid was formed. This was thought to be responsible for the increased dissolution rate observed.

Kaur, et al., (1980 a) elucidated the nature of interaction of griseofulvin and tolbutamide in solid dispersion with polyethylene glycol and polyoxyethylene glycol as carriers. No solid-solid interaction was

detected for griseofulvin-polyethylene glycol systems, suggesting that the increased dissolution rate reported by Chiou and Riegelman, (1969) may be due to surface properties. Kaur, et al., (1980 b) later showed that polyoxyethylene stearate was superior to polyethylene glycol in increasing the dissolution rate of poorly soluble griseofulvin and tolbutamide. This superiority was attributed to the micellar solubilization of the drugs in polyoxyethylene stearate.

Similarly El-Banna and Abdallah, (1980) attributed the superiority of polaxamer 188 in increasing the dissolution rate of phenylbutazone over polyethylene glycol to the surface activity of the former. Physico-chemical studies revealed solid solution formation with both carriers which explains the general increases in dissolution rates with both carriers.

Hoelgaard and Moller, (1975) compared the in-vitro dissolution rates of dispersions of various poorly soluble drugs with either polyethylene glycol or PVP to their optimally wetted suspensions. All the solid dispersions, except that of indomethacin, had a dissolution rate higher or just the same as the suspension.

Following a report by Tachibana and Nakamura, (1965) of a novel method of preparing aqueous dispersions of β-caroten by using water soluble PVP, it has been employed as a carrier for solid dispersions with many poorly soluble drugs. Stupak and Bates, (1972) reported increased dissolution rate and absorption of reserpine by coprecipitating it with PVP.

Simonelli, et al., (1969) investigated the effect of PVP of various molecular weights on the dissolution rate of sulfathiazole. Coprecipitation of sulfathiazole with PVP was found to markedly increase its dissolution rate. Lower molecular weight PVP were superior to those of higher molecular weights. These authors were able to describe a model that explains the mechanism of dissolution of sulfathiazole from the solid dispersions prepared. They proposed a PVP controlled external layer at high PVP weight fractions and a sulfathiazole controlled external layer at low PVP weight fractions. These workers, (1976) later concluded that the presence of an amorphous form of sulfathiazole in the solid dispersion was responsible for the increase in dissolution rate. The same observations were reported for nifedipine (Sugimoto, et al., 1980; 1981).

In addition to increasing the *in-vitro* dissolution rates of poorly soluble drugs, solid dispersions have been found to increase also the oral absorption of these drugs, either from powders, compressed tablets or capsule dosage form of these dispersions. This fact is attested by the increased toxicity of digitoxin from digitoxin-polaxamer 188 solid dispersions administered to mice orally (Reddy, *et al.*, 1976). Polaxamer, which is a high molecular weight polymer, is expected to form interstitial solid solutions with the small molecular weight, organic drug, digitoxin. The surface tension lowering ability of polaxamer was also of advantage.

Chiou and Riegelman, (1971b) observed complete oral absorption of griseofulvin from compressed tablets of griseofulvin-polyethylene glycol solid dispersion. However, absorption from the commercially available griseofulvin tablets was incomplete, irregular and prolonged.

Stoll, *et al.*, (1969) attributed the increased oral absorption of reserpine to an increased dissolution of the drug when coprecipitated with cholanic acid. This fast dissolving solid dispersion allows for a faster absorption of reserpine.

Some work has been carried out in an attempt to improve the dissolution characteristics and absorption of some benzothiadiazine derivatives through the solid dispersion approach. Hoelgaard and Moller, (1975) compared the dissolution profile of mechanically wetted and sonified hydrochlorothiazide suspension to it's solid dispersion in polyethylene glycol 6,000 and PVP 11,500. The dispersion in polyethylen glycol was superior to all the others, while the mechanically wetted and sonified suspension had identical dissolution profiles because the crystals, in both cases, had a small surface area. The superiority of polyethylene glycol is due to the formation of a reasonable amount of solid solutions.

Corrigan and Timoney, (1975) evaluated the dissolution characteristics of hydroflumethiazide when coprecipitated with PVP. The x-ray and infrared analysis revealed the presence of an amorphous form of hydroflumethiazide in the coprecipitated systems. Consequently the dissolution rate of hydrolfumethiazide from the compressed tablets was increased. The ability of PVP to retard crystal growth of hydroflumethiazide could be of an added advantage. Corrigan, et al., (1976) extended their studies to coprecipitates of PVP and hydrochlorothiazide. They compared the influence of PVP 10,000 and 44,000 on the dissolution rate

characteristics of the drug. Dissolution rate tests were performed using capsule formulations of the coprecipitates. The lower molecular weight PVP was found to be more effective in enhancing the in-vitro dissolution rate of hydrochlorothiazide. However, the results revealed that PVP retarded the initial dissolution rate of hydrochlorothiazide from the capsule dosage form, probably due to retardation in deaggregation and dispersion of the drug. Bioavailability studies by urine analysis showed that coprecipitation with PVP generally increased the bioavailability of hydrochlorothiazide.

El-Banna, et al., (1980) contributed by studying the phase diagram and dissolution rate characteristics of hydrochlorothiazide in solid dispersion with urea, where they detected the presence of solid solutions containing hydrochlorothiazide in the compositions of 10 % and 90 %. There was also an evidence of eutectic formation containing about 20 % and 37 % of hydrochlorothiazide in urea. Molecular complexes of urea and hydrochlorothiazide were also detected at hydrochlorothiazide-urea molar ratios of 1:5 and 1:10. Dissolution rate tests were carried out on solid dispersions containing various weight fractions of hydrochlorothiazide and urea. These authors were able to elucidate the mechanism that accounted for the

enhanced dissolution of hydrochlorothiazide from the solid dispersion. The extent of enhancement when compared to the physical mixture does not support a mechanism based on local solubilization effects of urea alone.

In another development, Deshpande and Agrawal, (1982 a) investigated the influence of polyethylene glycol on the dissolution rate of benzothiadiazine derivatives. There was a general increase in the rates of dissolution from dispersed systems when compared to the pure drugs alone. These authors, (1982 b) further investigated the influence of various carriers on the dissolution rate of hydrochlorothiazide. Urea was found to be superior to dextrose, polyethylene glycol 6,000, sorbitol and tartaric acid.

It is worth appreciating that the practical applicability of solid dispersion technique in improving drug products would not be complete if the effect of aging on the drug release pattern from these fast release systems are not elucidated. Generally, aging of solid dispersions have been shown to decrease the dissolution rates of dispersed systems.

In a review article Chiou and Riegelman, (1971 a) attributed the decrease to increased precipitation and particle size of the dispersed drug with age. These

phenomena are variously dependent on the storage time, temperature, humidity of the storage environment and the relative composition of the drug to the carrier in the system.

Chiou and Niazi, (1971) reported a decrease in dissolution rate of sulfathiazole from solid dispersions with urea after storage for one hour at 105°C. This was attributed to increased crystallinity of the sulfathiazole. Similar reports of decreased dissolution rate with age have been reported for indomethacin-polyethylene glycol solid dispersion systems (Allen and Kwan, 1969).

Ford and Rubinstein, (1980) evaluated the aging effects of storage time, temperature and relative humidity on the dissolution rate and hardness parameters of tablets prepared from indomethacin-polyethylene glycol 6,000 solid dispersions. Tablets obtained by in-situ granulation method, using the melt of the polyethylene glycol, showed decreased dissolution rates after storage at 25°C and 35°C, while the traditionally wet granulated tablets showed no decrease in dissolution rates, when stored under the same temperature conditions. The presence of humidity was however found to decrease the hardness and dissolution rates of tablets prepared by both methods.

A previous report by these authors, (1977) however showed that an increased dissolution rate of chlorpropamide was observed for aged solid dispersion systems of chlorpropamide with urea. These reports prove aging effects to be of considerable importance in evaluating the usefulness of the solid dispersion technique in drug products quality improvement.

It is evident from this review that the solid dispersion technique is of immense importance in the development of better pharmaceutical and drug products. The various mechanisms by which solid dispersion technique improves the dissolution profile of drugs can be clearly understood. Solid solution and eutectic formation and sometimes surface activity of the carrier are some contributory factors in increasing the dissolution characteristics of poorly soluble drugs dispersed in readily water soluble carrier.

Increased dissolution rates and absorption of drugs go a long way in reducing clinical failures in drug therapy; which most often are attributed to the non-availability of the drug at the site of action. It could also be a way of formulating a sustained release dosage form by selection of poorly soluble

carriers. Ghanem, et al., (1980 a) observed sustained release characteristics with tetracycline-acrylic resin dispersion systems.

Chiou and Smith, (1971) also conceived this technique as an approach to formulating organic liquid drugs with improved biopharmaceutical qualities.

A review of previous work reported on the dispersion of hydrochlorothiazide reveals that no dissolution rate studies have been carried out on compressed tablets of hydrochlorothiazide dispersed in either urea or PVP. Aging effects on the dissolution characteristics of tablets from these dispersions have not been reported either.

1.5 RESEARCH PROBLEM AND OBJECTIVES

The drug to be investigated in this work is hydrochlorothiazide. It is a diuretic belonging to the benzothiadiazide group. Diuretics are chemical agents or substances which are capable of increasing urine formation by the kidneys and hasten the elimination of fluid from the body.

The clinical utility of hydrochlorothiazide rests on the fact that it is potent and well tolerated when administered orally. It has been employed in the treatment of oedema, especially when associated with congestive heart failure. It is also useful in treating nephrotic syndromes irrespective of cause and in the management of mild to severe hypertension, when used in conjunction with other agents (Martindale, 1978).

Although the toxicity associated with the use of hydrochlorothiazide is low, numerous untoward effects are often experienced. Some of these include gastrointestinal tract disturbances such as nausea, vomiting and diarrhoe, hyperglycaemia and loss of potassium from the body due to prolonged use.

Hydrochlorothiazide is practically insoluble in water (Martindale, 1978) and aqueous fluids of the gastrointestinal tract and have therefore posed many bioavailability problems.

Many clinical failures in drug therapy have often been attributed to the non-availability of the drug at the site of action or in the systemic circulation. This makes it necessary for the dissolution profile of poorly soluble drugs to be established.

This project is aimed at utilizing the solid dispersion technique to improve the aqueous solubility of hydrochlorothiazide thereby increasing the dissolution rate and bioavailability of the drug. This will consequently allow for attainment of more clinically significant blood levels of the drug. Additionally, this could evolve a technology for formulating products of reduced dosages at the same time maintaining the therapeutic potency of the drug.

This study involves

(a) Preparation of coprecipitates of the hydrophobic drug hydrochlorothiazide with the readily water soluble carriers urea, PVP 10,000 and 44,000.

(b) Performing dissolution rate tests on the freshly prepared coprecipitate and also on the pure drug.

(c) Formulation of tablets from the various coprecipitates and from the pure hydrochlorothiazide powder. Determination of the potential qualities of these tablets by evaluating their properties as regards to hardness, friability, disintegration time, uniformity of active ingredient, weight variation and uniformity of diameter.

Dissolution rate tests shall then be performed on these tablets and compared. Direct compression will be used in order to prevent prior solubilization of hydrochlorothiazide due to the use of aqueous granulation fluids which may otherwise interfare with the dissolution rate tests.

(d) Aging studies shall be carried out by evaluating the effects of humidity and storage time on the disintegration and dissolution rates of these tablets.

CHAPTER TWO

2 PRELIMINARY INVESTIGATIONS

2.1 DRUGS AND CARRIERS USED AND THE CRITERIA FOR THEIR SELECTION

2.1.1 CRITERIA FOR DRUG AND CARRIER SELECTION

A carrier could be described as an inert water soluble substance (dispersion medium) supposedly made up of high molecular weight polymers in which the active ingredient is dispersed. A good carrier for effective solid dispersion technique are expected to meet the following criteria (Goldberg, et al., 1966a)

(a) Readily soluble in water
(b) Physiologically inert
(c) A melting point of not more than 200°C
(d) Thermal stability up to its melting point
(e) A relatively low vapour pressure

Factors c, d and e are significant only when the melt (fusion) method of preparing the dispersion is employed. For the solvent method, it is essential that the carrier be readily and completely soluble in the solvent used and that it is not denatured or decomposed by the solvent.

Other specific requirements for carriers which could influence the type of dispersion formed include:

(a) Molecular size

The essential criterion for the formation of an interstitial solid solution is that the molecular size of the carrier be much higher than that of the solute (drug). High molecular weight polymers, such as the polyethyelene glycols having a molecular weight ranging from 1,500 to 20,000 are therefore expected to form fast release solid solution systems with organic drug molecules usually of small molecular weights below 400 or 500.

(b) Supercooling and viscous effects.

The carrier should conform to favourable behaviour as regards fast cooling and viscous effects. Fast cooling could result in the formation of metastable solid dispersions which often show increased dissolution rates (Chiou and Riegelman, 1971 a). In addition, prevention of nucleation of crystalline form and crystal growth of sulfathiazole in solid dispersion with PVP have been reported

(Simmonelli, et al., 1970; 1976). These properties are highly desirable with various drug/carrier systems. In view of the above, PVP has been selected as a carrier for these investigations. Further more, urea which is also employed in this study, has an added adavantage of having mild diuretic effect. This property could potentiate the effectiveness of hydrochlorothiazide as a diuretic when coprecipitated with urea.

While the carriers should comply to the criteria discussed above, the drug should also meet certain requirements, some of which include (Goldberg, et al., 1966 a)

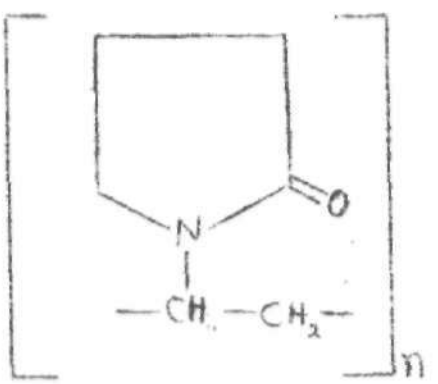
(a) Poor water solubility
(b) Therapeutically significant
(c) Thermal stability up to its melting point
(d) Relatively low vapour pressure
(e) Melting point of not more than 250°C

Similarly, factors c, d and e are more significant when the fusion method is employed. With the solvent method, the drug must be stable in the presence of the solvent employed. The use of hydrochlorothiazide in this study is justified by its poor water solubility, therapeutic significance

The main uses of hydrochlorothiazide is in the treatment of oedema of various origins and as an adjunct to reduced doses of hypotensive agents in the management of mild to severe hypertension (Martindale, 1978).

(b) Carriers

i) Polyvinylpyrrolidone, with the molecular formula $(C_6H_9NO)_n$, molecular weight of 111.1 x n and structural formula shown below, was supplied by the kind courtesy of Messrs, BDH Chemicals Ltd., Poole England.

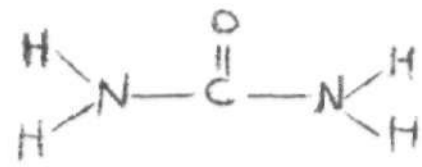


Polyvinylpyrrolidone is a polymerized form of vinylpyrrolidone. It is a white, slightly hygroscopic powder which readily dissolves in water giving a somewhat viscous, clear, colourless to a slightly yellow solution. It is also soluble in ethanol, chloroform, methanol, ethoxymethanol and isopropyl alcohol. It is insoluble in benzene and acetone.

Polyvinylpyrrolidone is used principally in pharmacy as a suspending agent, tablet binder, granulating agent and in the formulation of effervescent tablets (Martindale, 1978).

It has been employed as a carrier in solid dispersion with various poorly water soluble or even insoluble therapeutic substance (Mayersohn and Gibaldi, 1966 ; Bates, 1969; Simonelli, et al., 1969; Corrigan, et al., 1975; Hoelgaard and Moller, 1975; Simonelli, et al., 1976; Ghanem et al., 1980 b). Polyvinylpyrrolidone of molecular weights of 10,000 and 44,000 have been employed in this work.

ii) Urea, with the molecular formula $CO(NH_2)_2$, molecular weight of 60.06 and structural formula shownbelow, was supplied by the kind courtesy of Messrs BDH Chemicals Ltd., Poole, England.



Urea is a colourless, slightly hygroscopic, prismatic or a white crystalline powder having a cooling saline taste. It readily dissolves in water, giving a neutral solution. It is also soluble in alcohol, but insoluble in chloroform and ether. Urea has a melting point between 132°C and 134°C.

Urea has been used therapeutically as a diuretic when given orally. It has also been used in treating increased intracranial pressure due to cerebral oedema and to maintain output of urine after surgery, burns and trauma (Martindale, 1978; British Pharmacopoeia, 1980).

Urea has been employed as a carrier in solid dispersion with many water insoluble drugs (Sekiguchi and Obi, 1961; Goldberg, et al., 1966 c; Allen and Kwan, 1969; Chiou and Riegelman, 1971 b; Ford and Rubinstein, 1977; El-Banna, et al., 1978; 1980; Deshpande and Agrawal, 1982 b).

2.2 DETERMINATION OF THE WAVELENGTH OF MAXIMUM ABSORPTION (λ max) FOR HYDROCHLOROTHIAZIDE

2.2.1 METHOD

A 1 mg/ml solution of hydrochlorothiazide was prepared by dissolving 50 mg of accurately weighed drug in 50 ml of absolute methanol. 5 ml of this solution

was then diluted with distilled water to obtain a 100 μg/ml solution of hydrochlorothiazide in 10 % methanol solution. This was further diluted quantitatively with 10 % methanol solution to obtain a 20 μg/ml solution which was used for the analysis.

The absorbance of this solution was measured between 200 nm and 300 nm wavelengths by means of a spectrophotometer (Pye Unicam SP6-550, Cambridge, England) and Pye-Unicam silica cells. 10 % solution of methanol in distilled water was used as blank. The wavelength was then plotted against the absorbance values to determine the wavelength of maximum absorption.

2.2.2 RESULTS AND DISCUSSION

Tables 2:1 a and b show the absorbance values for the determination of the wavelength of maximum absorption. From these values and Fig. 2.1, two peaks were identified at 225 nm and 273 nm for which beer's law was obeyed to a miximum concentration of 5 and 10 μg/ml respectively. On this basis, 273 nm was selected as the wavelength of maximum absorption. All further analytical investigations were carried out at this wavelength.

Table 2:1

Determination of Wavelength of maximum absorption of hydrochlorothiazide in 10 % methanol solution in distilled water

A		B	
Wavelength (nm)	Absorbance	Wavelength (nm)	Absorbance
200	0.421	265	0.830
205	0.561	266	0.880
210	0.790	267	0.910
215	1.061	268	0.930
220	1.232	269	0.955
225	1.306	270	0.976
230	1.074	271	0.988
235	0.474	272	0.990
240	0.190	273	0.990
245	0.133	274	0.975
250	0.204	275	0.954
255	0.357		
260	0.587		
265	0.830		
270	0.976		
275	0.954		
280	0.730		
285	0.443		
2290	0.245		
295	0.165		
300	0.148		

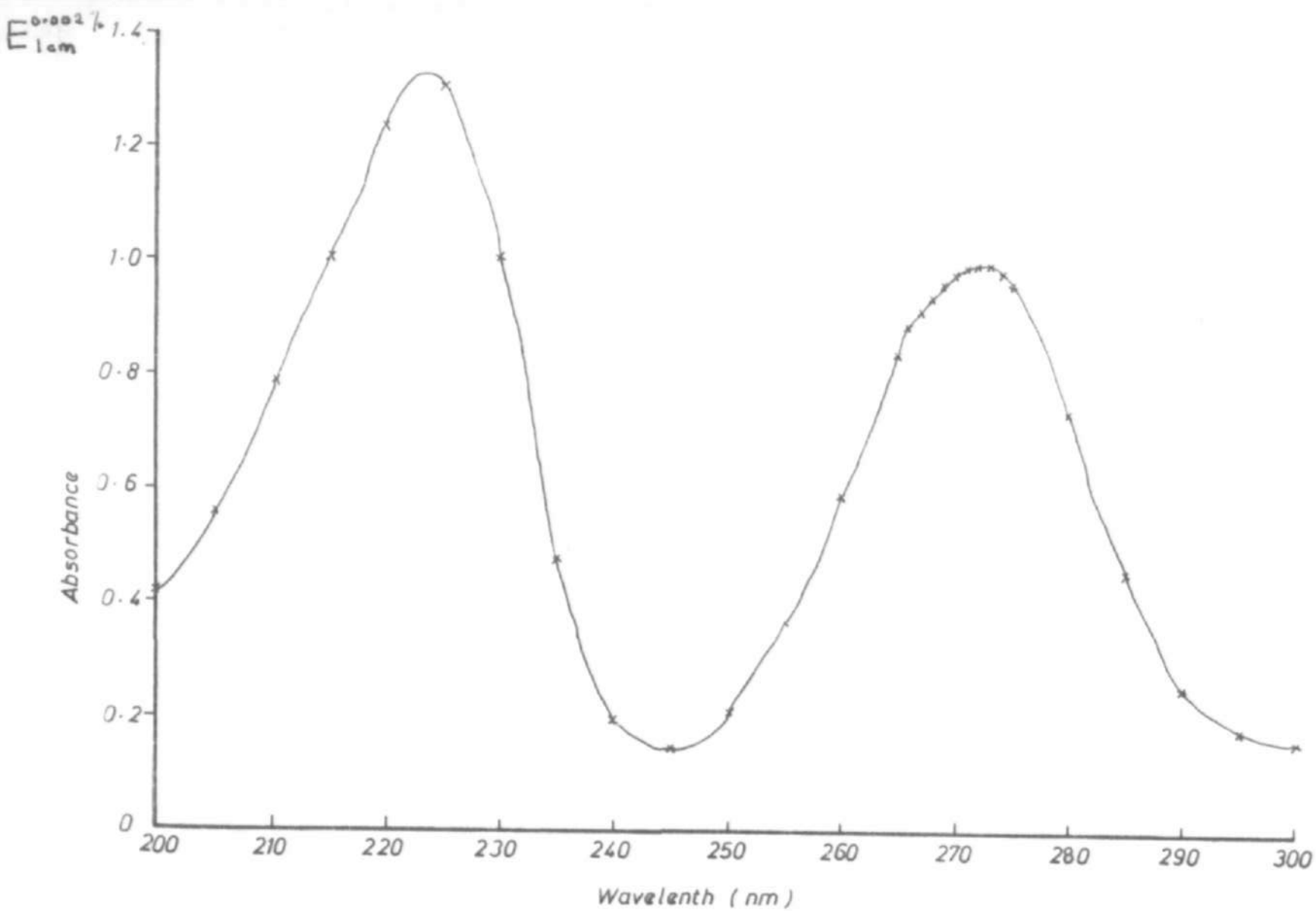


FIG 2.1 Determination of wavelength of maximum absorption for hydrochlorothiazide in 10% methanol solution in distilled water.

2.3 PLOTTING OF THE STANDARD CURVE

2.3.1 METHOD

From a stock solution containing 100 µg/ml of hydrochlorothiazide in 10 % methanol solution in water, solutions of concentrations ranging from 0.1 µg/ml to 60 µg/ml were prepared by quantitative dilution with already prepared 10 % methanol solution in distilled water.

The absorbance of these solutions were measured at 273 nm using 10 % methanol solution as blank and the values plotted against the corresponding concentrations to obtain a standard curve.

The coefficient of absorbance (K) for hydrochlorothiazide in 10 % methanol was also calculated.

$$\text{Coefficient of absorbance (K)} = \frac{\text{Absorbance}}{\text{Concentration}} = \text{slope of the curve}$$

2.3.2 RESULTS AND DISCUSSION

Table 2:2 and Figure 2.2 show the results for plotting the standard curve.

Beer's law was obeyed over a concentration range of 0.4 µg/ml to 10 µg/ml of hydrochlorothiazide in solution with corresponding absorbance values of

0.023 and 0.547 respectively. These points represent the lower and the upper limits of sensitivity of the spectrophotometer used. It is implicit therefore, that only absorbance values between these two limits would be reliable. The coefficient of absorbance calculated from Fig. 2.2 was 0.055.

Table 2:2

Plotting the standard curve

Concentration of hydrochlorothiazide (µg/ml) in 10 % methanol	Absorbance* at 273 nm.
100	1.502
60	1.452
50	1.426
25	1.137
20	0.989
19	0.948
18	0.910
17	0.876
16	0.820
15	0.777
10	0.547
5	0.276
4	0.220
3	0.167
2	0.112
1	0.050
0.5	0.030
0.4	0.023
0.3	0.012
0.2	0.008
0.1	0.002
0.0	0.000

*Each absorbance value is an average of two separate determinations.

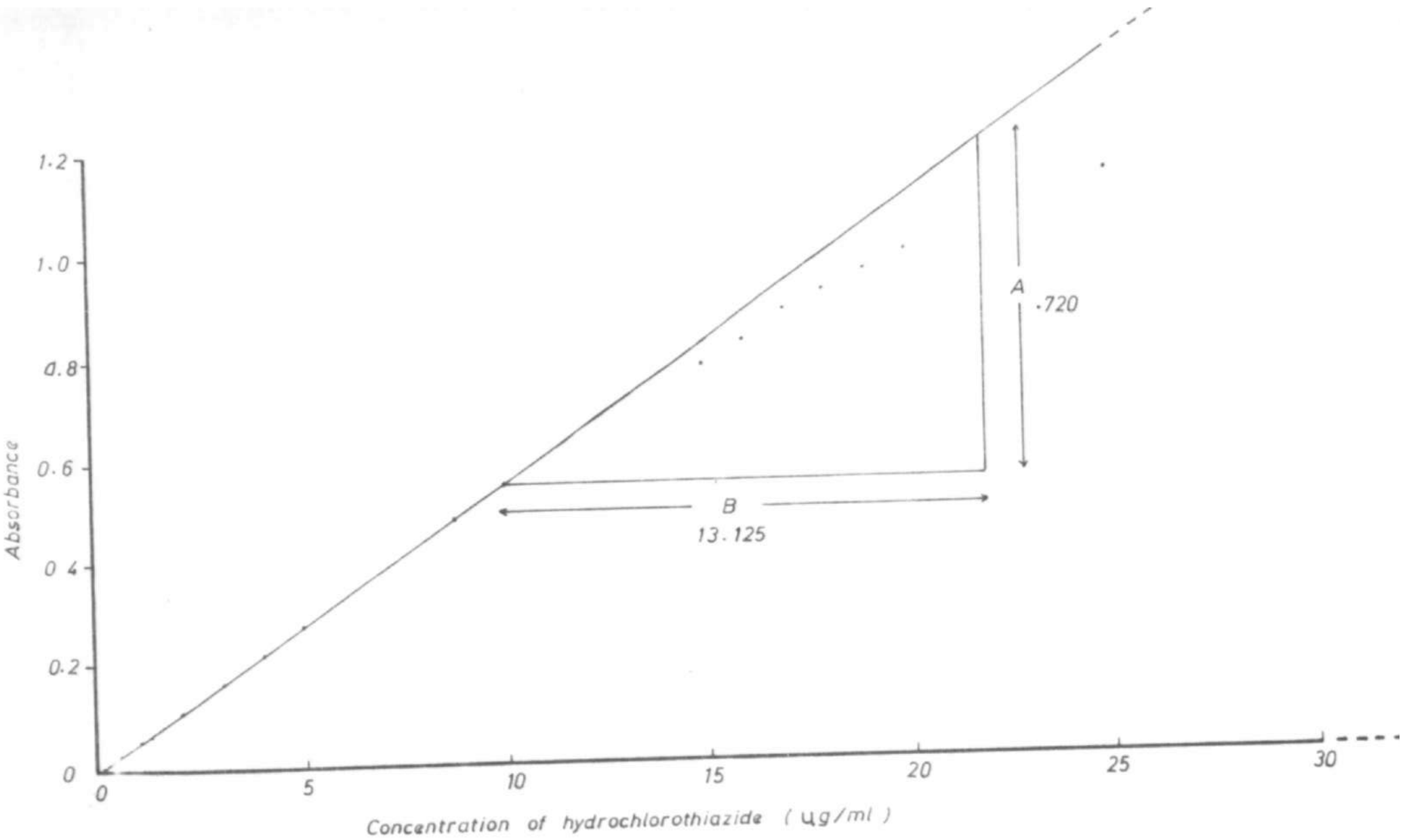


FIG. 2.2 Standard Beer's plot for hydrochlorothiazide in 10% methanol solution in distilled water.

2.4 DETERMINATION OF THE SOLUBILITY OF HYDROCHLOROTHIAZIDE IN WATER AT 37°C

2.4.1 METHOD

500 mg of hydrochlorothiazide powder was added to 100 ml of distilled water contained in a 250 ml volumetric flask and stoppered. The flasks and the contents were then shaken to equilibrium in a water bath shaker (Gallenkamp, England) maintained at 37°C for 36 hours.

5 ml aliquots were withdrawn, filtered through a millipore filter paper (pore diameter 0.45 μ) and quantitatively diluted with distilled water. The solution obtained was then assayed spectrophotometrically, using distilled water as the blank, to determine the hydrochlorothiazide content. This procedure was repeated twice.

2.4.2 RESULTS AND DISCUSSION

The solubility of hydrochlorothiazide in distilled water at 37°C was found to be 1.118 mg/ml.

2.5. AQUEOUS SOLUBILITY OF HYDROCHLOROTHIAZIDE AS A FUNCTION OF CARRIER CONCENTRATION

This experiment is designed to determine any possible interaction between hydrochlorothiazide and the carrier in aqueous solutions. It involves the

determination of the solubility of hydrochlorothiazide in solutions of the carriers of different concentrations in distilled water.

2.5.1 METHOD

500 mg of hydrochlorothiazide powder was added to 100 ml of the carrier solutions in distilled water. The carrier concentrations ranged from 0.1 % to 3 %, contained in 250 ml volumetric flasks. The rest of the procedure was the same as described earlier.

A preliminary investigation showed that the carriers employed do not absorb at 273 nm wavelength. However because of the high concentrations of the carriers used (up to 3 %), the blank employed here were solutions of the carriers of concentrations equivalent to that in the test sample and quantitatively diluted to the same extent. This was repeated twice for each carrier.

2.5.2 RESULTS AND DISCUSSION

Tables 2:3, 2:4 2:5 and Figure 2:3 show the results for the influence of carriers on the solubility of hydrochlorothiazide in distilled water. These results show that the aqueous solubility of hydrochlorothiazide is increased in the presence of all the carriers employed. Furthermore, the extent of

increase was found to be more with increasing concentration of the carrier in solution. However with PVP 10,000, an increase in the solubility of hydrochlorothiazide was observed only when PVP was in a concentration above 0.1 %. Because of the high water solubilities of these carriers, it may be possible that they brought about easier wetting of the rather hydrophobic hydrochlorothiazide thus increasing its solubility.

Table 2:3

Solubility of hydrochlorothiazide in solutions of PVP 10,000 of various concentrations in distilled water at 37°C

Concentration of PVP 10,000 in distilled water (% w/v)	Mean absorbance at 273 nm	Concentration of hydrochlorothiazide in solution (mg/ml)
0.1	0.219	0.995
0.2	0.220	1.000
0.3	0.225	1.023
0.5	0.244	1.109
1.0	0.263	1.195
2.0	0.306	1.418
3.0	0.340	1.582

*Dilution factor is 250

Table 2:4

Solubility of hydrochlorothiazide in solutions of PVP 44,000 of various concentrations in distilled water at 37°C

Concentration of PVP 44,000 in distilled water (% w/v)	Mean absorbance at 273 nm	Concentration * of hydrochlorothiazide in solution (mg/ml)
0.1	0.253	1.150
0.2	0.259	1.177
0.3	0.264	1.200
0.5	0.273	1.241
1.0	0.293	1.332
2.0	0.334	1.518
3.0	0.378	1.718

Table 2:5

Solubility of hydrochlorothiazide in solutions of urea of various concentrations in distilled water

Concentration of urea in distilled water (% w/v)	Mean absorbance at 273 nm	Concentration * of hydrochlorothiazide in solution (mg/ml)
0.1	0.282	1.282
0.2	0.284	1.291
0.3	0.289	1.314
0.5	0.292	1.327
1.0	0.305	1.386
2.0	0.332	1.509
3.0	0.358	1.627

*Dilution factor is 250

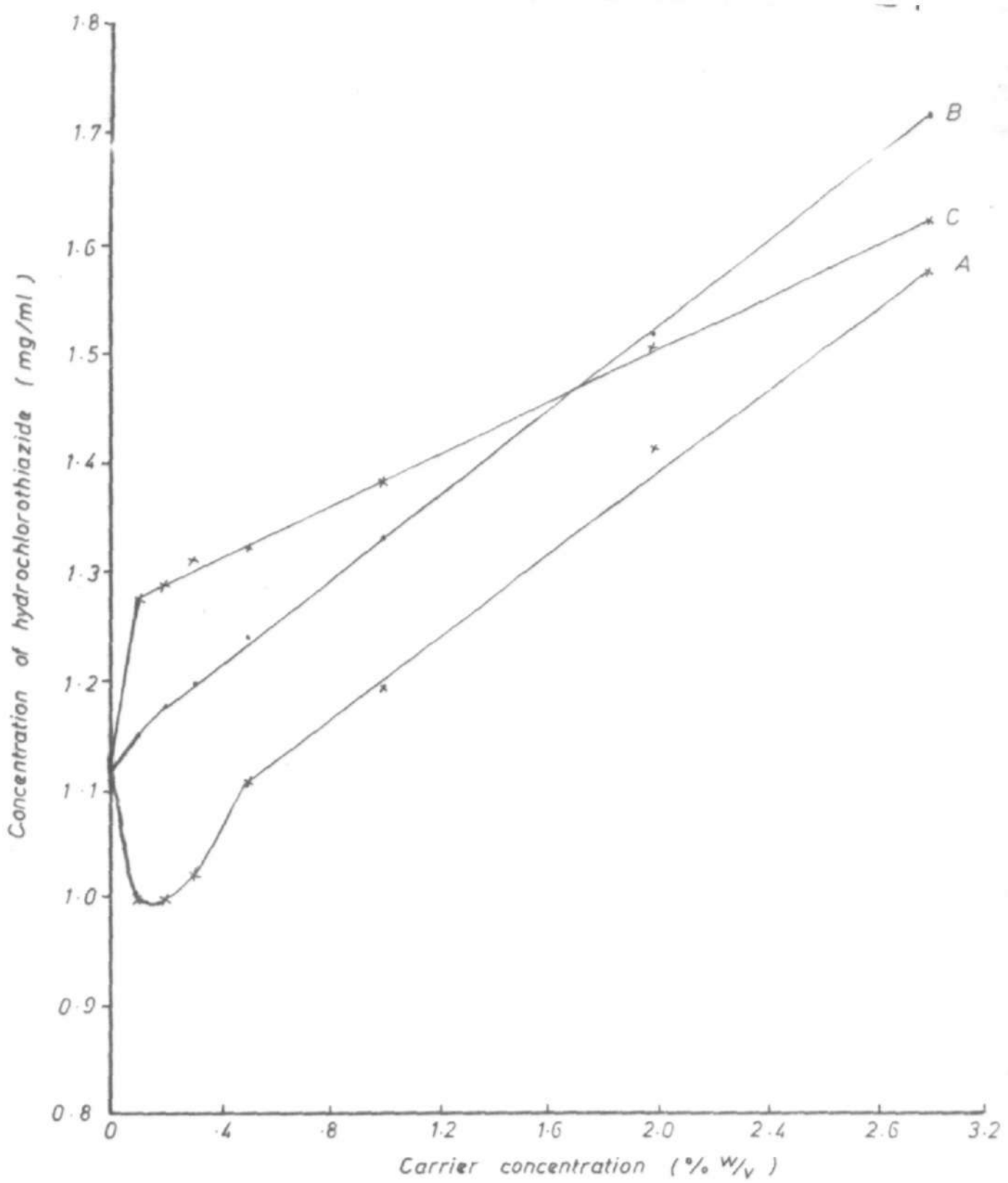


FIG. 2.3 Aqueous solubility of hydrochlorothiazide as a function of carrier concentration.

A - polyvinylpyrrolidone 10,000.

B - polyvinylpyrrolidone 44,000.

C - urea.

CHAPTER THREE

3. PREPARATION AND DISSOLUTION STUDIES OF THE COPRECIPITATES OF HYDROCHLOROTHIAZIDE WITH THE VARIOUS CARRIERS

3.1 METHOD OF SAMPLE PREPARATION

3.1.1 SOLVENT METHOD

The solvent method was used to prepare the solid dispersions (coprecipitates) of hydrochlorothiazide with all the carriers. Only the minimum amount of solvent (methanol) required to dissolve all the drug and carrier to form a homogeneous solution was used in each case.

The physical mixture of hydrochlorothiazide and the different carriers were dissolved in a minimum amount of methanol to form a true homogeneous solution. The methanol was then evaporated at room temperature under vacuum in a desiccator. The resultant solid mass was further dried in a desiccator under vacuum in the presence of phosphorus pentaoxide as a desiccant for two days. The dry solid mass was then pulverised using a glass pestle and mortar and sieved. Samples with particle size between 250 μ and 355 μ were collected and used for the *in-vitro* dissolution rate tests.

Dispersions containing 10, to 50 % w/w of hydrochlorothiazide in the various carriers were prepared.

3.1.2 PHYSICAL MIXTURE

These were prepared by mechanically mixing accurately weighed quantities of hydrochlorothiazide and the carriers in a glass pestle and mortar, for about ten minutes. The resultant homogeneously blended mixture was collected and stored for in-vitro dissolution rate studies. Physical mixtures containing hydrochlorothiazide in a concentration of 10, 20, 30, 40 and 50 % w/w in each carrier were prepared.

3.1.3 HYDROCHLOROTHIAZIDE POWDER

This was used as supplied by the manufacturer. The sample was not recrystallised from methanol or any organic solvent and particle size reduction was not necessary since the drug was already in a fine state of subdividion.

3.2 DETERMINATION OF THE STABILITY OF HYDROCHLOROTHIAZIDE IN THE COPRECIPITATES

It is essential, that the hydrochlorothiazide is physically and chemically stable to the presence of the solvent and during the preparative procedures.

This made it necessary for the stability of hydrochlorothiazide in the coprecipitates to be ascertained. Two methods, the ultraviolet spectrophotometric and the thin layer chromatographic techniques, were used.

3.2.1 ULTRA-VIOLET SPECTROPHOTOMETRY

3.2.1.1 METHOD

An accurately weighed quantity of the coprecipitate containing 10 mg of hydrochlorothiazide was dissolved in 100 ml of distilled water. 2 ml of this solution was quantitatively diluted with distilled water to 50 ml. The resultant solution was then assayed spectrophotometrically at 273 nm wavelength to determine hydrochlorothiazide content.

The hydrochlorothiazide content was compared to the theoretically calculated value. The extent of deviation of the experimental value from the theoretical value is a measure of instability of the drug in the dispersion. Preliminary investigation indicated that the carriers used in this study do not absorb ultra-violet radiation at 273 nm wavelength; therefore, interference of the assay by these carriers was precluded.

3.2.1.2 RESULTS AND DISCUSSION

Tables 3.1 to 3.3 show the results for the determination of the stability of hydrochlorothiazide in coprecipitates prepared with various carriers. The drug content for all the samples with the three carriers ranged from 98.2 % to 101.8 % of the theoretical value which is 10 mg.

These results indicate (within the limits of experimental error) that the hydrochlorothiazide was stable throughout the preparative procedure and that it was not decomposed or degraded by the solvent used in preparing the coprecipitates.

Table 3:1 Stability of hydrochlorothiazide in it's coprecipitate with PVP 10,000

% hydrochlorothiazide content in the coprecipitate	Mean absorbance at 273 nm*	Equivalent hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% of theoretical content
10	0.218	9.91	10.00	99.1
20	0.219	9.95	10.00	99.5
30	0.220	10.00	10.00	100.0
40	0.219	9.95	10.00	99.5
50	0.219	9.95	10.00	99.5

*Each absorbance value is an average of two separate determinations.

Table 3:2 Stability of hydrochlorothiazide in its coprecipitate with PVP 44,000.

% hydrochlorothiazide content in the coprecipitate	Mean absorbance at 273 nm*	Equivalent hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% of theoretical content
10	0.221	10.05	10.00	100.5
20	0.214	10.18	10.00	101.8
30	0.218	9.91	10.00	99.1
40	0.216	9.82	10.00	98.2
50	0.222	10.09	10.00	100.9

*Each absorbance value is an average of two separate determinations.

Table 3:3 Stability of hydrochlorothiazide in its coprecipitate with urea.

% hydrochlorothiazide content in the coprecipitate	Mean absorbance at 273 nm*	Equivalent hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% of theoretical content
10	0.224	10.18	10.00	101.8
20	0.222	10.09	10.00	100.9
30	0.217	9.86	10.00	98.6
40	0.223	10.14	10.00	101.4
50	0.223	10.14	10.00	101.4

*Each absorbance value is an average of two separate determinations.

3.2.2 THIN LAYER CHROMATOGRAPHY

Chromatography is a separation technique based on the differential distribution of a mixture between two phases one of which is percolated through the other. For effective functioning of this technique, it is essential that the test material be of molecular dimension. This is usually achieved by vaporization or by putting them in solution.

Thin layer chromatographic technique operates on the adsorption principle, whereby separation of various components in a mixture is brought about by their differences in affinity for the support material (adsorbent). It is of optimum significance too, that the adsorption be reversible so as to allow for the advancement of the components, by the carrier phase, from the point of application.

3.2.2.1 PREPARATION OF PLATES

A slurry of the adsorbent was prepared by mixing 40 g of silica gel-G60 (Merck, England) with 80 ml of distilled water thoroughly for about two minutes. The slurry was put in a spreading device which was then drawn accross a series of 10 cm x 20 cm glass plates, depositing a uniform coating of it in a preadjusted thickness of 250 μ. The plates were allowed to set and dry in air for about 24 hours. They were further dried at 110^{o}C for about one hour to activate them for use in the analysis.

3.2.2.2 METHOD

Test samples: Solutions of the coprecipitates containing an equivalent of 0.1 % w/v of hydrochlorothiazide in methanol.

Standard: 0.1 % w/v solution of pure hydrochlorothiazide in methanol.

Solvent system: Ethyl acetate : Benzene (4:1).

Development: Ascending technique to 12 cm height.

Using micropipettes, 0.05 ml of the test samples and the standard solutions were spotted on the activated chromatographic plates. Enlargement of the spots was prevented by drying in between applications by means of a current of cold air from an automated air blower. The chromatogram was then developed using the ascending technique in the solvent system (contained in a Shandon chromatank) to a height of 12 cm. The plate was then removed and dried at 50°C.

Identification of the spots of hydrochlorothiazide was done under ultra-violet radiation of 264 nm wavelength.

2.2.2.3 RESULTS AND DISCUSSION

Figure 3.1 show the results of the thin layer chromatographic determination of stability. Visualization of the developed chromatogram under ultra-violet radiation revealed a single fluorescing spot in each case (indicated as A, B and C on Fig. 3.1) representing the position of

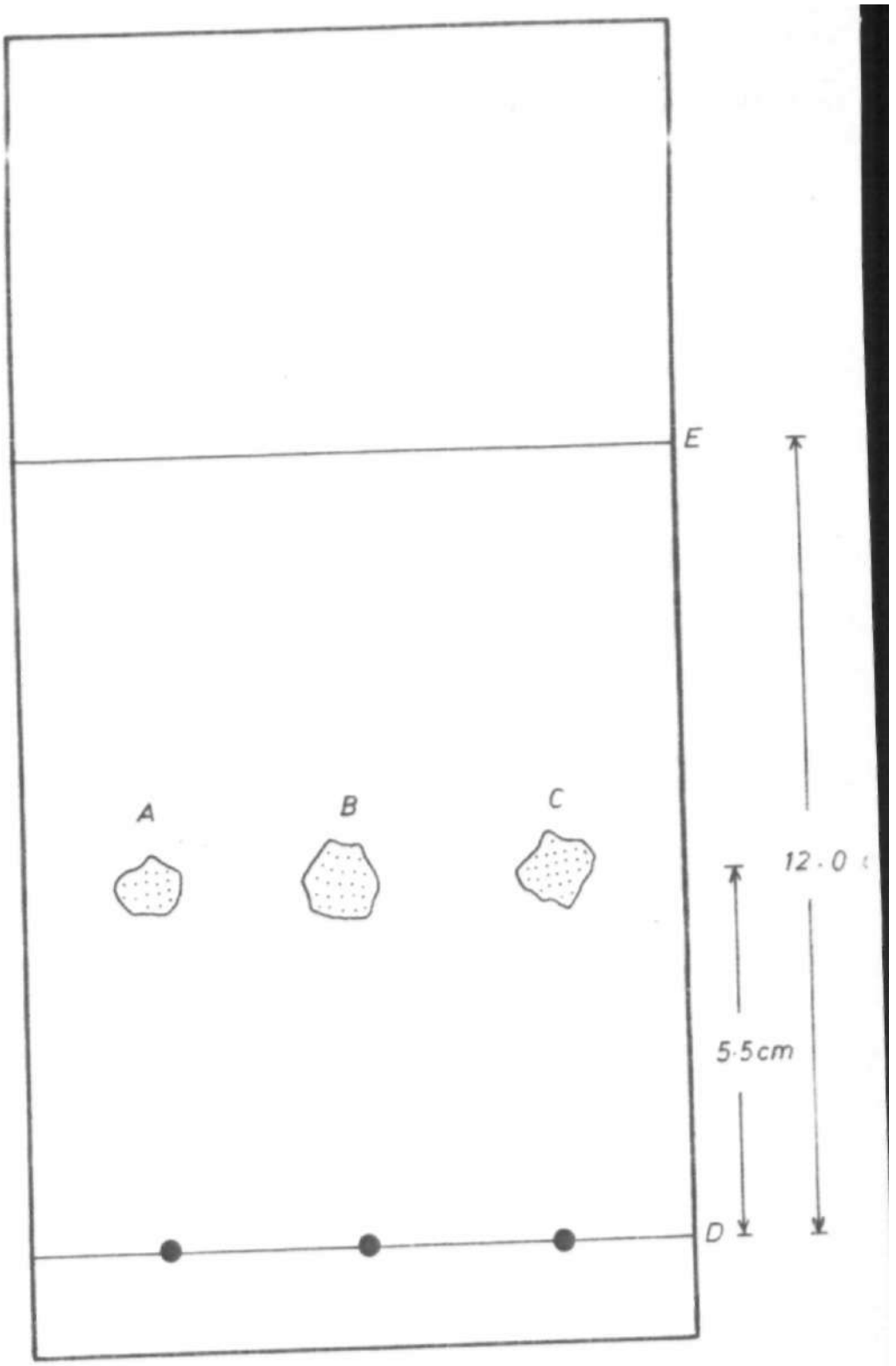


FIG. 3:1

Developed thin layer chromatogram of pure hydrochlorothiazide (B); 30% coprecipitates of hydrochlorothiazide with urea (A) and polyvinylp pyrrolidone 10,000 (C).

D - Baseline for sample application

E - Solvent front

Solvent system = Ethyl acetate : Benzene (4:1)

Development = Ascending technique

Rf value = 0.458.

hydrochlorothiazide contained in the test samples and the standard solution. All the spots had ascended to the same distance and therefore had the same R_f values of 0.458.

$$R_f = \frac{\text{Distance moved by spot (cm)}}{\text{Distance moved by solvent (cm)}}$$

$$= \frac{5.5 \text{ cm}}{12.0 \text{ cm}} = 0.458$$

As no other spot was observed, it could be inferred that there was no decomposition of hydrochlorothiazide after coprecipitation with the various carriers. However, it was not possible by mere visualization to quantify the amount of hydrochlorothiazide contained in each spot. This implies that the thin layer chromatographic technique should always be supplemented by other methods in order to ascertain the stability of this drug in the dispersion.

3.3 INFRARED STUDIES

3.3.1 Method

The potassium bromide (KBr) disk method was used for the infrared determinations at solid state. 30 % dispersions of hydrochlorothiazide in PVP 10,000 and urea were used as test samples. Pure hydrochlorothiazide, PVP and urea were used as comparative standards.

The test material and solid KBr were mixed in appropriate proportions. The uniformly blended mixture was compressed into a disc at a pressure of about 9 tons. The almost transparent disc was mounted on the infrared spectrophotometer (Perkin-Elmer type 710E, connecticut, USA) and scanned using pure KBr disc as reference standard.

3.3.2 RESULTS AND DISCUSSION

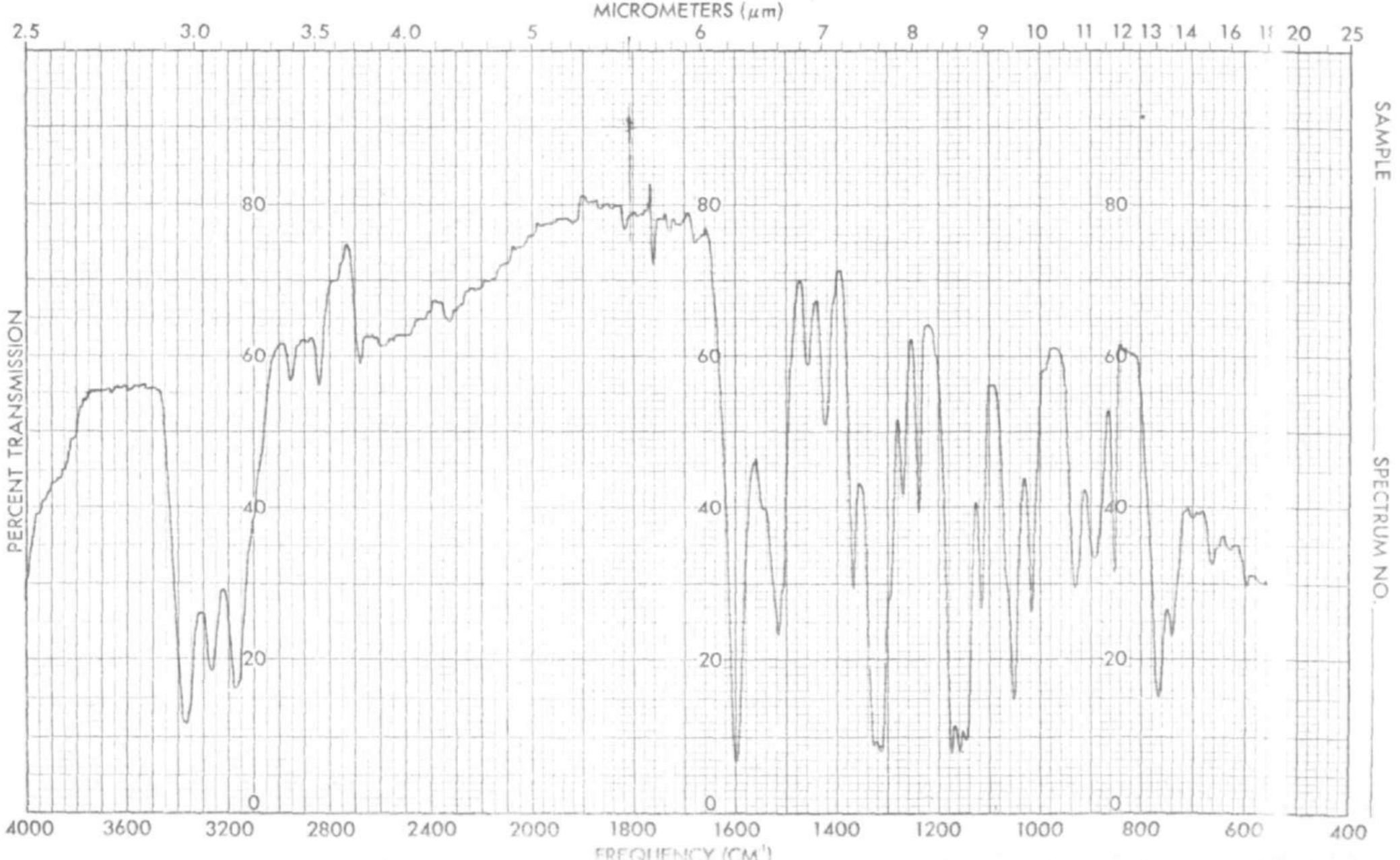
Figures 3.2 to 3.6 show the infrared spectra of pure hydrochlorothiazide, urea, PVP. and 30 % dispersions of hydrochlorothiazide with urea and PVP 10,000. A comparison of the spectra of the pure drug and carriers to that of the coprecipitates do not show any significant shift or change in the major peaks, especially between frequencies, 1,300 cm^{-1} and 36,000 cm^{-1}. This, therefore, precludes any ppssible solid-solid interaction between the drug and any of the two carriers at this composition.

PERKIN-ELMER

CONCENTRATION
THICKNESS
PHASE Solid in KBr
REMARKS FIG. 3.2

SCAN MODE ACCY. ☐ SURVEY ☐
HI ENERGY ☐ CAL. ☐
RESOLUTION ☐
OPERATOR Chris DATE 26/9/74

SPECTRUM NO. 277
SAMPLE PURE HYDROCHLOROTHIAZIDE
ORIGIN



CONCENTRATION _____

THICKNESS _____

PHASE Solid in KBr

REMARKS FIG. 3.3

SCAN MODE ACCY. ☐ SURVEY ☐

HI ENERGY ☐ CAL. ☐

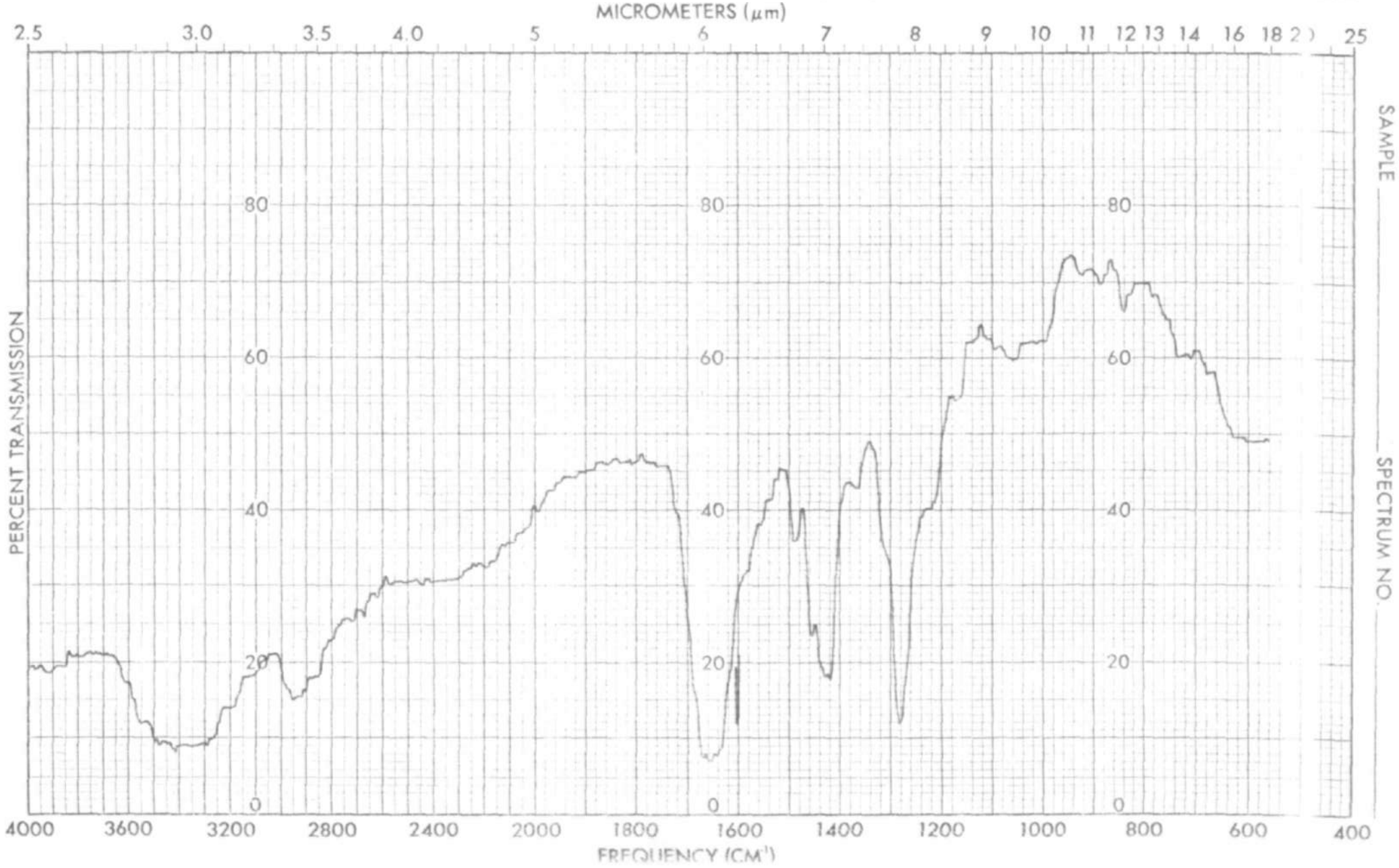
RESOLUTION ☐

OPERATOR Chris DATE 26/9/84

SPECTRUM NO. 278

SAMPLE PURE POLY VINYLPYRR[illegible] -
LIDONE 10,000 (PVP)

ORIGIN _____



CONCENTRATION _____

THICKNESS _____

PHASE Solid in KBr

REMARKS Fig. 3.4

SCAN MODE ACCY. ☐ SURVEY ☐

HI ENERGY ☐ CAL. ☐

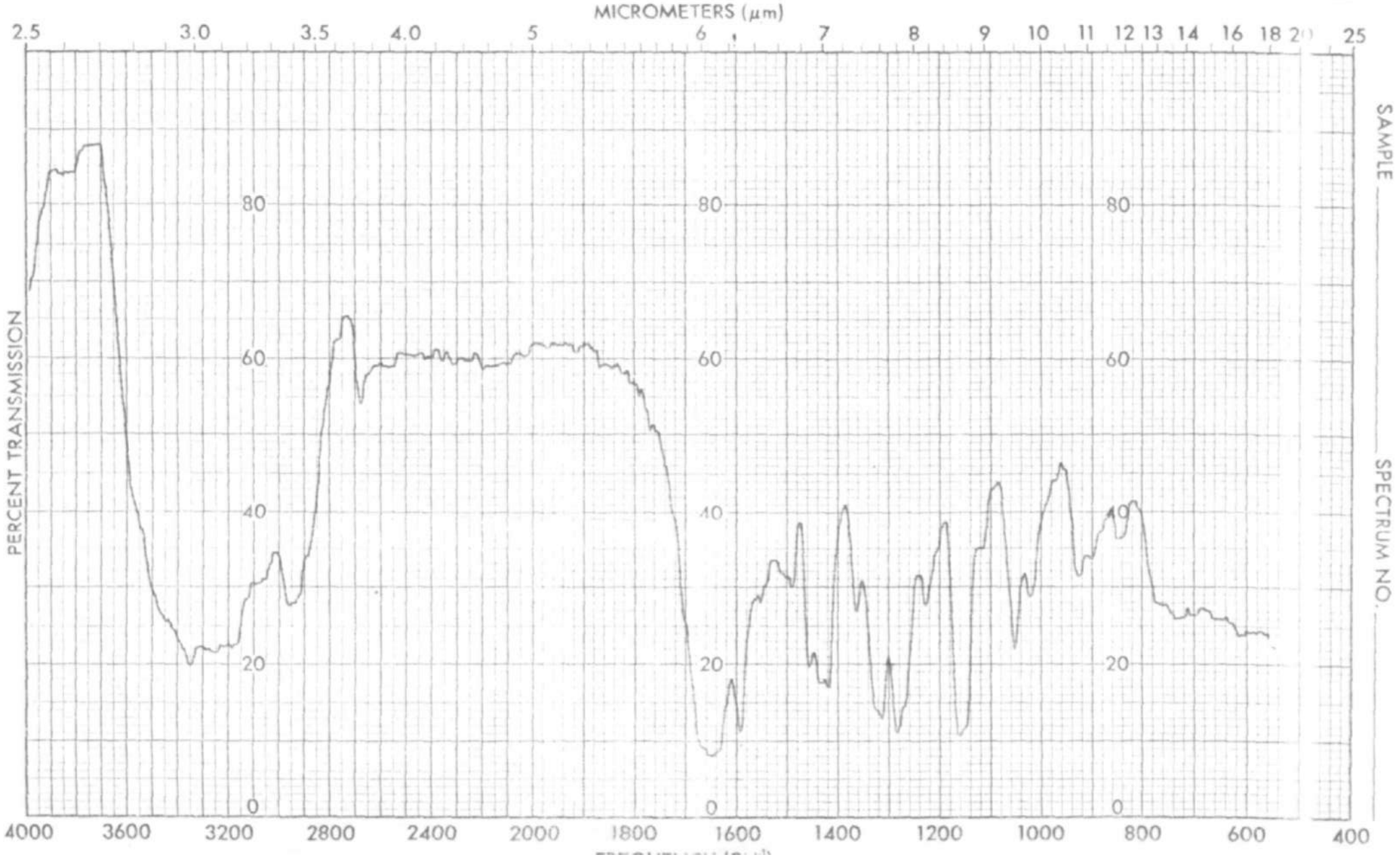
RESOLUTION ☐

OPERATOR Chris DATE 26/7/84

SPECTRUM NO. 229

SAMPLE 30% HYDROCHLOROTHIAZIDE -PVP 10,000 COPRECIPITATE

ORIGIN _____



CONCENTRATION _____

THICKNESS _____

PHASE Solid in KBr

REMARKS Fig. 3.5

SCAN MODE ACCY. ☐ SURVEY ☐

HI ENERGY ☐ CAL. ☐

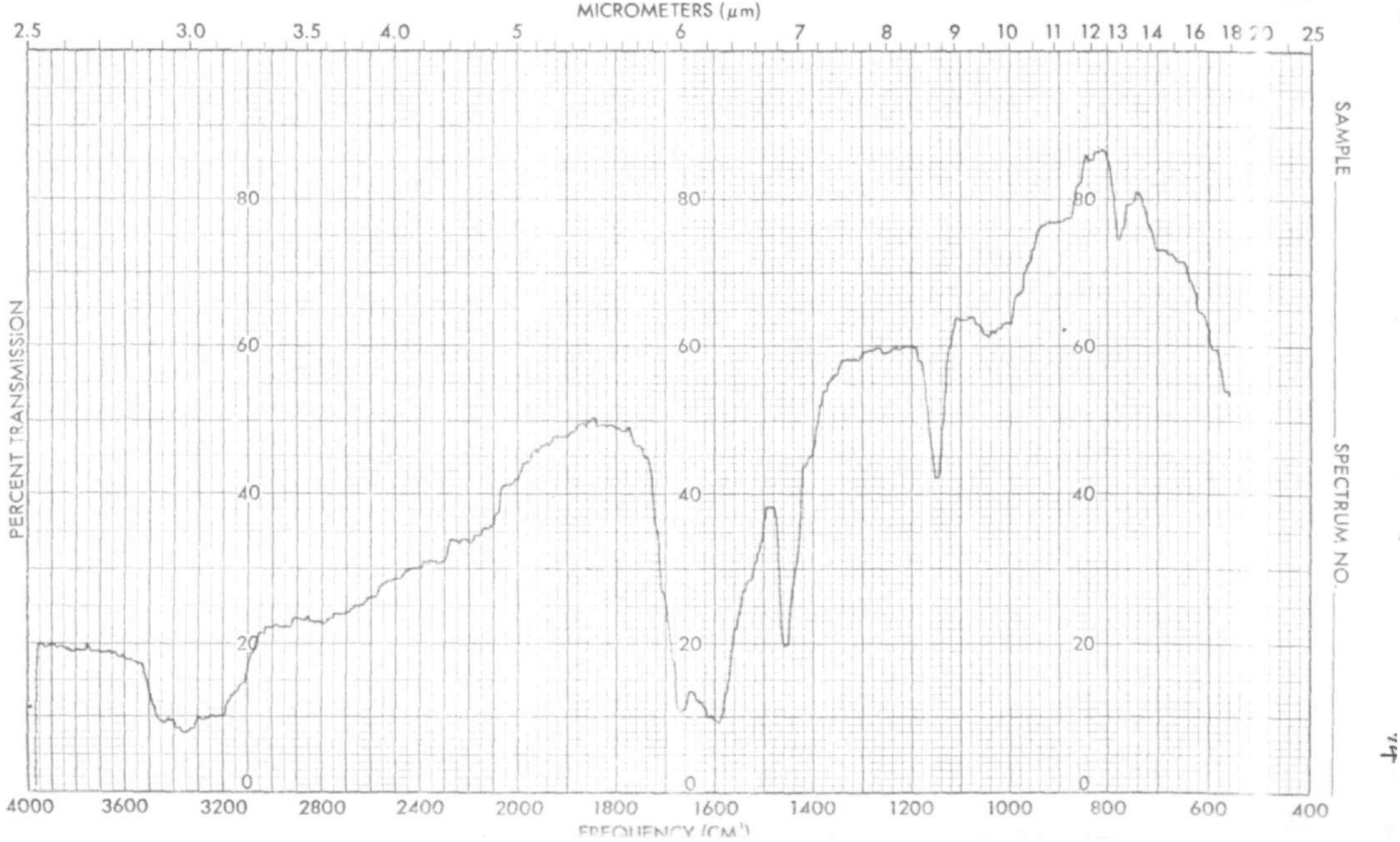
RESOLUTION ☐

OPERATOR Chin DATE 26/9/84

SPECTRUM NO. 280

SAMPLE PURE UREA

ORIGIN _____



PERKIN-ELMER

CONCENTRATION _____

THICKNESS _____

PHASE Solid in KBr

REMARKS FIG. 3.6

SCAN MODE ACCY. ☐ SURVEY ☐

HI ENERGY ☐ CAL. ☐

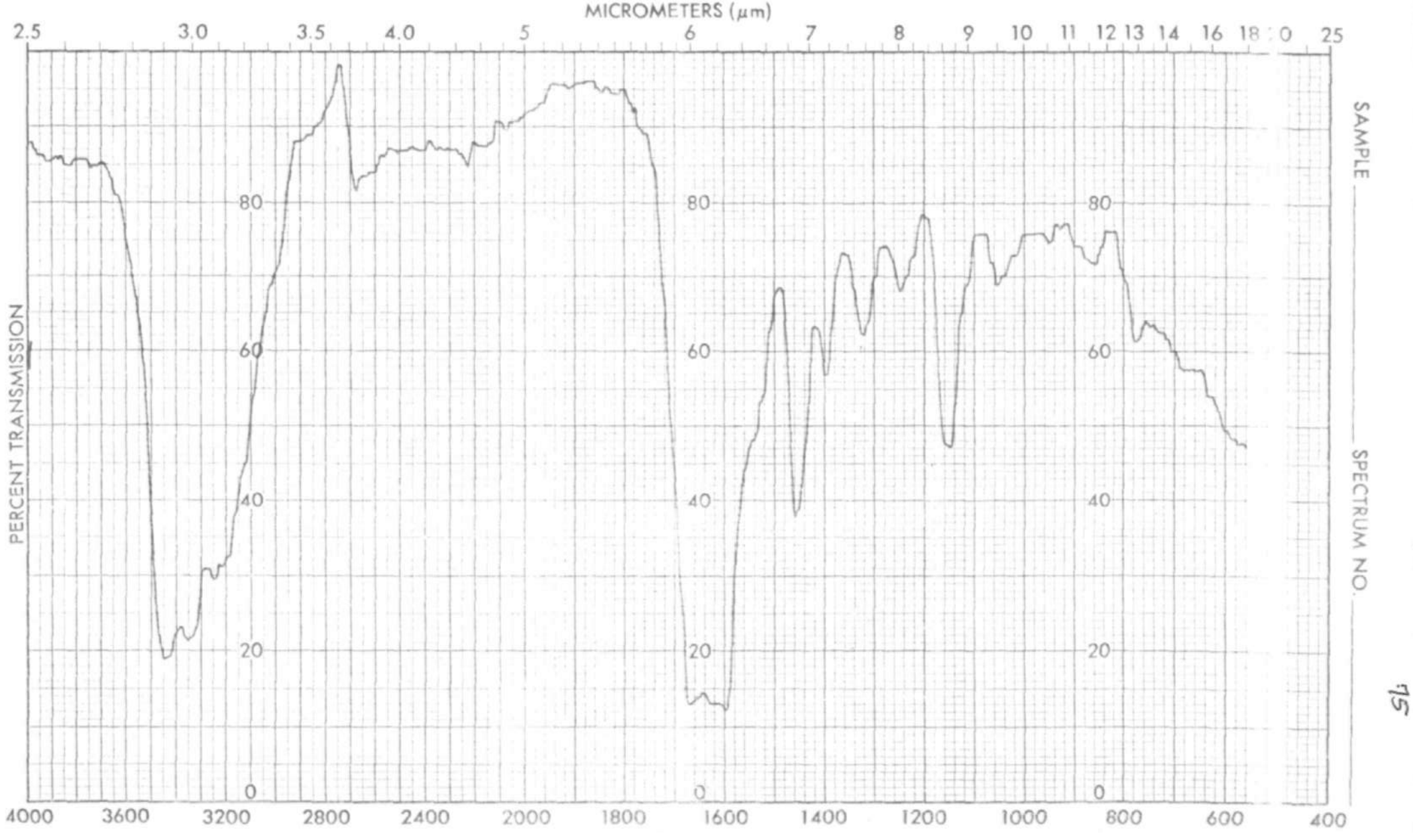
RESOLUTION ☐

OPERATOR Chris DATE 26/9/84

SPECTRUM NO. 281

SAMPLE 30% HYDROCHLOROTHIAZIDE - UREA COPRECIPITATE.

ORIGIN _____



3.4 EVALUATING THE UNIFORMITY OF HYDROCHLOROTHIAZIDE IN THE COPRECIPITATES AND PHYSICAL MIXTURES

In order for the in-vivo dissolution rate data to be valid as a true characteristic of the samples employed in this study, it is necessary that the hydrochlorothiazide be homogeneously distributed throughout the carrier either as physical mixtures or coprecipitates. This may be achieved by ensuring proper mixing of the components of the physical mixture and a true homogeneous solution of the components in an adequate amount of the solvent used in preparing the dispersions. Formation of a true solution of the drug and carrier in the solvent could also preclude nucleation which could lead to independent crystallization of the components.

3.4.1 METHOD

A quantity of the sample (coprecipitate and physical mixture) containing an equivalence of 5 mg of hydrochlorothiazide was accurately weighed and dissolved in 100 ml of distilled water. 5 ml of this solution was quantitatively diluted with distilled water to 50 ml. The resultant solution was then assayed spectrophotometrically for hydrochlorothiazide content.

This procedure was carried out twice for each sample.

3.4.2 RESULTS AND DISCUSSION.

Tables 3.4 to 3.8 show the results for the determination of uniformity of hydrochlorothiazide in the samples used. These results show acceptable standards of uniformity of hydrochlorothiazide in the samples investigated. This is evident by the proximity of the drug content for the two determinations for each sample.

Table 3:4 Uniformity of hydrochlorothiazide in hydrochlorothiazide - PVP 10,000 coprecipitates

% hydrochloro-thiazide content in the dispersion	Absorbance at 273 nm	Hydrochloro-thiazide content (mg)	Theoretical hydro-chloro-thiazide content (mg)	% of theoretical content
10	0.272	4.95	5.00	99.0
	0.273	4.96	5.00	99.2
20	0.275	5.00	5.00	100.0
	0.274	4.98	5.00	99.6
30	0.275	5.00	5.00	100.0
	0.272	4.95	5.00	99.0
40	0.274	4.98	5.00	99.6
	0.274	4.98	5.00	99.6
50	0.273	4.96	5.00	99.2
	0.273	4.98	5.00	99.6

Table 3:5 Uniformity of hydrochlorothiazide in hydrochlorothiazide- PVP 10,000 physical mixtures

% Hydrochlorothiazide content in the dispersion	Absorbance at 273 nm	Hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% of theoretical content
10	0.272	4.95	5.00	99.0
	0.278	5.05	5.00	101.0
20	0.274	4.98	5.00	99.6
	0.275	5.00	5.00	100.0
30	0.272	4.95	5.00	99.0
	0.271	4.93	5.00	98.6
40	0.274	4.98	5.00	99.6
	0.275	5.00	5.00	100.0
50	0.278	5.05	5.00	101.0
	0.280	5.09	5.00	101.8

Table 3:6 Uniformity of Hydrochlorothiazide in hydrochlorothiazide PVP 44,000 coprecipitates

% Hydrochlorothiazide content in the dispersion	Absorbance at 273 nm	Hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% of theoretical content
10	0.249	4.53	5.00	90.5
	0.259	4.71	5.00	94.2
20	0.278	5.05	5.00	101.0
	0.278	5.05	5.00	101.0
30	0.275	5.00	5.00	100.0
	0.272	4.95	5.00	99.00
40	0.274	4.98	5.00	99.6
	0.272	4.95	5.00	99.0
50	0.278	5.05	5.00	101.0
	0.272	4.95	5.00	99.0

Table 3:7 Uniformity of hydrochlorothiazide in hydrochlorothiazide - PVP 44,000 physical mixtures.

% Hydrochlorothiazide content in the dispersion	Absorbance at 273 nm	Hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% of theoretical conent
10	0.275	5.00	5.00	100.0
	0.281	5.11	5.00	102.2
20	0.275	5.00	5.00	100.0
	0.271	4.93	5.00	98.6
30	0.274	4.98	5.00	99.6
	0.272	4.95	5.00	99.0
40	0.270	4.91	5.00	98.2
	0.275	5.00	5.00	100.0
50	0.274	4.98	5.00	99.6
"	0.270	4.91	5.00	98.2

Table 3:8 Uniformity of hydrochlorothiazide in hydrochlorothiazide - urea coprecipitates

% hydrochlorothiazide content in the dispersion	Absorbance at 273 nm	Hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% of theoretical content
10	0.281	5.11	5.00	102.2
	0.275	5.00	5.00	100.0
20	0.275	5.00	5.00	100.0
	0.277	5.04	5.00	100.8
30	0.272	4.95	5.00	99.0
	0.274	4.98	5.00	99.6
40	0.279	5.07	5.00	101.4
	0.278	5.05	5.00	101.0
50	0.278	5.05	5.00	101.0
	0.278	5.05	5.00	101.0

3.5 IN-VITRO DISSOLUTION RATE STUDIES OF THE POWDER SAMPLES

3.5.1 APPARATUS

The dissolution rate test methodology was similar to that described by Goldberg, et al., (1965a) plate 3:1. The basic parts of the apparatus include

a) An adhesive tape (selotape) that holds the test sample.

b) A rectangular frame, 7.0 cm x 3.5 cm with a handle 1.5 cm at the top and a cross bar, 1.5 cm from the top, for mounting the selotape.

c) A beaker modified to contain a bracket to position the frame in contact with the dissolution medium.

d) A plastic paddle which served as a stirrer and attached to an Erweka variable speed motor shaft. The motor allow speeds to be varried between 25 r.p.m. and 200 r.p.m

The 600 ml beaker and its contents was immersed in a water bath maintained at 37°C by means of a thermostatically controlled heater, fitted with a stirrer. Enough time was allowed before the start of

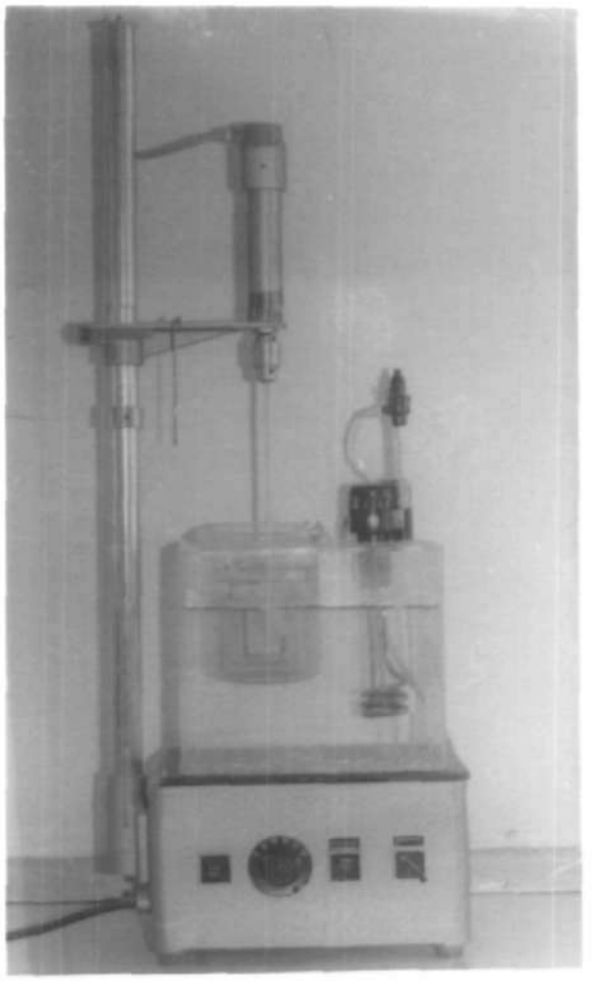


Plate 3.1 The tape method dissolution rate test apparatus

of each dissolution test run to allow the dissolution medium to attain normal (uniform) flow pattern.

3.5.2 METHOD

A piece of selotape was fastened to the frame to provide an adhesive surface for the test sample. The test sample, equivalent to 10 mg of hydrochlorothiazide, was weighed and sprayed on the surface of the tape as a monolayer. This was confirmed by means of a magnifying glass.

The frame and the sample was then positioned, by means of the frame holder, in the dissolution medium, at a constant distance from the stiring paddle. The dissolution medium was 400 ml distilled water maintained at 37°C and stirred by a paddle at a speed of 50 r.p.m. 5 ml aliquots were withdrawn from the medium at times ranging from 0 min. to 90 min. filtered through a millipore filter of pore size 0.45 µm and quantitatively diluted with distilled water to 25 ml. The solution obtained was then assayed spectrophotometrically at 273 nm wavelength. The amount of hydrochlorothiazide released was calculated using the formula of Wurster and Taylor, (1965) which allows for correction for previous samples removed.

$$Cn = Cn\ (meas.) + \frac{5}{400}\sum_{s=1}^{n-1} Cs(meas.)$$

where Cn = Concentration of hydrochlorothiazide at the nth sampling, if previous samples were not removed.

Cn (meas.) = The spectrophotometric concentration of hydrochlorothiazide at the nth sampling

Cs(meas.) = Previous spectrophotometric concentrations of hydrochlorothiazide measured.

5 = Volume (ml) of sample removed from the dissolution medium during each sampling

400 = Total volume of the dissolution medium.

For example:

To calculate the concentration of hydrochlorothiazide (Cn) for the second sampling (after 10 minutes) for the dissolution rate of pure hydrochlorothiazide powder, Table 3.9.

Previous concentration of hydrochlorothiazide released after 5 min. $= \frac{.69}{400}$ mg = .001725 mg/ml
= 1.725 µg/ml

Spectrophotometric concentration of hydrochlorothiazide released after 10 min. i.e. the nth sampling

$= \frac{.98}{400}$ mg = .002450 mg/ml
= 2.45 µg/ml.

Corrected (true) concentration of hydrochlorothiazide released (Cn) after 10 min.

$$= 2.450 + \frac{5}{400} \times 1.725\ \mu g/ml$$

$$= 2.450 + .022\ \mu g/ml$$

$$= 2.472\ \mu g/ml$$

Amount of hydrochlorothiazide released in 400 ml of dissolution medium.

$$= 2.472 \times 400\ \mu g.$$

$$= 988.8\ \mu g \text{ or } .9888\ mg.$$

Theoretical amount of hydrochlorothiazide in test sample = 10 mg.

Percentage of hydrochlorothiazide released into solution at 10 min.

$$= \frac{.9888}{10} \times \frac{100\ \%}{1}$$

$$= 9.888\ \% = 9.9\ \%$$

The samples tested were pure hydrochlorothiazide powder and dispersions of hydrochlorothiazide in PVP 10,000, 44,000 and urea containing hydrochlorothiazide in an amount ranging from 10 to 50 % w/w.

3.5.3 PROBLEMS ASSOCIATED WITH THE TAPE METHOD OF DISSOLUTION RATE TESTING AND THE PRECAUTIONARY MEASURES NECESSARY

The test material analysed by the tape method of dissolution rate testing is frequently a multiparticulate system which may consist of a network of particles (of varying sizes and shapes) positioned by means of an adhesive surface. This means that the effective surface of the particles exposed to the dissolution medium is reduced. This may subsequently lead to a decrease in the dissolution rate of the test material as indicated by the Noyes-Whitney equation shown below.

$$\frac{dc}{dt} = KS\ (Cs-C)$$

$\frac{dc}{dt}$ = dissolution rate of the test material

K = constant that pertains to the diffusion characteristics of the test material.

S = surface area of the dissolving material

Cs = solubility of the dissolving material in the medium.

C = Concentration of the dissolving material in the medium at anytime, t.

The Noyes-Whitney equation operates on the film theory of dissolution which holds that each dissolving particle is surrounded by a thin film of the dissolution medium which is saturated by the molecules of the dissolving material and that the rate of dissolution of the particle depends on the rate at which the drug molecules diffuse from the saturated thin film into the bulk of the dissolution medium. Assuming 'sink' conditions, where C is so small compared to Cs that the quantity Cs-C is equal to Cs, it would be expected that the drug molecules from the thin film diffuse freely into the bulk of the medium because of the large concentration gradient created between them. Under these conditions, it would follow from the Noyes-Whitney equation that the dissolution rate will be dependant solely on the surface area of the particles exposed to the medium.

Other major problems that can lead to variation in dissolution rate data are the difficulty of reproducing the particulate density (number of particles per unit area of the adhesive surface) and the geometrical positioning of the particles on the adhesive surface. These become more serious when the degree of assymetry of the particles is high. These defects could also lead to a reduction of the surface

available to the dissolution medium with a consequent decrease in the dissolution rate.

Despite these drawbacks, the validity of dissolution rate data could be maintained if certain precautions are taken which include:

1) Making sure that the length of the stir paddle at least equals the length of the adhesive surface available for the test material

2) The stir paddle is positioned vertically in such a way that no portion of the tape (adhesive surface) extends beyond the length of the paddle.

These will minimise the effect of density variation and geometric assymetry of the particles.

3) The distance between the stir paddle and the particles surface be maintained during all the runs of the dissolution rate tests.

4) All aliquots withdrawn from the dissolution medium are filtered through a millipore filter paper to avoid exaggerated dissolution rates arising from particles which might be swept off from the adhesive surface into the medium during the test.

3.5.4 RESULTS AND DISCUSSION

Tables 3.9 to 3.34 and Figures 3.7 to 3.12 show the results for the dissolution rate test of the various samples employed. Each absorbance reading recorded is an average of at least three separate determinations.

Table 3:9 Dissolution rate test data for pure hydrochlorothiazide in distilled water at 37°C.

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.019	0.69	6.9
10	0.027	0.98	9.9
15	0.037	1.35	13.7
20	0.048	1.75	17.9
30	0.066	2.40	24.6
45	0.090	3.27	33.6
60	0.113	4.11	42.4
75	0.133	4.84	50.2
90	0.150	5.45	56.9

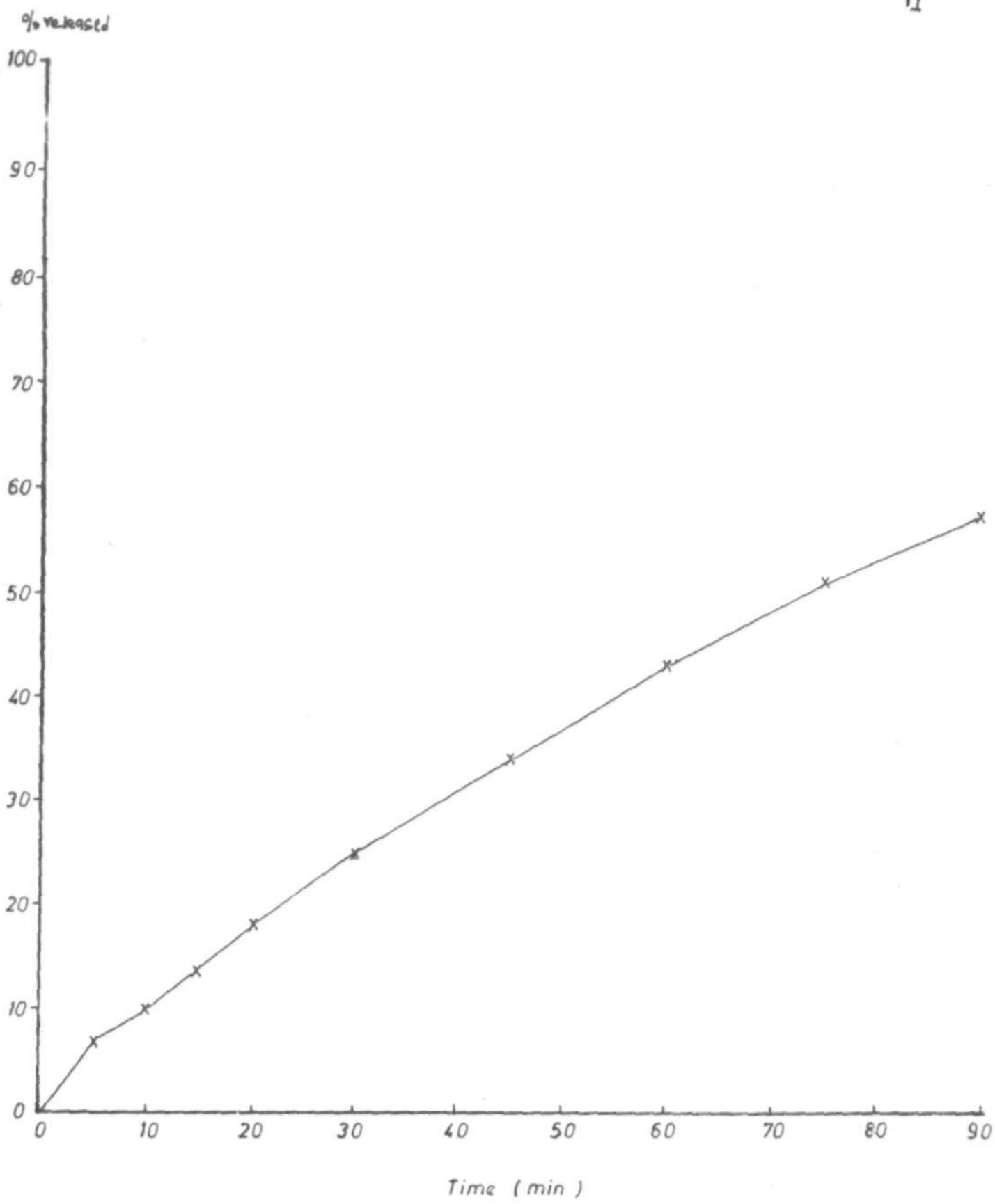


FIG. 3.7 Dissolution profile of pure hydrochlorothiazide in distilled water at 37° C.

Table 3:10 Dissolution rate test data for 10 % hydrochlorothiazide - PVP 10,000 physical mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.147	5.35	53.5
10	0.189	6.87	69.4
15	0.208	7.56	77.1
20	0.219	7.96	82.1
30	0.235	8.55	89.0
45	0.246	8.95	94.0
60	0.255	9.27	98.4
75	0.258	9.38	100.6
90	0.255	9.27	100.7

Table 3:11 Dissolution rate test data for 10 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/400 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.264	9.60	96.0
10	0.267	9.71	98.3
15	0.265	9.64	98.8
20	0.263	9.56	99.2
30	0.260	9.46	99.4
45	0.258	9.38	99.8
60	0.255	9.27	99.9
75	-	-	-
90	-	-	-

Table 3:12 Dissolution rate test data for 10 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.107	3.89	38.9
10	0.145	5.27	53.2
15	0.169	6.15	62.6
20	0.186	6.76	69.5
30	0.211	7.67	79.5
45	0.239	8.69	90.6
60	0.250	9.09	95.7
75	0.259	9.42	100.1
95	0.259	9.42	101.3

Table 3:13 Dissolution rate test data for 10 % hydrochlorothiazide - PVP 44,000 coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.205	7.45	74.5
10	0.238	8.65	87.4
15	0.248	9.02	92.2
20	0.251	9.13	94.4
30	0.256	9.31	97.4
45	0.256	9.31	93.5
60	0.257	9.35	100.1
75	0.254	9.24	100.2
90	-	-	-

Table 3:14 Dissolution rate test data for 10 % hydrochlorothiazide -urea coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/400 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.132	4.80	48.0
10	0.165	6.00	60.6
15	0.186	6.76	69.0
20	0.203	7.38	76.0
30	0.230	8.36	86.7
45	0.245	8.91	93.3
60	0.257	9.35	98.8
75	0.261	9.49	101.3
90	0.259	9.42	101.8

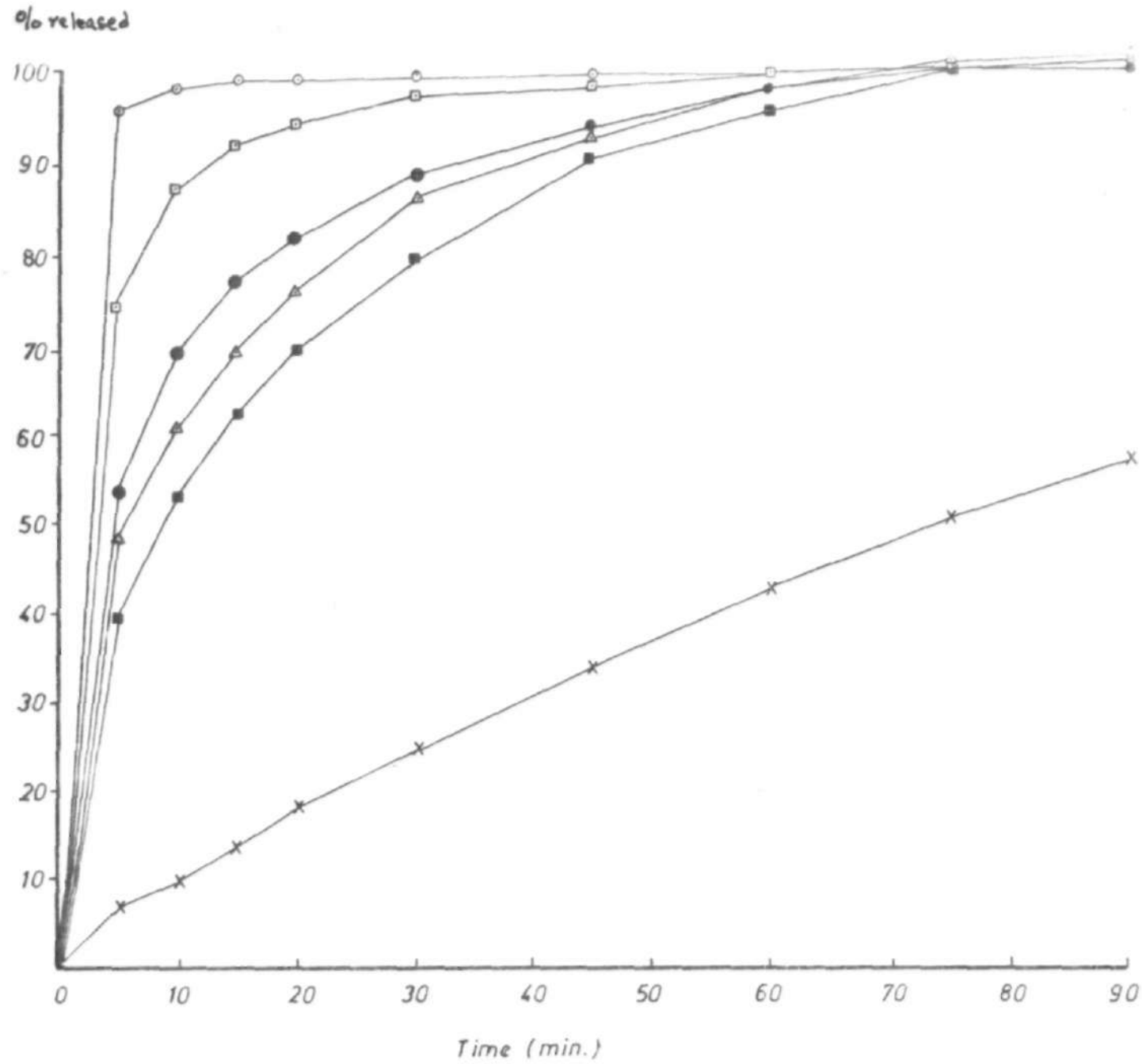


FIG. 3:8 Dissolution profiles of pure hydrochlorothiazide (x) 10% hydrochlorothiazide - urea coprecipitate (▵), 10% hydrochlorothiazide - polyvinylpyrrolidone 10,000 coprecipitate (⊙); physical mixture (●) ; 10% hydrochlorothiazide - polyvinylpyrrolidone 44,000 coprecipitate (⧈) and physical mixture (■) in distilled water at 37° C.

Table 3:15 Dissolution rate test data for 20 % hydrochlorothiazide - PVP 10,000 physical mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.124	4.51	45.1
10	0.163	5.93	59.9
15	0.186	6.76	68.9
20	0.200	7.27	74.8
30	0.223	8.11	84.2
45	0.245	8.91	93.2
60	0.257	9.35	98.7
75	0.257	9.35	99.9
90	0.254	9.24	99.9

Table 3:16 Dissolution rate test data, for 20 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.269	9.78	97.8
10	0.268	9.75	98.7
15	0.266	9.67	99.1
30	0.263	9.56	99.3
30	0.260	9.46	99.4
45	0.258	9.38	99.8
60	0.256	9.31	100.3
75	-	-	-
90	-	-	-

Table 3:17 Dissolution rate test data for 20 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.121	4.40	44.0
10	0.156	5.67	57.3
15	0.183	6.65	67.8
20	0.198	7.20	74.1
30	0.221	8.04	83.4
45	0.243	8.84	92.4
60	0.256	9.31	98.2
75	0.255	9.27	99.0
90	0.252	9.16	99.0

Table 3:18 Dissolution rate test data for 20 % hydrochlorothiazide - PVP 44,000 coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.210	7.64	76.4
10	0.268	9.75	98.5
15	0.265	9.64	98.6
20	0.263	9.56	99.0
30	0.262	9.53	99.9
45	0.261	9.49	100.7
60	0.259	9.42	101.2
75	0.257	9.35	101.6
90	0.254	9.24	101.7

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Table 3:19 Dissolution rate test data for 20 % hydrochlorothiazide - urea coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.072	2.62	26.2
10	0.108	3.93	39.6
15	0.130	4.73	48.1
20	0.150	[illegible]	35.9
30	0.180	6.55	67.6
45	0.214	7.78	80.7
60	0.235	8.51	89.0
75	0.251	9.13	96.2
90	0.259	9.42	100.3

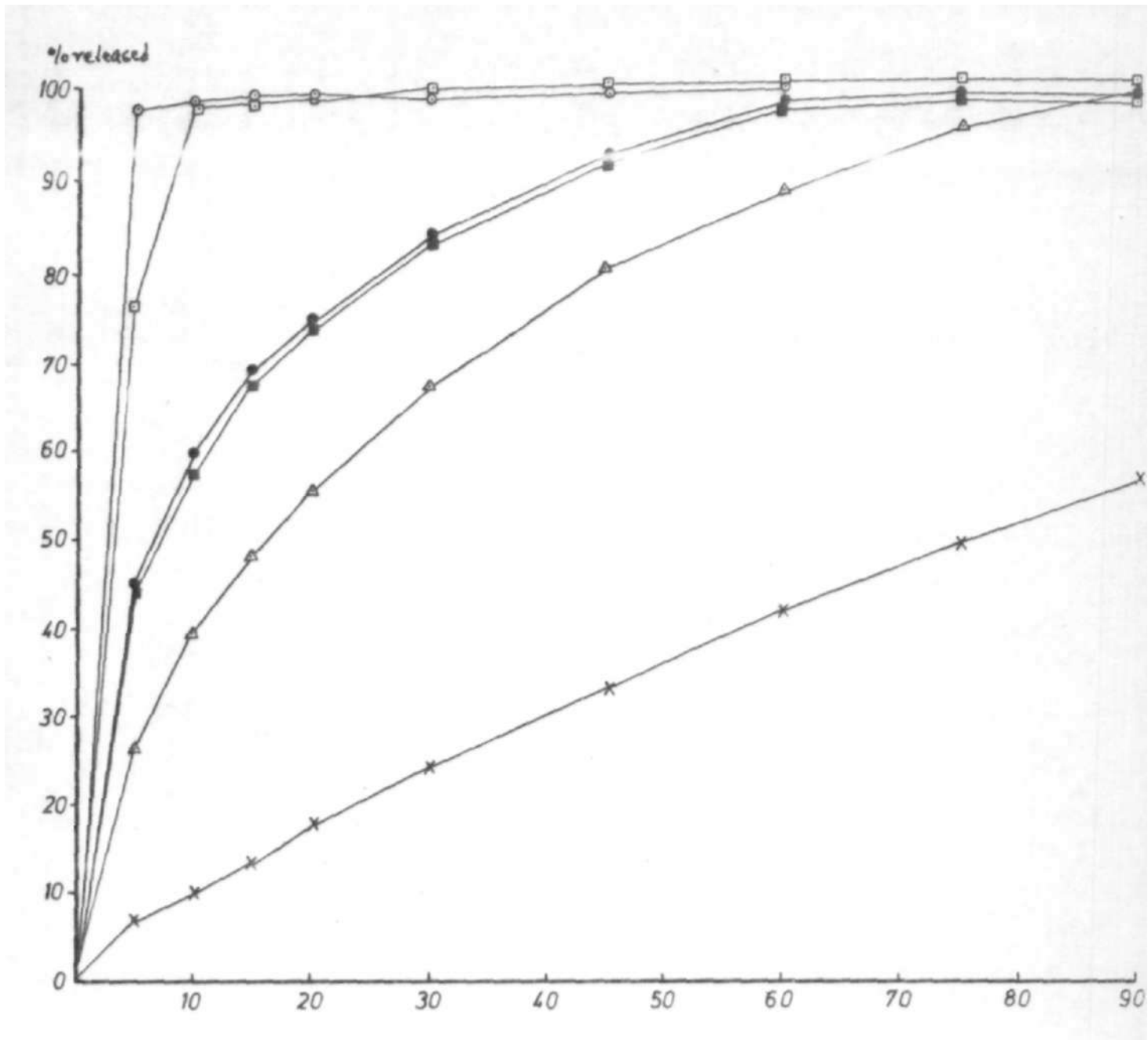


FIG. 3:9 Dissolution profiles pure hydrochlorothiazide (x), 20% hydrochlorothiazide - urea coprecipitate (▲), 20% hydrochlorothiazide - polyvinyl pyrroldone 10,000 coprecipitate (⊙); phyical mixture (●); 20% hydrochlorothiazide - polyvinylpyrroldone 44,000 coprecipitate (⊡) and physical mixture (■) in distilled water at 37° C.

Table 3:20 Dissolution rate test data for 30 % hydrochlorothiazide - PVP 10,000 physical mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/400 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.109	3.96	39.6
10	0.146	5.31	53.6
15	0.180	6.55	66.6
20	0.211	7.67	78.7
30	0.227	8.25	85.4
45	0.246	8.95	93.5
60	0.254	9.24	97.5
75	0.255	9.27	99.0
90	00.254	9.24	99.8

Table 3:21 Dissolution rate test data for 30 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.231	8.40	84.0
10	0.260	9.45	95.6
15	0.266	9.67	98.9
20	0.265	9.64	99.8
30	0.263	9.56	100.2
45	0.262	9.53	101.1
60	0.260	9.46	101.6
75	0.259	9.34	101.6
90	0.254	9.24	101.8

Table 3:22 Dissolution rate test data for 30 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.106	3.85	38.5
10	0.144	5.24	52.9
15	0.176	6.40	65.1
20	0.198	7.20	73.9
30	0.220	8.00	82.8
45	0.242	8.80	91.8
60	0.253	9.20	96.9
75	0.253	9.20	98.1
90	0.252	9.16	98.8

Table 3:23 Dissolution rate test data for 30 % hydrochlorothiazide - PVP 44,000 coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.159	5.78	57.8
10	0.227	8.25	83.2
15	0.244	8.87	90.5
20	0.248	9.02	93.1
30	0.250	9.09	94.9
45	0.255	9.27	97.8
60	0.256	9.31	99.4
75	0.255	9.27	100.1
90	0.254	9.24	100.0

Table 3:24 Dissolution rate test, for 30 % hydrochlorothiazide - urea coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.067	2.44	24.4
10	0.102	3.71	37.4
15	0.125	4.55	46.3
20	0.142	5.16	52.9
30	0.174	6.33	65.3
45	0.208	7.56	78.4
60	0.225	8.18	85.5
75	0.242	8.80	92.7
90	0.254	9.24	98.2

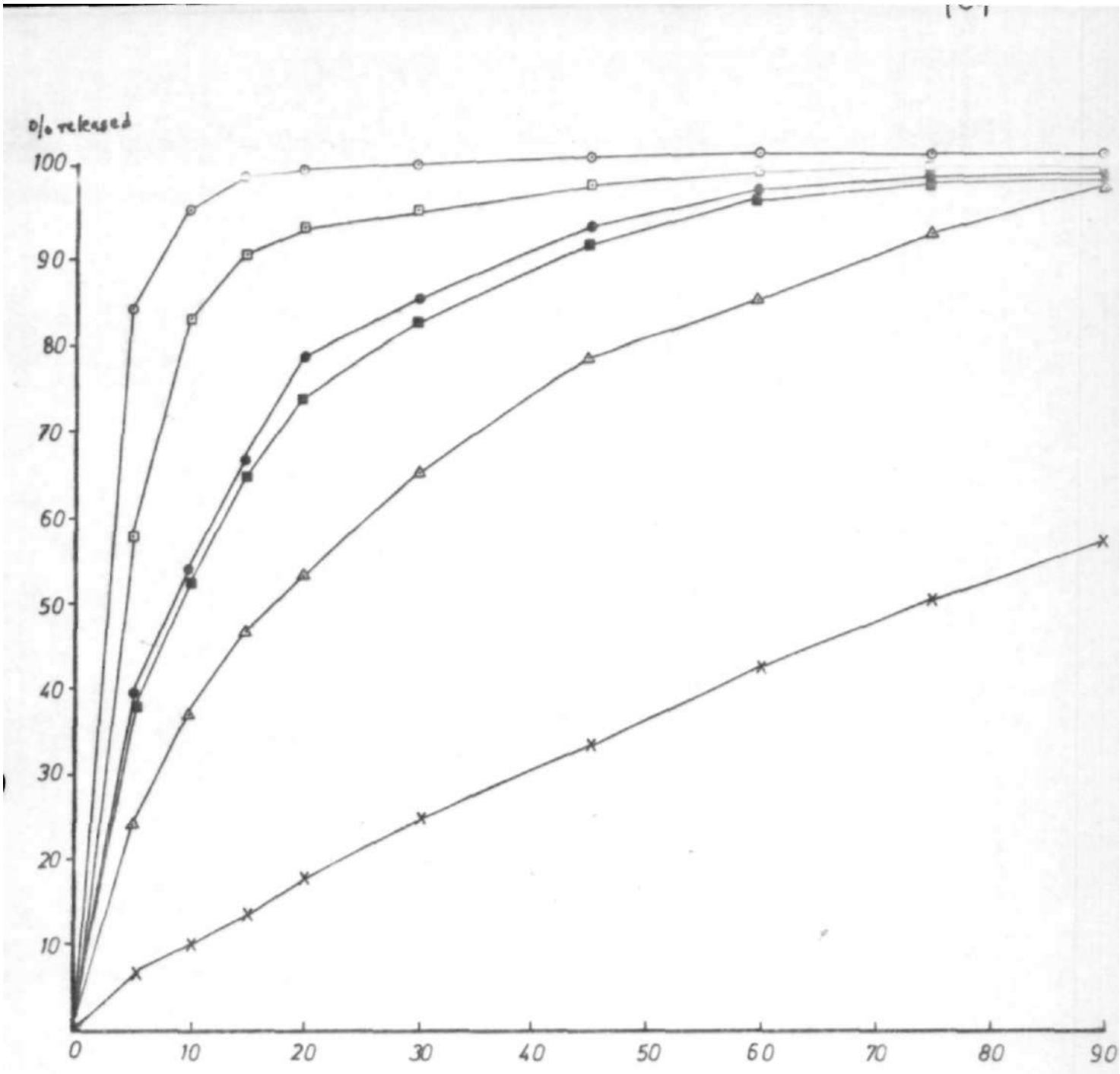


FIG. 3:10

Dissolution profiles of pure hydrochlorothiazide (x); 30% hydrochlorothiazide - urea coprecipitate (▲); 30% hydrochlorothiazide-polyvinylpyrrolide 10.000 coprecipitate (⊙); physical mixture (●); 30% hydrochlorothiazide - polyvinylpyrrolidone 44,000 coprecipitate (⧈); and physical mixture (■) in distilled water at 37° C.

Table 3:25 Dissolution rate test data for 40 % hydrochlorothiazide - PVP 10,000 physical mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% Hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.096	3.49	34.9
10	0.128	4.65	47.0
15	0.159	5.78	58.8
20	0.178	6.47	66.4
30	0.208	7.56	78.1
45	0.236	8.58	89.3
60	0.248	9.02	94.8
75	0.256	9.31	98.8
90	0.254	9.24	99.3

Table 3:26 Dissolution rate test data for 40 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/400 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.195	7.09	70.9
10	0.251	9.13	92.2
15	0.257	9.35	95.5
20	0.261	9.49	98.1
30	0.263	9.56	100.0
45	0.262	9.53	100.8
60	0.259	9.42	101.0
75	0.256	9.31	101.0
90	0.252	9.16	100.7

Table 3:27 Dissolution rate test data for 40 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.085	3.09	30.9
10	0.126	4.58	46.2
15	0.156	5.67	57.7
20	0.173	6.29	64.6
30	0.201	7.31	75.6
45	0.231	8.40	87.4
60	0.246	8.95	93.9
75	0.252	9.16	98.3
90	0.250	9.09	98.7

Table 3:28 Dissolution rate test data for 40 % hydrochlorothiazide - PVP 44,000 coprecipitates in distiled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of Hydrochloro-thiazide released (mg/400 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.154	5.60	56.0
10	0.216	7.85	79.2
15	0.228	8.29	84.6
20	0.237	8.62	88.9
30	0.246	8.95	93.3
45	0.250	9.09	95.8
60	0.253	9.20	98.1
75	0.250	9.09	98.1
90	0.247	8.98	98.1

Table 3:29 Dissolution rate test data for 40 % hydrochlorothiazide - urea coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/400 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.057	2.07	20.7
10	0.093	3.38	34.1
15	0.120	4.36	44.3
20	0.136	4.95	50.7
30	0.168	6.11	63.0
45	0.200	7.27	75.3
60	0.220	8.00	83.5
75	0.238	8.65	91.0
90	0.246	8.95	95.7

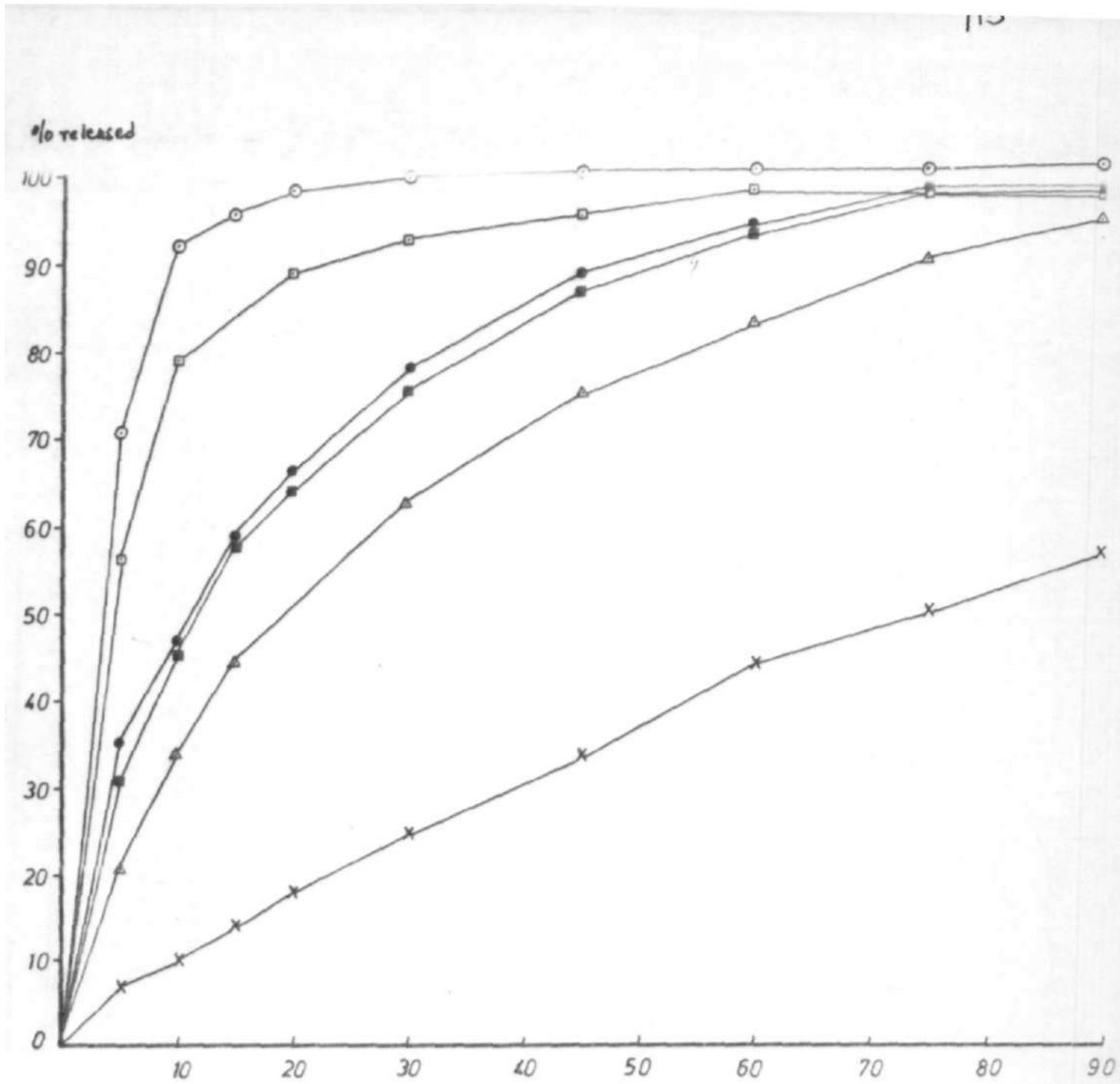


FIG. 3:11 Dissolution profiles of pure hydrochlorothiazide (x), 40% hydrochlorothiazide - urea coprecipitate (△) 40% hydrochlorothiazide - polyvinylpyrrolidone 10,000 coprecipitate (⊙); physical mixture (●); 40% hydrochlorothiazide - polyvinylpyrrolidone 44,000 coprecipitate (▫) and physical mixture (■) in distilled water at 37° C.

Table 3: 30 Dissolution rate test data for 50 % hydrochlorothiazide - PVP 10,000 physica. mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/400 ml)	% hydrochloro-thiazide released
0	0.000	0.0	0.0
5	0.089	3.24	32.4
10	0.125	4.55	45.9
15	0.145	5.27	53.7
20	0.157	5.71	58.7
30	0.180	6.55	67.8
45	0.208	7.56	78.8
60	0.220	8.00	84.1
75	0.230	8.36	88.7
90.	0.233	8.47	89.8

Table 3:31 Dissolution rate test data for 50 % hydrochlorothiazide - PVP 10,000 coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/400 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.139	5.05	50.5
10	0.178	6.47	65.3
15	0.197	7.16	73.0
20	0.208	7.56	77.9
30	0.223	8.11	84.4
45	0.234	8.51	89.4
60	0.243	8.84	93.8
75	0.250	9.09	97.4
90	0.254	9.24	100.0

Table 3:32 Dissolution rate test data for 50 % hydrochlorothiazide - PVP 44,000 physical mixtures in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.077	2.80	28.0
10	0.111	4.04	40.8
15	0.127	4.62	47.1
20	0.141	5.13	52.7
30	0.162	5.89	61.0
45	0.181	6.58	68.1
60	0.195	7.09	74.5
75	0.205	7.45	79.0
90	0.211	7.67	82.0

Table 3:33 Dissolution rate test data for 50 % Hydrochlorothiazide - PVP 44,000 coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/400 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.083	3.02	30.2
10	0.117	4.25	42.9
15	0.143	5.20	52.9
20	0.156	5.67	58.3
30	0.177	6.44	66.7
45	0.202	7.35	76.6
60	0.217	7.89	82.9
75	0.227	8.25	87.5
90	0.236	8.58	91.0

Table 3:34 Dissolution rate test data for 50 % hydrochlorothiazide - urea coprecipitates in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/400 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.032	1.16	11.6
10	0.055	2.00	20.1
15	0.073	2.65	26.9
20	0.089	3.25	33.1
30	0.120	4.36	44.7
45	0.153	5.56	57.3
60	0.180	6.55	67.9
75	0.202	7.33	76.7
90	0.218	7.93	83.4

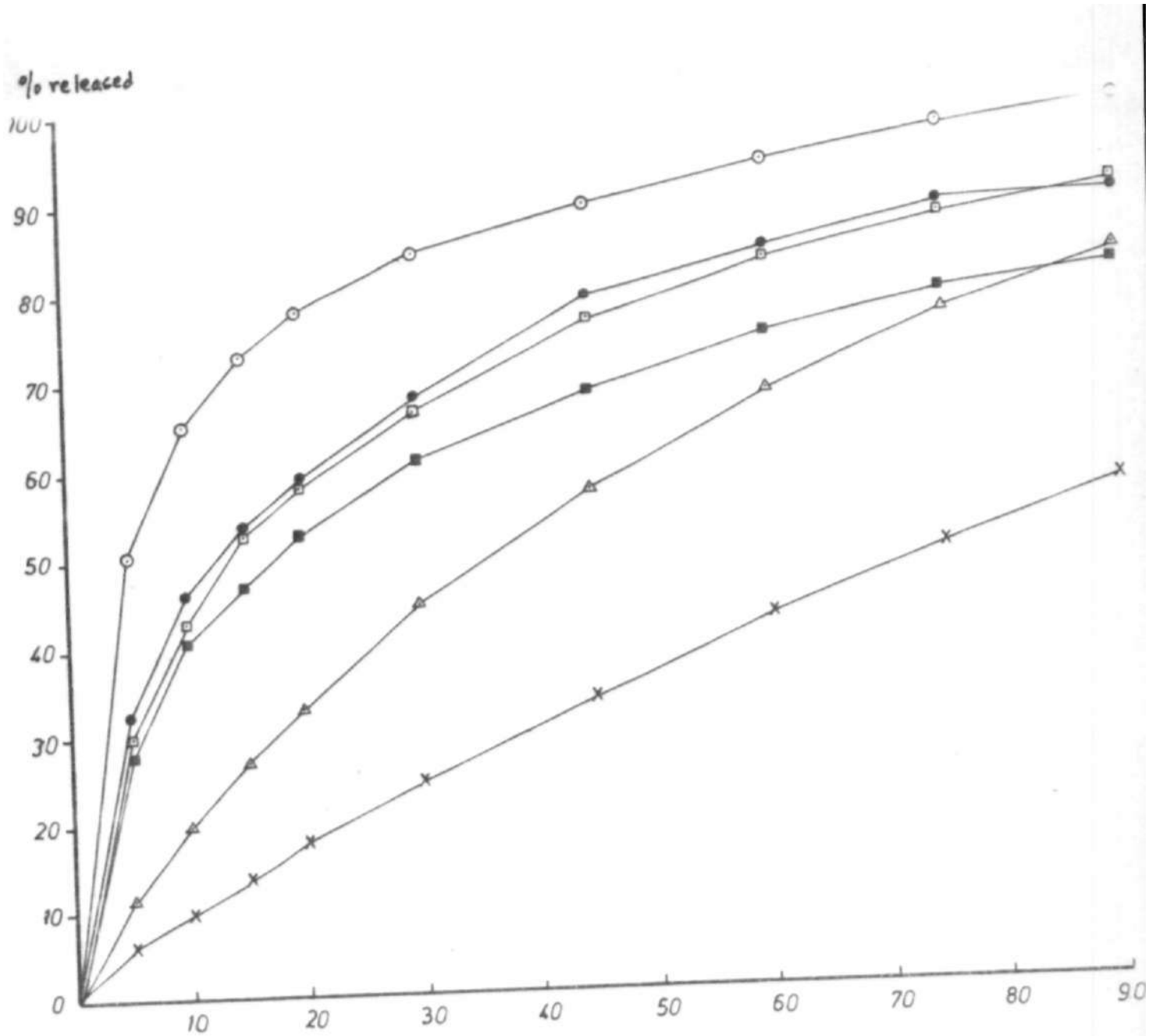


FIG. 3:12 Dissolution profile of pure hydrochlorothiazide (x); 50% hydrochlorothiazide - urea coprecipitate (△); 50% hydrochlorothiazide - polyvinylpyrrolidone 10,000 coprecipitate (○); physical mixture (●) 50% hydrochlorothiazide - polyvinylpyrrolidone 44·000 coprecipitate (▫) and physical mixture (▪) in distilled water at 37°C

Table 3:35 Times taken for 60 %, 75 %, 90 % (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution from it's dispersions with urea

Dispersion	T_{60} (min)	T_{75} (min)	T_{90} (min)
10 % Coprecipitate	10.0	19.3	38.0
20 % Coprecipitate	23.8	39.0	62.5
30 % Coprecipitate	26.0	41.0	70.0
40 % Coprecipitate	27.5	44.5	73.5
50 % Coprecipitate	49.5	72.5	above 90

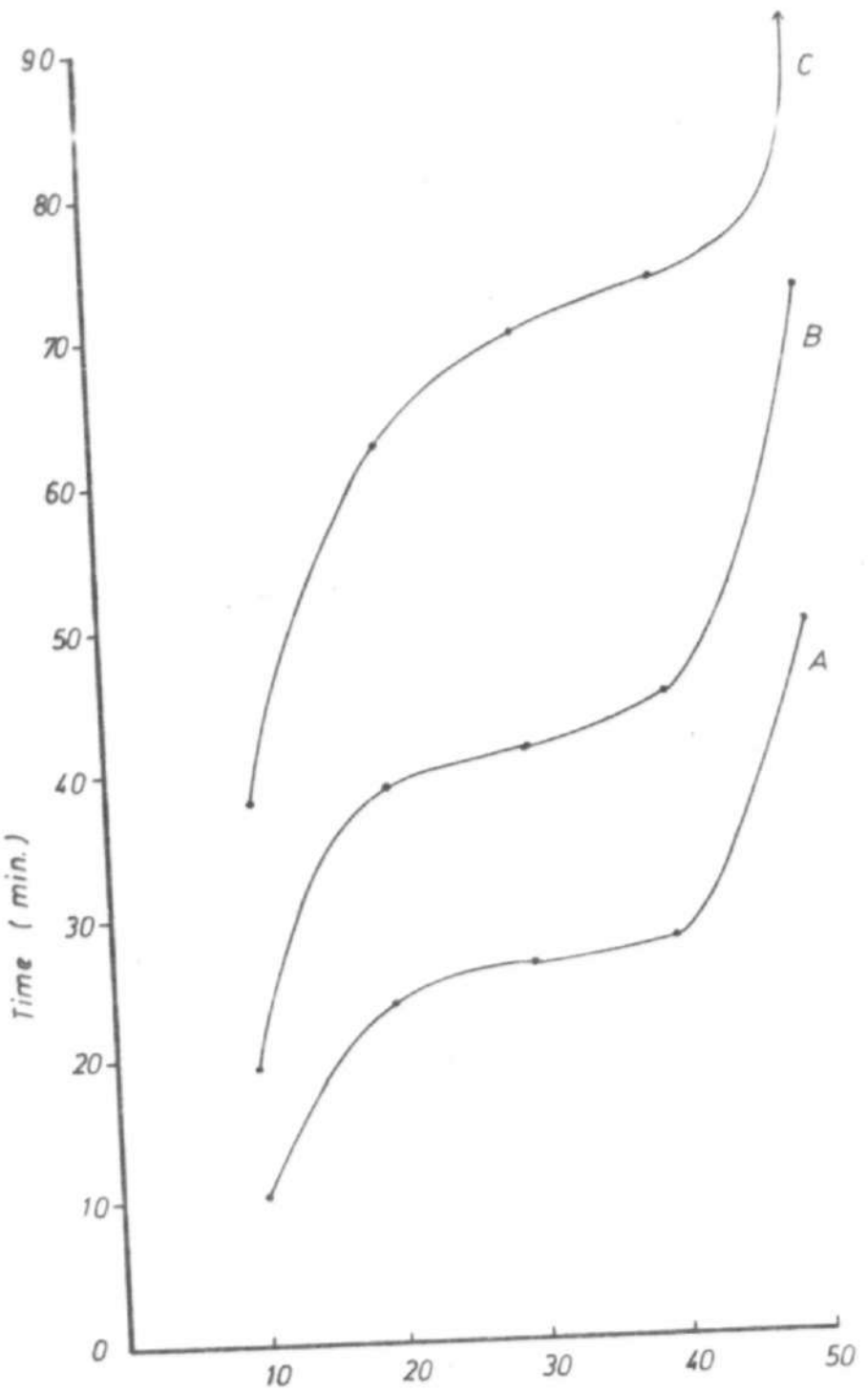


FIG. 3:13 Times required for 60%, 75% and 90% (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution from hydrochlorothiazide - urea coprecipitates of various compositions.

A - T_{60}; B - T_{75} ; C - T_{90}.

Table 3:36 Times taken for 60 %, 75 %, 90 % (T_{60}, T_{75}, T_{90}) of Hydrochlorothiazide to go into solution from it's dispersions with PVP 10,000

		T_{60} (min)	T_{75} (min)	T_{90} (min)
10 %	Coprecipitate	3.3	4.0	4.8
	Physical - mixture	7.2	13.8	33.0
20 %	Coprecipitate	3.0	4.0	4.5
	Physical - mixture	10.0	20.5	40.0
30 %	Coprecipitate	3.5	4.5	7.5
	Physical mixture	12.5	18.5	38.0
40 %	Coprecipitate	4.3	6.0	9.5
	Physical mixture	15.8	27.3	47.5
50 %	Coprecipitate	8.3	17.0	47.0
	Physical mixture	21.5	39.8	90.0

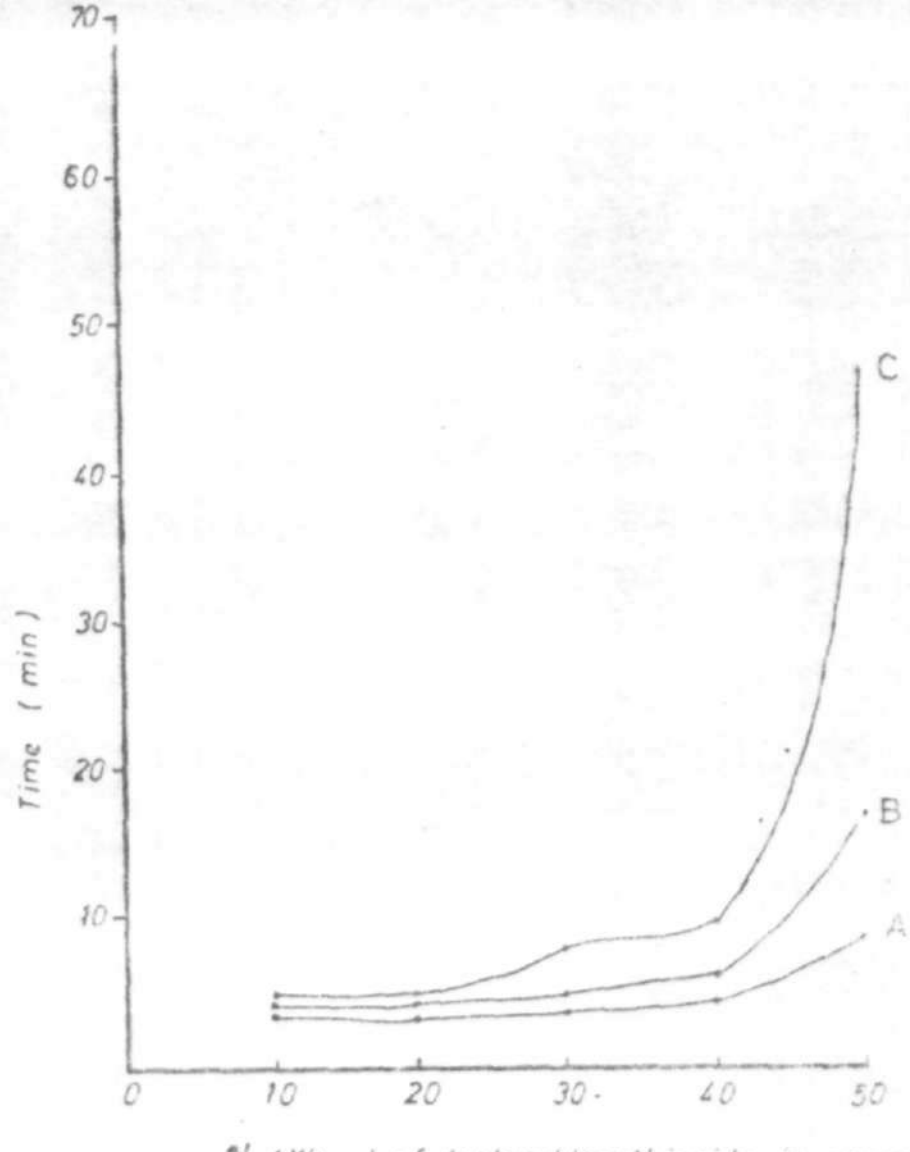


FIG. 3.14 Times required for 60%, 75% and 90% (T_{60}, T_{75}, T_{90}) OF hydrochlorothiazide to go into solution from hydrochlorothiazide - polyvinylpyrrolidone 10.000 coprecipitates of various compositions.

A - T_{60}; B - T_{75}; C - T_{90}.

Table 3:37 Times taken for 60 %, 75 %, 90 % (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution from it's dispersions with PVP 44,000

Dispersion		T_{60} (min)	T_{75} (min)	T_{90} (min)
10 %	Coprecipitate	3.3	4.0	4.8
	Physical mixture	13.7	25.5	44.0
20 %	Coprecipitate	3.0	5.0	8.0
	Physical mixture	11.5	21.5	41.5
30 %	Coprecipitate	5.5	8.5	14.5
	Physical mixture	13.0	21.5	42.5
40 %	Coprecipitate	6.0	9.1	22.5
	Physical mixture	16.8	29.5	52.0
50 %	Coprecipitate	22.5	43.0	86.0
	Physical mixture	29.0	61.5	above 90

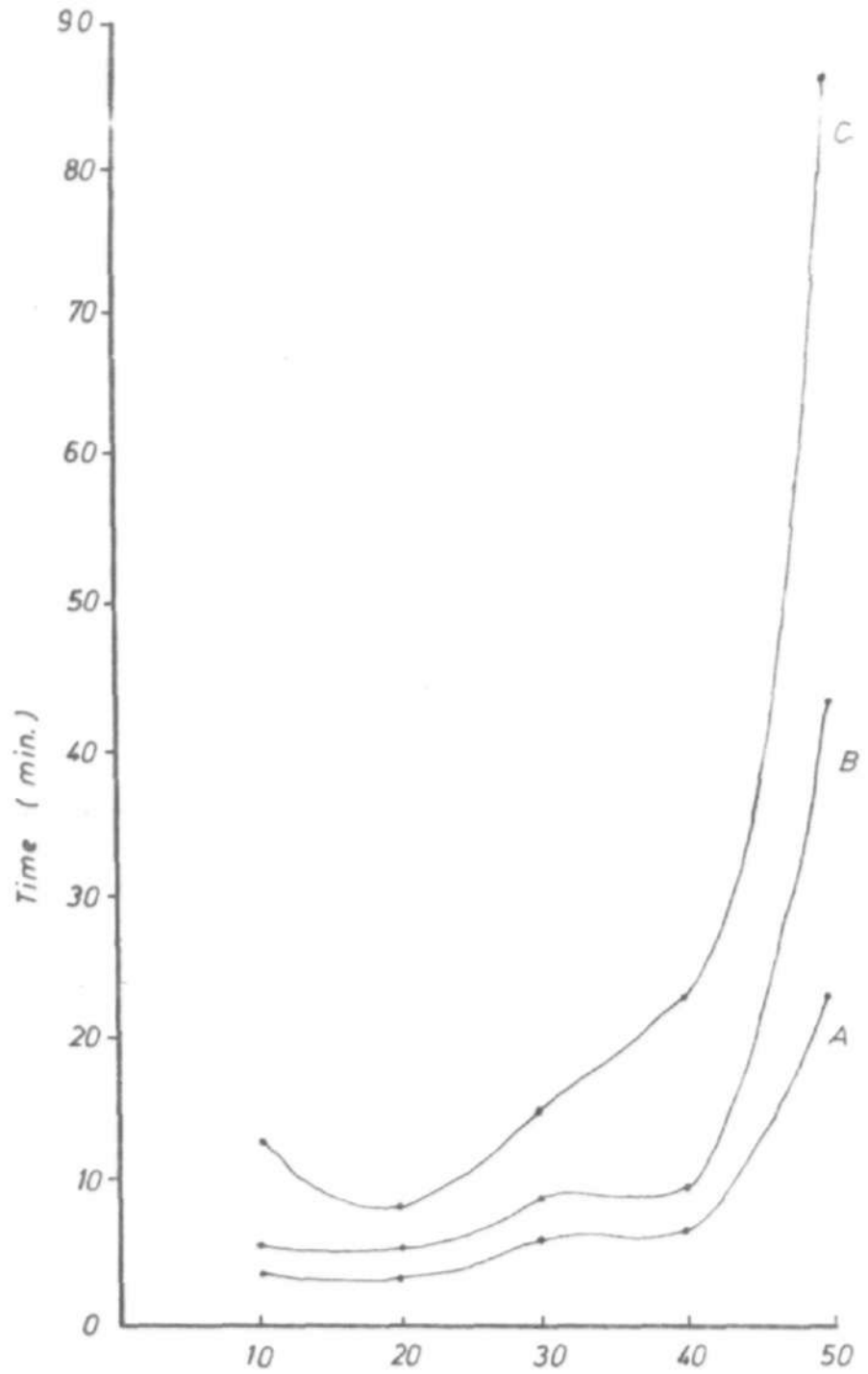


FIG. 3:15

Times required for 60%, 75% and 90% (T_{60}, T_{75}, T_{90}) of hydrochlorothiazide to go into solution from hydrochlorothiazide - polyvinylpyrrolidone 44.000 coprecipitates of various compositions.

A - T_{60}; B - T_{75}; C - T_{90}.

DISCUSSION

The results show that the dissolution rates of hydrochlorothiazide from its coprecipitates with PVP 10,000 and 44,000 were superior to the physical mixtures of corresponding compositions. Further, with both the coprecipitates and the physical mixtures, PVP 10,000 was superior to PVP 44,000 in enhancing the dissolution rate of hydrochlorothiazide.

Dissolution rate increase from the physical mixtures over that of the pure drug may be explained by the local solubiliztaion effect of PVP at the microenvironment of the drug particle. Theoretically, it may not be expected that the physical mixture (where drug and carrier exist independently) show a dissolution rate superior to the pure drug alone as the two components are expected to dissolve independently. However, a possible explanation to the contrasting observation is that the PVP dissolves quickly in the aqueous dissolution medium, attaining a very high microenvironment concentration in the mixed diffusion layers of both components. That is to say that the diffusion layers of hydrochlorothiazide and the carriers overlapped. This may result in increased solubility of hydrochlorothiazide in the diffusion layer with a consequent increase in dissolution rate. This is further attested by increases in the aqueous solubility of hydrochlorothiazide in the presence of the carriers.

The effectiveness of PVP in enhancing the dissolution rate of poorly water soluble drugs has been found to be dependant on the average molecular weight or the chain length of the polymer. Simonelli, et al., (1969), Corrigan, et al., (1976) and Kassem, et al., (1982) have reported that smaller molecular weight PVP is superior to those of higher molecular weights in enhancing the dissolution rates of sulfathiazole and hydrochlorothiazide. Similar observations have been made in this study with PVP 10,000 which was found to be superior to PVP 44,000 in increasing the dissolution rate of hydrochlorothiazide. However, Deshpande and Agrawal, (1984) have found PVP 44,000 to be better than PVP 10,000 in increasing the dissolution rate of chlorpropamide. From these results, it may be inferred that the effectiveness of PVP polymers in enhancing the dissolution rates of poorly soluble drugs might not only be dependant on the average molecular weight of the polymer, but also on the chemical nature of the drug.

Coprecipitation of poorly soluble drugs have been found to generally increase their solubility and dissolution rate (Mayersohn and Gibaldi, 1966; Bates, 1969; Simonelli, et al., 1969) and also their absorption rate (Gibaldi, et al., 1968; Stupak and Bates, 1972). Such increases have variously been attributed to the existence of either a eutectic mixture, colloidal dispersion, molecular complexations, solid and glass solutions of the drug in carrier

or any two or more of them existing simultaneously. A phase diagram could not be constructed for hydrochlorothiazide - PVP systems investigated (due to limited facilities), however, the infrared spectra of these systems (Fig. 3.2 to 3.4) did not indicate any possibility of complex formation or solid-solid interaction between the two components. This is based on the fact that the major peaks of hydrochlorothiazide (Fig. 3.2) and PVP (Fig. 3.3), particularly those between frequencies 3600cm^{-1} and 1300 cm^{-1}, did not shift or disappear due to coprecipitation as evident in Fig. 3.4.

It is implicative, therefore, that the increased dissolution rates observed with hydrochlorothiazide - PVP coprecipitates may be due to particle size reduction or even the existence of hydrochlorothiazide in a thermodynamically unstable amorphous form, which usually have a higher solubility than the crystalline form. Similar explanations have been given for increases in the dissolution rates of sulfathiazole (Simonelli, et al., 1969; 1976), hydroflumethiazide (Corrigan and Timoney, 1975) and hydrochlorothiazide (Bloch, et al., 1982). All these changes are precluded in physical mixtures and as such the superiority of hydrochlorothiazide dissolution rate from coprecipitates compared to the physical mixtures is expected.

The results further revealed that the dissolution rates of hydrochlorothiazide from PVP coprecipitates increased with increasing composition of PVP in the dispersion up to 80 % w/w, above which a slight decrease was observed (Fig. 3.14 and 3.15). It could be envisaged that at high PVP weight fraction, the hydrochlorothiazide is completely embeded in the PVP matrix or may exist on the external surface at low PVP weight fractions. Considering factors related to solubility and diffusibility, the carrier is believed to dissolve quickly releasing the drug into solution. However, at low PVP weight fractions, it may become less available for the drug molecules and a layer of the pure drug at the external surface becomes increasingly a controlling factor for the dissolution rate. Further at high PVP weight fractions (above 80 %), the drug is completely embeded in the carrier in such a way that the diffusion front of hydrochlorothiazide, compared to that of PVP, is slightly distant from the solvent. This may mean that the rate at which hydrochlorothiazide is released into solution is dependant on the rate at which the PVP goes into solution. Although PVP is readily soluble in water, a slight decrease in the dissolution rate of hydrochlorothiazide would still be expected. Similar explanations were held for sulfathiazide - PVP dispersed systems (Simonelli, et al., 1969). This is in agreement with the diffusional model earlier proposed by Higuchi, (1967). The dissolution rates of

hydrochlorothiazide from its coprecipitates with urea, though lower than from the PVP coprecipitates, were superior to the pure drug alone. El-Banna, et al., (1980) have constructed a phase diagram for the hydrochlorothiazide-urea system. They proposed eutectic formation containing 20 and 37 % w/w, and solid solution containing 10 and 90 % w/w of hydrochlorothiazide in the dispersion. They also proposed molecular complexation having molecular ratios of 10:1 and 5:1 with respect to the carrier and drug. However, the infrared spectra for 30 % hydrochlorothiazide-urea system (Fig. 3.2, 3.5 and 3.6) precluded reasonable solid-solid interaction between the two components. On these basis, increased dissolution rate of hydrochlorothiazide may be attributed to particle size reduction through eutectic formation, solid solution formation which is evident from the marked differences in the $T_{60\ \%}$, $T_{75\ \%}$ and $T_{90\ \%}$ values of 10 % hydrochlorothiazide-urea dispersions compared to 20, 30 and 40 % dispersions where there was no significant change in these parameters (Fig. 3.13), coupled with the solubilization effect of urea at the microenvironment of hydrochlorothiazide particles. These factors increased the surface area exposed to the medium with better wetting and a consequent increase in solubility. Reduction in electrostatic attractive forces between the drug molecules may also be a contributory factor.

The superiority of PVP to urea in increasing the dissolution rate of hydrochlorothiazide may be due to differences in the nature in which hydrochlorothiazide exist in the different carriers. Similar explanations were given for solid dispersions of acetohexamide and spironolactone in various water soluble polymers (Kassem, et al., 1982 a, b). The ability of PVP to prevent nucleation and crystal growth could be of added advantage over urea.

The variability in the $T_{60\ \%}$, $T_{75\ \%}$ and $T_{90\ \%}$ values observed with the urea coprecipitates may be a measure of the degree of variability in the nature in which hydrochlorothiazide exist in this carrier. Similarly the almost constant values for these parameters for the PVP coprecipitates (containing 10 - 30 % w/w hydrochlorothiazide) may suggest the existence of the drug in the same form over these concentration range. These agree very well with the findings of El-Banna, et al., (1980) for hydrochlorothiazide-urea system and the proposal that the amorphous form of the drug may be responsible for increased dissolution rates from the coprecipitates with PVP.

Based on these findings, one may conclude that PVP, particularly the smaller molecular weight polymer, (PVP 10,000) offers the best approach to improving the solubility and dissolution rate of poorly soluble drugs.

CHAPTER FOUR

4. FORMULATION STUDIES

4.1 INTRODUCTION

Tablets have been defined by the USP XIX, (1975) as "solid dosage forms containing medicinal substances with or without suitable diluents which may be prepared by compression or moulding".

Tablets, as solid dosage forms have been in use for a very long time and have increasingly gained more popularity over other dosage forms. Furthermore, a lot of research have been concluded on how to improve the technique of their production and also obviate the problems associated with their design; with a view to a better utilization and effectiveness of the medicament. The stringent formulation requirements of most modern medicaments, the many advantages of tablet medication coupled with the economy associated with it's large-scale manufacture have led to a decrease in the prescribing of other dosage forms such as pills, powders, cachets and granules. Some other advantages associated with tablet medication include, accuracy of dosage, physical stability, chemical stability and retention of optimal physiological activity over extended storage periods and the ease and convenience of administration.

It is well known that the way a tablet is formulated may affect the biological availability of the medicament contained there in. This makes it mandatory for the manufacturers to achieve a good balance between the factors that are necessary to produce an elegant tablet and those that affect the effective utilization of the medicament. For good quality tablets to be obtained after compression, the material must possess some basic characteristics; one of which is fluidity; (the ability of the material to flow freely) lack of which may cause serious quality deficiencies in the tablet such as excessive weight variation and non uniformity in the tablet contents. These may result into inconsistent doses of the medicament. The thickness and hardness of the tablets so produced may also be varied. The other is compressibility, which is the property of forming a stable solid mass when pressure is applied. The therapeutic dose of most modern medicaments is low and as such are not sizable enough to be compressed alone. This coupled with the fact that the material (medicament) may have limited compressibility and the limitations of available equipment, makes it apparently inevitable to include 'additives' in tablet formulae. This step is particularly necessary when the tablets are expected to meet standards as regards disintegration, dissolution rate, friability and other

physical tests. Bulking agents are sometimes added to increase the volume and weight of the material to a practically compressible amount. Some bulking agents may also improve flow characteristics and compressibility. The need for lubricants, glidants and antiadherents in promoting powder flow and minimizing various frictional forces between the compressed tablet, punches and die wall cannot be overemphasised. It is sometimes essential to use binders to 'glue' the powders together into granules or a stable solid tablet mass. The binder adds to the cohesive strength between them thus making compression easier and more effective. Binders may be used either as a dry powder or a solution. Whichever method is used in incorporating it, the quantity must be carefully adjusted so as to produce tablets that will disintegrate and dissolve to release the active ingredient when swallowed. The choice of the binding agent may also rest on its compatibility with the drug and other ingredients and the binding force required. In order for the drug to be released rapidly from the tablet, it is essential that it breaks down (disintegrates) rapidly after administration. This desirable characteristic has often been achieved by the addition of disintegrating agents to tablet formulae.

The technique for preparing tablets may follow one or a combination of several established methods (Gunsel and Kanig, 1970). These include:

(1) Dry methods

(a) Direct Compression

(b) Granulation by compression

(2) Wet methods

(a) Wet granulation

(b) Special procedures

The materials employed in this work include coprecipitates of a poorly soluble drug with readily soluble carriers. It is therefore supposed that the use of 'wet' granulation method could cause solubilization of the drug-carrier system prior to the tests thus invalidating the dissolution rate data. The direct compression method was therefore adopted. Additionally, it is expected that with the direct compression method, the availability of the drug for absorption will be good due to the absence of adhesive granulating agents and morever the elimination of the moistening and drying stages will obviate many stability problems associated with the wet granulation process.

4.2 THE DIRECT-COMPRESSIBLE VEHICLE: MICROCRYSTALLINE CELLULOSE

This was supplied by the kind courtesy of Medac Nig. Ltd.

Microcrystalline cellulose is derived from a special grade of purified alpha wood cellulose by acid hydrolysis to remove the amorphous cellulose portions, yielding needle-like microcrystalline particles. It is a highly compressible material that produces hard tablets which nevertheless disintegrate rapidly in aqueous media due to swelling of the particles. Additionally, microcrystalline cellulose improves the flowability and compressibility of other materials in the tablet formular.

4.3 WORKING FORMULA AND CALCULATIONS

The pure hydrochlorothiazide and the 30 % dispersions (coprecipitates) of hydrochlorothiazide in urea and PVP 10,000 were used for tablet formulation. Each tablet was formulated to contain 50 mg of hydrochlorothiazide. Polyvinylpyrrolidone 10,000 and microcrystalline cellulose were added as bulking agents while maize starch served as the disintegrant. Infact these three substances could also act as dry binders. To improve the flow characteristics of the powder, magnesium stearate was added.

Calculations: for 30 % coprecipitates.

30 mg of hydrochlorothiazide is contained in 100 mg of coprecipitate.

Therefore 50 mg of hydrochlorothiazide will be contained in $100 \times \frac{50 \text{ mg}}{30}$ of coprecipitate

= 166.6 mg.

Therefore each tablet contained 166.6 mg of the coprecipitate of hydrochlorothiazide with either urea or PVP 10,000.

Table 4:1 Working formula for tablet manufacture employing pure hydrochlorothiazide

Substance	Quantities for One tablet	200 tablets	% of total weight
Hydrochloro-thiazide	50.0 mg	10.0 g	10.0
PVP 10,000	272.6 mg	54.5 g	54.5
Micro-crystalline cellulose	150.0 mg	30.0 g	30.0
Maize starch	25.0 mg	5.0 g	5.0
Magnesium stearate	2.5 mg	0.5 g	0.5
Total	500.1 mg	100.0 g	100.0

Table 4:2 Working formula for tablet manufacture employing coprecipitates of hydrochlorothiazide with either urea or PVP 10,000

Substance	Quantities for One tablet	200 tablets	% of Total weight
Coprecipitate	166.6 mg	33.3 g	33.3
PVP 10,000	156.0 mg	31.2 g	31.2
Microcrystalline cellulose	150.0 mg	30.0 g	30.0
Maize starch	25.0 mg	5.0 g	5.0
Magnesium stearate	2.5 mg	0.5 g	0.5
Total	500.1 mg	100.0 g	100.0

The following equipment was used for the production and testing of physical characteristics of the tablets.

1. Single punch tabletting machine: - Erweka type Eko N.r 10008, West German
2. Micrometer screw gauge:- Moore and Wright, Sheffield England
3. Friabilator: Hoffman - La Roche, Switzerland
4. Hardness tester:- Stokes-Monsanto, Pennwalt, New York.
5. Disintegration tester:- Erweka, West Germany
6. Dissolution rate tester:- Erweka type DT Nr. 43091, West Germany.

4.4 METHOD OF TABLET FORMULATION

The coprecipitates were powdered by means of a glass pestle and mortar and sieved. Particles of sizes between 90 μ and 106 μ were collected and used for the preparation of tablets. Adequate quantities of the ingredients for formulating 200 tablets (tables 4:1 and 4:2) were accurately weighed and mixed thoroughly in a cube mixer. The uniformly blended powder mixture was then compressed by means of a single punch Erweka tabletting machine. The compression was carried out manually. Tablets with weights of about 500 mg each and containing an equivalent amont of 50 mg hydrochlorothiazide were produced.

The hydrochlorothiazide was already in a fine powder form and therefore sieving was not necessary prior to use.

4:5 PHYSICAL TESTS ON THE TABLETS

The tablets prepared were subjected to a series of tests in order to assess their potential qualities.

The weight and size variation must be kept within strict, though practically attainable limits, otherwise dose variation might be significant. Although tablets must possess sufficient mechanical

strength to withstand normal handling hazards, they should (if so designed) disintegrate within a reasonable time after administration as this may have a direct bearing to the absorption and systemic availability of the drug.

4:5:1 WEIGHT VARIATION

4:5:1:1 METHOD:

Twenty tablets, brushed gently to remove excess powder, were weighed independently and the average weight calculated. The percentage deviation of individual tablet weights from the average weight were also calculated. The tablets are considered to have a satisfactory weight uniformity, if not more than two deviate from the average by more than 5 % and none vary by up to twice that weight.

4:5:1:2 RESULTS AND DISCUSSION

Tables 4.3 to 4.5 show results for the weight variation studies. The highest positive deviation obtained with the tablets prepared from the pure hydrochlorothiazide was 6 % while the highest negative deviation was 3.4 %. Generally only one tablet had a deviation from the average weight by more than 5 %.

For tablets prepared from 30 % dispersion of hydrochlorothiazide with urea, the highest positive deviation was 3.4 % while the highest negative deviation was 2.8 % of the average tablet weight. On the whole no single tablet weight deviated from the average by up to 5 %.

The highest positive deviation obtained with tablets prepared from the coprecipitate of hydrochlorothiazide with PVP 10,000 was 2.4 % and the highest negative deviation was 1.8 %. None had a deviation of up to 5 %.

It is evident from these results that tablets from all the three formulae have an acceptable standard of weight uniformity and have therefore passed the test.

Table 4:3 Weight variation of tablets prepared from pure hydrochlorothiazide

Average weight of 20 tablets is 497 mg

Weight of Tablet (mg)	% of average weight	% deviation from average weight
527	106.0	+6.0
515	103.6	+3.6
489	98.4	-1.6
490	98.6	-1.4
509	102.4	+2.4
496	99.8	-0.2
484	97.4	-2.6
497	100.0	0.0
492	99.0	-1.0
480	96.6	-3.4
509	102.4	+2.4
490	98.6	-1.4
489	98.4	-1.6
481	96.8	-3.2
494	99.4	-0.6
509	102.4	+2.4
490	98.6	-1.4
491	98.8	-1.2
490	98.6	-1.4
510	102.6	+2.6

Table 4:4 Weight variation of tablets prepared from 30 % hydrochlorothiazide – urea coprecipitate average weight of twenty tablets is 503 mg

Weight of tablet (mg)	% of average weight	% deviation from average weight
500	99.4	-0.6
497	98.8	-1.2
500	99.4	-0.6
503	100.0	0.0
502	99.8	-0.2
496	98.6	-1.4
509	101.2	+1.2
507	100.8	+0.8
497	98.8	-1.2
520	103.4	+3.4
498	99.0	-1.0
516	102.6	+2.6
498	99.0	-1.0
504	101.2	+1.2
489	97.2	-2.8
500	99.4	-0.6
498	99.0	-1.0
504	101.2	+1.2
513	102.0	+2.0
504	101.2	+1.2

Table 4:5 Weight variation of tablets prepared from 30 % hydrochlorothiazide - PVP 10,000 coprecipitate.
Average weight of 20 tablets is 501 mg

Weight of tablet (mg)	% of average weight	% deviation from average weight
499	99.6	-0.4
508	101.4	+1.4
496	99.0	-1.0
505	100.8	+0.8
495	98.8	-1.2
513	102.4	+2.4
499	99.6	-0.4
512	102.2	+2.2
492	98.2	-1.8
498	99.4	-0.6
509	101.6	+1.6
496	99.0	-1.0
505	100.8	+0.8
499	99.6	-0.4
493	98.4	-1.6
500	99.8	-0.2
500	99.8	-0.2
497	99.2	-0.8
502	100.2	+0.2
492	98.2	-1.8

4.5.2 UNIFORMITY OF DIAMETER OF TABLETS

4.5.2.1 METHOD.

Ten tablets were selected at random and their diameters measured by means of a micrometer screw gauge. These were compared to the theoretical diameter of the tablets which correspond to the diameter of the die used in producing the tablets. A deviation of up to $\pm$ 5 % is acceptable for tablets with diameter of up to 12.5 mm. (British pharmacopoeia, 1980).

4.5.2.2 RESULTS AND DISCUSSION

Tables 4.6 to 4.8 show the diameters of various tablets produced from pure hydrochlorothiazide and its coprecipitates with urea and PVP 10,000. From these results, none of the tablets had a deviation from the theoretical tablet diameter (12 mm) of up to $\pm$ 5 %. They are therefore considered to be of acceptable uniformity in diameter.

Table 4:6 Uniformity of diameter of tablets prepared from pure hydrochlorothiazide:
Theoretical tablet diameter 12.0 mm

Diameter of tablet (mm)	% of theoretical diameter	% deviation from theoretical diameter
12.10	100.8	+0.8
12.00	100.0	0.0
12.00	100.0	0.0
12.00	100.0	0.0
12.05	100.4	+0.4
12.10	100.8	+0.8
12.05	100.4	+0.4
12.00	100.0	0.0
12.00	100.0	0.0
12.01	100.1	+0.1

Table 4.7 Uniformity of diameter of tablets prepared from hydrochlorothiazide - urea coprecipitate: Theoretical tablet diameter: 12.0 mm

Diameter of tablet (mm)	% of theoretical diameter	% deviation from theoretical diameter
12.07	100.6	+0.6
12.10	100.8	+0.8
12.05	100.4	+0.4
12.05	100.4	+0.4
12.04	100.3	+0.3
12.11	100.9	+0.9
12.09	100.8	+0.8
12.00	100.0	0.0
12.00	100.0	0.0
12.04	100.3	+0.3

Table 4.8 Uniformity of diameter of tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate.

Theoretical tablet diameter: 12.0 mm

Diameter of tablet (mm)	% of theoretical diameter	% deviation from theoretical diameter
12.04	100.3	+0.3
12.00	100.0	0.0
12.02	100.2	+0.2
12.02	100.2	+0.2
12.03	100.3	+0.3
12.03	100.3	+0.3
12.01	100.1	+0.1
12.00	100.0	0.0
12.02	100.2	+0.2
12.01	100.1	+0.1

4.5.3 FRIABILITY TEST

4.5.3.1 METHOD

Ten tablets were brushed gently with a camel hair brush and weighed together on an analytical balance. All the ten tablets were then put in a Roche Friabilator and rotated at 25 r.p.m. for four minutes; that is 100 revolutions. The tablets were then removed and gently brushed again to remove excess powder and weighed. The

loss in weight and thus the percentage loss in weight over the original weight were calculated. A weight loss of up to 0.8 % is generally considered acceptable.

$$\text{Percentage weight loss} = \frac{(\text{Original weight} - \text{Final weight}) \times 100}{\text{Original weight}},$$

4.5.3.2 RESULTS AND DISCUSSION

Table 4.9 show the results for the friability tests on all the three formulations. The weight loss obtained with all the three sets of tablets used ranged from 0.61 % to 0.71 % which is less than 0.8 %. This means that the tablets are strong enough to resist the hazards of normal handling which may cause them to chip.

Table 4:9 Friability test performed on tablets prepared from pure hydrochlorothiazide and it's coprecipitate with urea and PVP 10,000

Tablets prepared with	Original weight of ten tablets (g)	Final weight of ten tablets (g)	Loss in weight (g)	% loss in weight
Pure hydrochlorothiazide	4.950	4.920	0.030	0.61
Hydrochlorothiazide - urea coprecipitate	4.971	4.936	0.035	0.71
PVP 10,000	4.960	4.925	0.035	0.71

4.5.4 HARDNESS TEST

4.5.4.1 METHOD

The Stokes - Monsanto hardness tester was used for this investigation. One tablet is placed between the two plungers and compressed between them by means of a threaded bolt and compressible string. The pressure at which the tablet breaks is indicated by a pointer which moves along a gauge as the string is compressed. Ten tablets from each formulation were tested individually.

4.5.4.2 RESULTS

Table 4:10 Hardness test on tablets prepared from pure hydrochlorothiazide and its coprecipitates with urea and PVP 10,000

Tablet serial number	Breaking Force (kg)		
	Tablets from pure hydrochlorothiazide	Tablets from hydrochlorothiazide-urea coprecipitate	Tablets from hydrochlorothiazide-PVP 10,000
1	4.0	4.0	4.0
2	3.9	4.0	4.0
3	4.0	4.2	4.0
4	4.0	4.0	4.2
5	3.8	4.0	4.0
6	3.9	3.8	4.0
7	4.0	4.0	4.0
8	4.0	3.9	3.8
9	4.1	4.0	4.0
10	3.8	4.0	3.9
Average	3.95	3.99	3.99

4.5.5 UNIFORMITY OF CONTENTS

4.5.5.1 METHOD

Ten tablets were weighed individually and each crushed to make a powder. Each powder was mixed uniformly with 100 ml of distilled water. 2 ml of this solution was filtered through a millipore filter paper (Pore diameter 0.45 μ) and further diluted to 100 ml with distilled water. The solution obtained was then assayed spectrophotometrically, at 273 nm wavelength, for hydrochlorothiazide content.

The USP XIX, (1975) recommends that at least nine of the ten tablets tested should contain $\pm$ 15 % of the labelled amount of drug and that none exceeds $\pm$ 25 %.

4.5.5.2 RESULTS AND DISCUSSION

Tables 4.11 to 4.13 show the results for determination of the uniformity of hydrochlorothiazide in the three different tablet formulations. The results revealed that all the formulations met the required USP standards for uniformity of contents and have therefore passed the test. The even distribution of hydrochlorothiazide in the various tablets produced

could be attributed to an effective mixing procedure. [illegible] of the various tablet [illegible].

Table 4:11 Uniformity of contents of tablets prepared from pure hydrochlorothiazide

Absorbance at 273 nm	Equivalent hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% Hydrochlorothiazide content
0.278	50.5	50.0	101.0
0.269	48.9	50.0	97.8
0.287	52.2	50.0	104.4
0.278	50.5	50.0	101.0
0.278	50.5	50.0	101.0
0.281	51.1	50.0	102.2
0.274	49.8	50.0	99.6
0.274	49.8	50.0	99.6
0.279	50.7	50.0	101.4
0.269	48.9	50.0	97.8

Table 4:12 Uniformity of contents of tablets prepared from hydrochlorothiazide - urea coprecipitate

Absorbance at 273 nm	Equivalent hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% hydrochlorothiazide content
0.278	50.5	50.0	101.0
0.280	50.9	50.0	101.8
0.280	50.9	50.0	101.8
0.283	51.5	50.0	103.0
0.285	51.8	50.0	103.6
0.283	51.5	50.0	103.0
0.280	50.9	50.0	101.8
0.275	50.0	50.0	100.0
0.279	50.7	50.0	101.4
0.283	51.5	50.0	103.0

Table 4:13 Uniformity of contents of tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate

Absorbance at 273 nm	Equivalent hydrochlorothiazide content (mg)	Theoretical hydrochlorothiazide content (mg)	% hydrochlorothiazide content
0.277	50.4	50.0	100.8
0.277	50.4	50.0	100.8
0.276	50.2	50.0	100.4
0.278	50.5	50.0	101.0
0.278	50.5	50.0	101.0
0.276	50.2	50.0	100.4
0.277	50.4	50.0	100.8
0.277	50.4	50.0	100.8
0.278	50.5	50.0	101.0
0.278	50.5	50.0	101.0

4.5.6 DISINTEGRATION TEST

4.5.6.1 METHOD

The disintegration test was carried out using the basket-rack method as described in the USP XIX, (1975). The medium was distilled water maintained at 37°C by means of a thermostatically controlled water bath. The disintegration times of six tablets from each of the three formulations were recorded individually and the average calculated. Disintegration in this context implies a state in which any residue of the tablet remaining on the screen of the test apparatus is a soft mass having no palpable firm core.

4.5.6.2 RESULTS AND DISCUSSION

Table 4:14 shows the disintegration times of tablets from the three formulations. The USP recommends an average of 15 minutes for plain uncoated tablets to disintegrate completely. It is therefore clearly seen from these results that the tablets have passed the disintegration test.

Table 4:14 Disintegration times (in minutes) of tablets prepared from pure hydrochlorothiazide and its coprecipitates with urea and PVP 10,000 in distilled water at 37°C

Tablet serial number	Tablets prepared from pure hydrochlorothiazide	Tablets prepared from hydrochlorothiazide-urea coprecipitate	Tablets prepared from hydrochlorothiazide - PVP coprecipitate
1	10.1	10.0	11.0
2	9.8	10.1	11.2
3	10.2	10.5	11.5
4	10.9	11.3	12.2
5	12.0	11.5	12.5
6	12,0	12,2	13.5
Average	10.8	10.9	12.0

4.5.7 DISSOLUTION RATE STUDIES

4.5.7.1 METHOD

The rotating basket method described in the USP XIX (1975) was used to determine the dissolution profile of the tablets. The dissolution medium was 900 ml of distilled water maintained at 37°C by means of a thermostatically controlled water bath heater. The basket was rotated at 150 r.p.m..

5 ml aliquots were withdrawn, filtered through a millipore filter paper (pore diameter 0.45 μ) and quantitatively diluted to 25 ml with distilled water. The resulting solutions were then assayed spectrophotometrically at 273 nm wavelength to determine the hydrochlorothiazide content. Every 5 ml of the test sample removed was replaced with 5 ml of distilled water at the same temperature to maintain a constant volume of the medium. Corrections was made for the amount of drug previously withdrawn in each case using the method of Wurster and Taylor, (1965).

4.5.7.2 RESULTS AND DISCUSSION

Tables 4:15 to 4:17 and figure 4:1 show the results of the dissolution rate test performed on the tablets. Tablets formulated from the pure hydrochlorothiazide had the least dissolution rate when compared to those for which the coprecipites of hydrochlorothiazide with urea and PVP 10,000 were used. This difference is expected as coprecipitates are fast release systems and are expected to release the drug faster into solution than the pure crystalline form of the drug. Tablets prepared from the coprecipitate of hydrochlorothiazide with PVP had dissolution rates superior to those from the coprecipitates with urea.

This is in agreement with previous observations (3.4.4) made with the powder samples.

Table 4:15 Dissolution rate data for tablets prepared from pure hydrochlorothiazide in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/900 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.056	4.58	9.2
10	0.100	8.18	16.4
15	0.162	13.25	26.6
20	0.205	16.77	33.8
30	0.296	24.22	48.9
45	0.372	30.44	61.6
60	0.432	35.35	71.8
75	0.495	40.50	82.5
90	0.540	44.18	90.3

Table 4:16 Dissolution rate data for tablets prepared from hydrochlorothiazide - urea coprecipitate, in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/900 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.106	8.67	17.3
10	0.200	16.36	32.8
15	0.296	24.22	48.7
20	0.355	29.05	58.6
30	0.429	35.10	71.1
45	0.479	39.19	79.6
60	0.499	40.83	83.4
75	0.540	44.18	90.5
90	0.579	47.37	97.4

Table 4:17 Dissolution rate for tablets prepared from hydrochlorothiazide - PVP 10,000 coprecipitate, in distilled water at 37°C

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/900 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.115	9.41	18.8
10	0.211	17.26	34.6
15	0.308	25.20	50.6
20	0.372	30.44	61.4
30	0.485	39.68	80.2
45	0.572	46.80	95.0
60	0.595	48.68	99.2
75	0.595	48.68	99.8
90	0.593	48.52	100.0

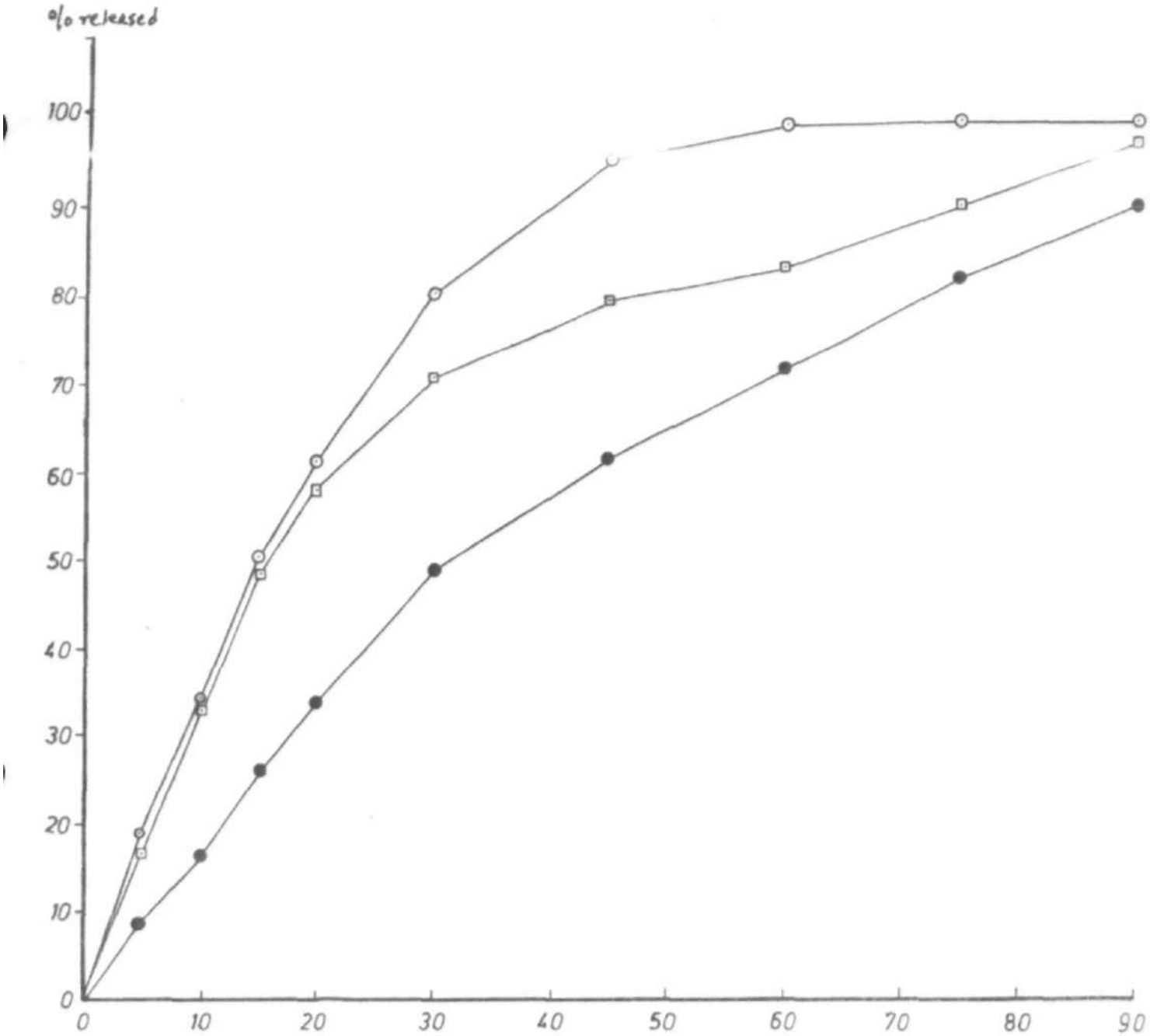


FIG. 4:1 Dissolution profiles of tablets prepared from pure hydrochlorothiazide (●); 30% coprecipitates of hydrochlorothiazide with urea (⊡) and polyvinylpyrrolidone 10,000 (⊙) in distilled water at 37° C.

CHAPTER FIVE

AGING STUDIES

It is well established that aging has a significant effect on the dissolution rate of solid dispersed systems (Allen and Kwan, 1969; Chiou and Niazi, 1971; Ford and Rubinstein, 1977; 1980). This has been attributed to various changes that occur in the system which, to a great extent, depends on the nature of interaction existing between the components of the system or even changes in the physical nature of the drug alone. Aging effects associated with solid dispersions could be manifested as precipitation of the drug from supersaturated solid and glass solutions or crystal transformation of substances that are polymorphic in nature. This and other physico-chemical changes that may occur in such systems have been reviewed by Chiou and Riegelman, (1971a).

The aging studies were designed to find out the effect of storage (of tablets formulated from pure hydrochlorothiazide and from its coprecipitates with urea and PVP 10,000) under various humidity conditions and the storage time on the drug release pattern (dissolution profile).

5.1 STORAGE CONDITIONS

The storage conditions employed in this study were 98 % and 75 % relative humidity and ordinary room conditions having a humidity ranging from 6 % to 30 % and a temperature from 20°C to 35°C. The 98 % R.H. was maintained in a desiccator by means of a saturated solution of disodium phosphate while a saturated solution of sodium chloride provided 75 % R.H. conditions. The tablets were stored under these conditions for a duration of 105 days.

5.2 EVALUATION OF AGED TABLETS

5.2.1 DISSOLUTION RATE TESTS

5.2.1.1 METHOD

Dissolution rate tests were performed on the aged tablets after storage for 40 and 105 days under the various conditions stipulated. These were carried out using the method described earlier (4.5.7). Dissolution rate tests were carried out thrice for each formulation stored under each experimental condition.

5.2.2 DISINTEGRATION TESTS

5.2.2.1 METHOD

Disintegration tests were carried out after storage for 105 days. The basket-rack method described earlier (4.2.6) was used. Six tablets were used in each case and the average disintegration time recorded.

5.3 RESULTS AND DISCUSSION

After 40 days of storage, it was observed that all the tablets stored under 98 % R.H. had absorbed so much moisture that they lost their consistency. This made it impossible for the dissolution rate tests to be carried out on these tablets. Though tablets stored under 75 % R.H. still maintained their consistency, the tablets prepared from hydrochlorothiazide coprecipitates with urea were softer than all the others. There was however little or no change in the physical texture of tablets stored under 6 to 30 % R.H.

After 105 days of storage, the tablets made from hydrochlorothiazide coprecipitate with urea, which were stored under 75 % R.H. had absorbed so much moisture that they lost their consistency.

Tablets formulated from the pure hydrochlorothiazide and its coprecipitate with PVP 10,000 stored under the same conditions still maintained their texture and consistency. Infact those from coprecipitates with PVP 10,000 had hardened. On the other hand, tablets prepared from hydrochlorothiazide-urea coprecipitate and stored under 6 to 30 % R.H. had absorbed moisture and were a little bit soft to touch. Other tablets however, did not change significantly.

Tables 5.1 to 5.11 and Figures 5.1 to 5.3 show the results for the dissolution rate tests performed on the aged tablets stored under the different experimental conditions. Table 5.12 shows the average disintegration times for the various tablets after storage for 105 days.

These results show that the disintegration time of tablets prepared from the pure hydrochlorothiazide and its coprecipitate with PVP 10,000 were increased after storage under 6 to 30 % and 75 % R.H. for 105 days. Contrary to these observations, there was a dramatic reduction in the disintegration time of tablets prepared from hydrochlorothiazide-urea coprecipitates and stored under the same conditions. Infact the average

disintegration time of these tablets was reduced to about one fiftieth when compared to that of freshly prepared tablets from the same hydrochlorothiazide-urea coprecipitate. It may be inferred from those results that the presence of urea increased the water absorption capacity of these tablets. As earlier mentioned (2.1.2c), urea is slightly hygroscopic in nature. This may also be the rational explanation to the change in texture and consistency of tablets prepared from hydrochlorothiazide-urea coprecipitate when exposed to a moist environment (of 75 % and 98 % R.H.) for a long time. Additionally, it can clearly be appreciated that the amount of moisture absorbed increases with increasing R.H. of the storage environment.

Although PVP has some hygroscopic characteristics too, it seem to have a unique aging pattern. The aged tablets were a little bit harder than the freshly prepared tablets. This could explain the observed protracted disintegration times of tablets formulated from pure hydrochlorothiazide and it's coprecipitate with PVP 10,000.

The dissolution rate data revealed that the tablets prepared from hydrochlorothiazide-urea coprecipitate were most sensitive to moisture. The effect of moisture was clearly seen to be dependent on the length of time for which the tablets were exposed to the moist environment. Generally, increased dissolution rates were observed for these products and this could be due

Table 5,1 Dissolution rate data for aged tablets prepared from pure hydrochlorothiazide in distilled water at 37°C

Duration of Storage: 40 days R.H. : 6 to 30 %

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/900 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.047	3.85	7.7
10	0.093	7.61	15.3
15	0.142	11.62	23.4
20	0.196	16.04	32.3
30	0.276	22.58	45.6
45	0.355	29.05	58.8
60	0.398	32.56	66.1
75	0.435	35.59	75.6
90	0.486	39.68	81.1

Table 5.2 Dissolution rate data for aged tablets prepared from pure hydrochlorothiazide in distilled water at 37°C

Duration of storage: 105 days
R. H. 6 to 30 %

Time (minutes)	Mean absorbance at 37°C	Amount of hydrochlorothiazide released (mg/900 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.061	4.99	10.0
10	0.115	9.41	18.9
15	0.179	14.65	29.5
20	0.250	20.45	41.3
30	0.354	28.96	58.7
45	0.440	36.40	72.9
60	0.500	40.90	83.1
75	0.536	43.85	89.4
90	0.553	45.25	92.7

Table 5.3 Dissolution rate data for abed tablet prepared from pure hydrochlorothiazide in distilled water at 37°C Duration of storage: 40 days R.H. 75 %.

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/900 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.069	5.65	11.3
10	0.127	10.39	20.8
15	0.186	15.22	30.6
20	0.237	19.39	39.1
30	0.328	26.84	54.2
45	0.408	33.38	67.6
60	0.440	36.00	73.2
75	0.466	38.13	77.9
90	0.470	38.45	79.0

Table 5.4 Dissolution rate data for aged tablets prepared from pure hydrochlorothiazide in distilled water at 37°C. Duration of storage: 105 days R.H. 75 %

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/900 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.077	6.30	12.6
10	0.135	11.05	22.2
15	0.196	16.04	32.3
20	0.242	19.80	40.0
30	0.335	27.41	55.4
45	0.413	33.79	68.5
60	0.448	36.65	74.6
75	0.471	39.03	79.7
90	0.478	39.11	80.3

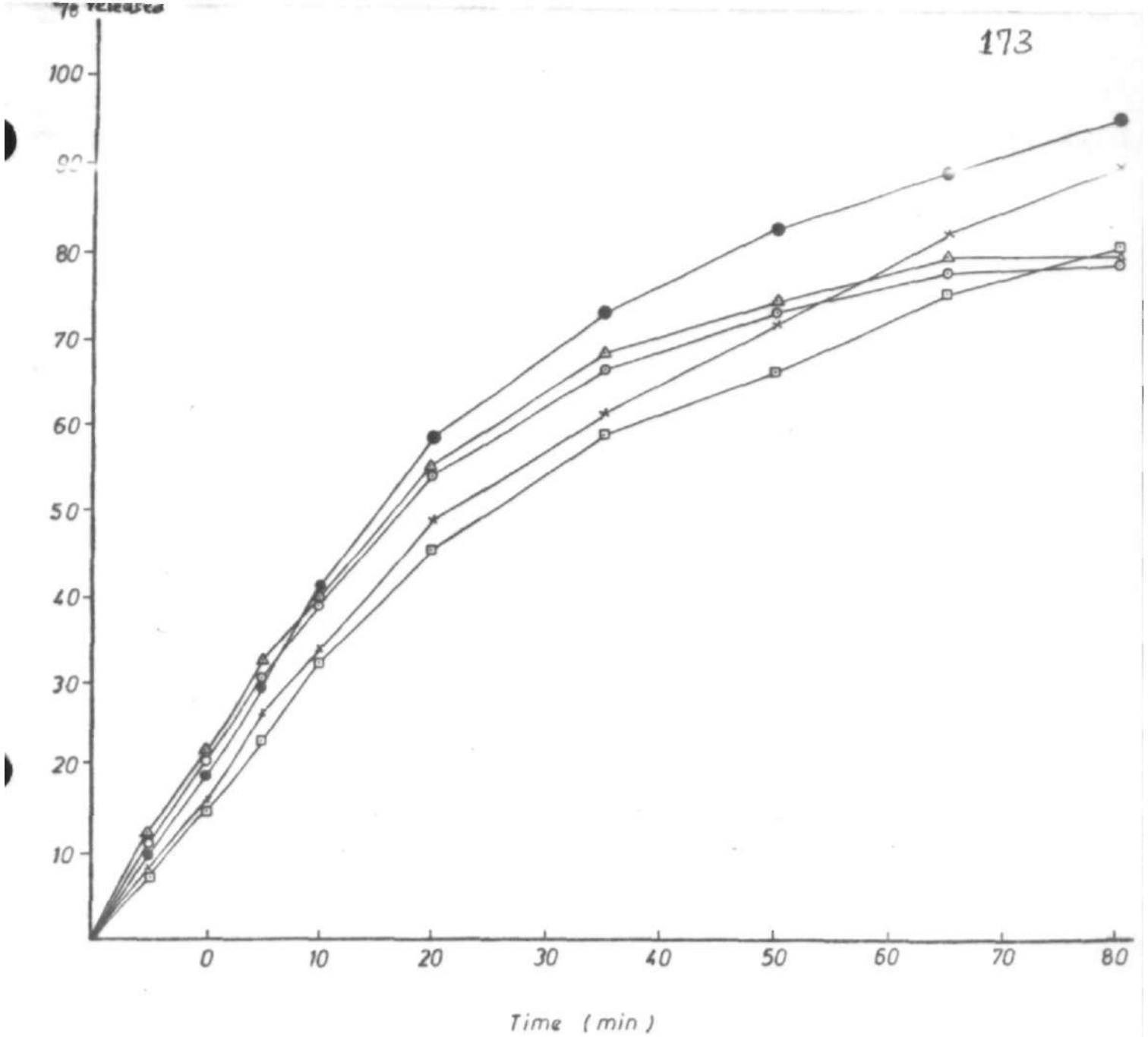


FIG. 5:1 Dissolution profiles of fresh and aged tablets (after storage at various relative humility conditions for 40 and 105 days) prepared from pure hydrochlorothiazide in distilled water at 37°C.

x Fresh tablets.

▫ Tablets stored under room conditions for 40 days.

● Tablets stored under room conditions for 105 days.

⊙ Tablets stored under 75% relative humidity for 40 days.

▲ Tablets stored under 75% relative humidity for 150 days.

Table 5.5 Dissolution rate data for aged tablets prepared from hydrochlorothiazide-urea coprecipitate in distilled water at 37°C.
Duration of storage: 40 days
R.H: 6 to 30 %

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/900 ml)	% hydrochlorothiazide released
0	0,000	0.00	0.0
5	0.270	22.09	44.2
10	0.310	25.36	51.0
15	0.350	28.64	57.8
20	0.392	32.07	65.0
30	0.449	36.40	74.0
45	0.485	39.70	81.0
60	0.513	41.98	84.7
75	0.534	43.69	89.9
90	0.556	45.49	94.0

Table 5.6 Dissolution rate data for aged tablets prepared from hydrochlorothiazide-urea coprecipitate in distilled water at 37°C.
Duration of storage: 40 days
R.H. 75 %

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/900 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.474	38.78	77.6
10	0.485	39.68	79.8
15	0.494	40.42	81.7
20	0.500	40.91	83.1
30	0.518	42.38	86.5
45	0.532	43.52	89.3
60	0.556	45.49	93.7
75	0.576	47.13	97.5
90	0.591	48.35	100.5

Table 5.7 Dissolution rate data for aged tablets prepared from hydrochlorothiazide-urea coprecipitates in distilled water at 37°C.
Duration of storage: 105 days
R.H.: 6 to 30 %

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochlorothiazide released (mg/900 ml)	% hydrochlorothiazide released
0	0.000	0.00	0.0
5	0.324	26.51	53.0
10	0.360	29.45	59.2
15	0.402	32.89	66.4
20	0.425	34.77	70.5
30	0.463	37.88	77.1
45	0.497	40.66	83.1
60	0.528	43.20	88.6
75	0.544	44.51	91.7
90	0.546	44.67	92.5

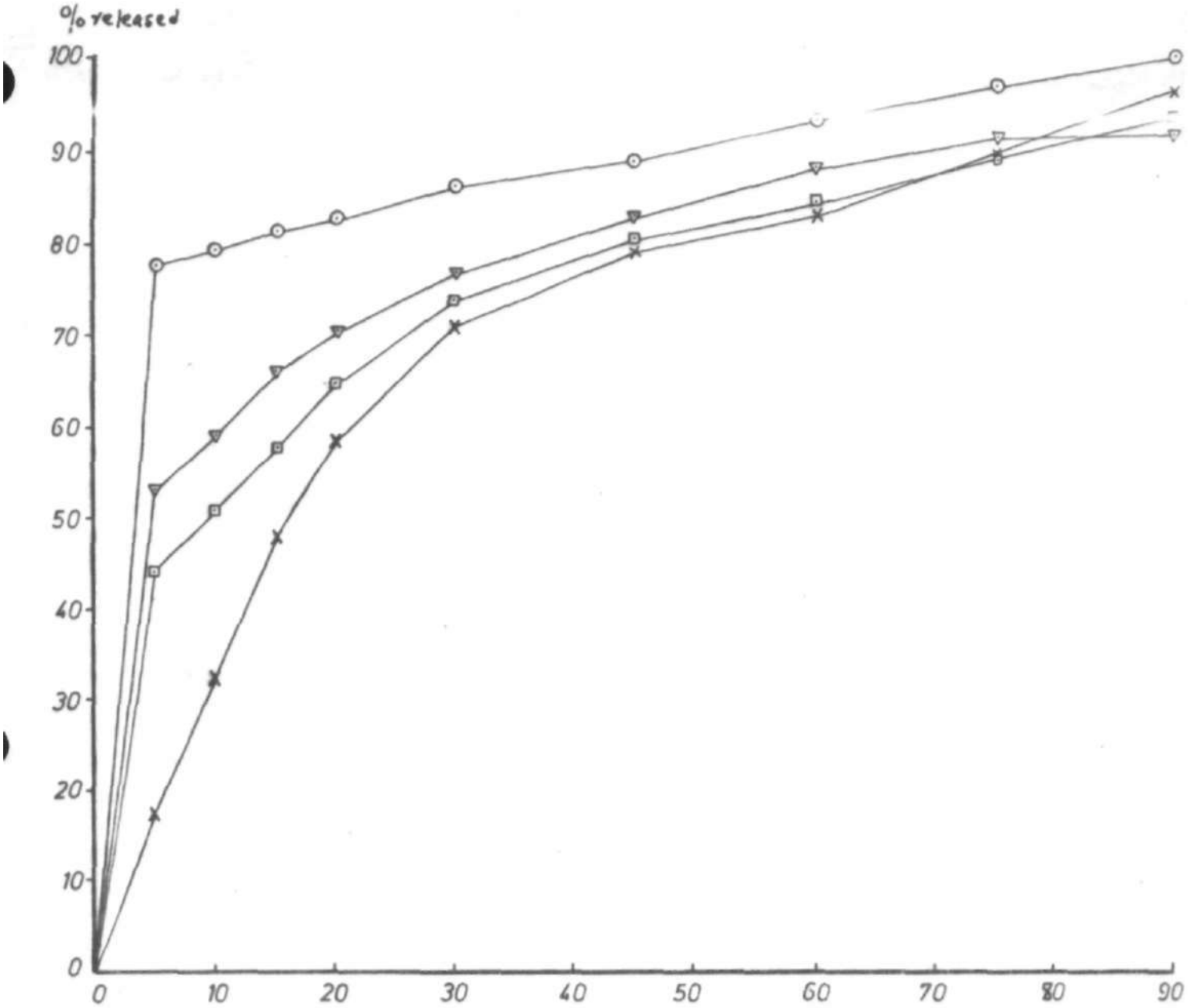


FIG. 5 : 2 Dissolution profiles of fresh and aged tablets (after storage at various relative humidity conditions for 40 and 105 days) prepared from 30% hydrochlorothiazide - urea coprecipitate in distilled water at 37° C.

x Freshly prepared tablets

▫ Tablets stored under room conditions for 40 days.

▲ Tablets stored under room condition for 105 days.

⊙ Tablets stored under 75% relative humidity for 40 days.

Table 5.8 Dissolution rate data for aged tablets prepared from hydrochlorothiazide-PVP 10,000 coprecipitate in distilled water at 37°C
Duration of storage: 40 days
R.H. 6 to 30 %

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/900 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.098	8.02	16.0
10	0.168	13.75	27.6
15	0.245	20.05	40.3
20	0.323	26.43	53.3
30	0.425	34.77	70.3
45	0.520	42.55	86.2
60	0.544	44.51	90.6
75	0.561	45.90	93.9
90	0.579	47.37	97.4

Table 5.9 Dissolution rate data for aged tablets prepared from hydrochlorothiazide-PVP 10,000 coprecipitate in distilled water at 37°C.
Duration of storage: 105 days
R.H.: 6 to 30 %

Time (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/900 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.137	11.20	22.4
10	0.226	18.49	37.1
15	0.307	25.12	50.6
20	0.386	31.58	63.8
30	0.495	40.50	82.0
45	0.583	47.70	96.8
60	0.593	48.52	99.0
75	0.596	48.76	100.0
90	0.599	49.01	101.0

Table 5.10 Dissolution rate data for aged tablets prepared from hydrochlorothiazide-PVP 10,000 coprecipitate in distilled water at 37°C.
Duration of storage: 40 days.
R.H. 75 %

Time in (minutes)	Mean absorbance at 273 nm	Amount of hydrochloro-thiazide released (mg/900 ml)	% hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.093	7.61	15.2
10	0.149	12.19	24.5
15	0.200	16.36	32.9
20	0.244	19.96	40.3
30	0.306	25.04	50.7
45	0.393	32.15	65.2
60	0.422	34.53	70.3
75	0.445	36.41	74.5
90	0.475	38.86	79.8

Table 5.11 Dissolution rate data for aged tablets prepared from hydrochlorothiazide-PVP 10,000 coprecipitate in distilled water at 37°C.

Duration of storage: 105 days.
R.H.: 75 %

Time (minutes)	Mean absorbance at 273 nm	Amount of Hydrochloro-thiazide released (mg/900 ml)	% Hydrochloro-thiazide released
0	0.000	0.00	0.0
5	0.095	7.77	15.5
10	0.170	13.91	27.9
15	0.221	18.08	36.4
20	0.256	20.95	42.3
30	0.333	27.25	55.2
45	0.428	35.02	71.0
60	0.453	37.06	75.5
75	0.486	39.76	81.3
90	0.510	41.73	85.7

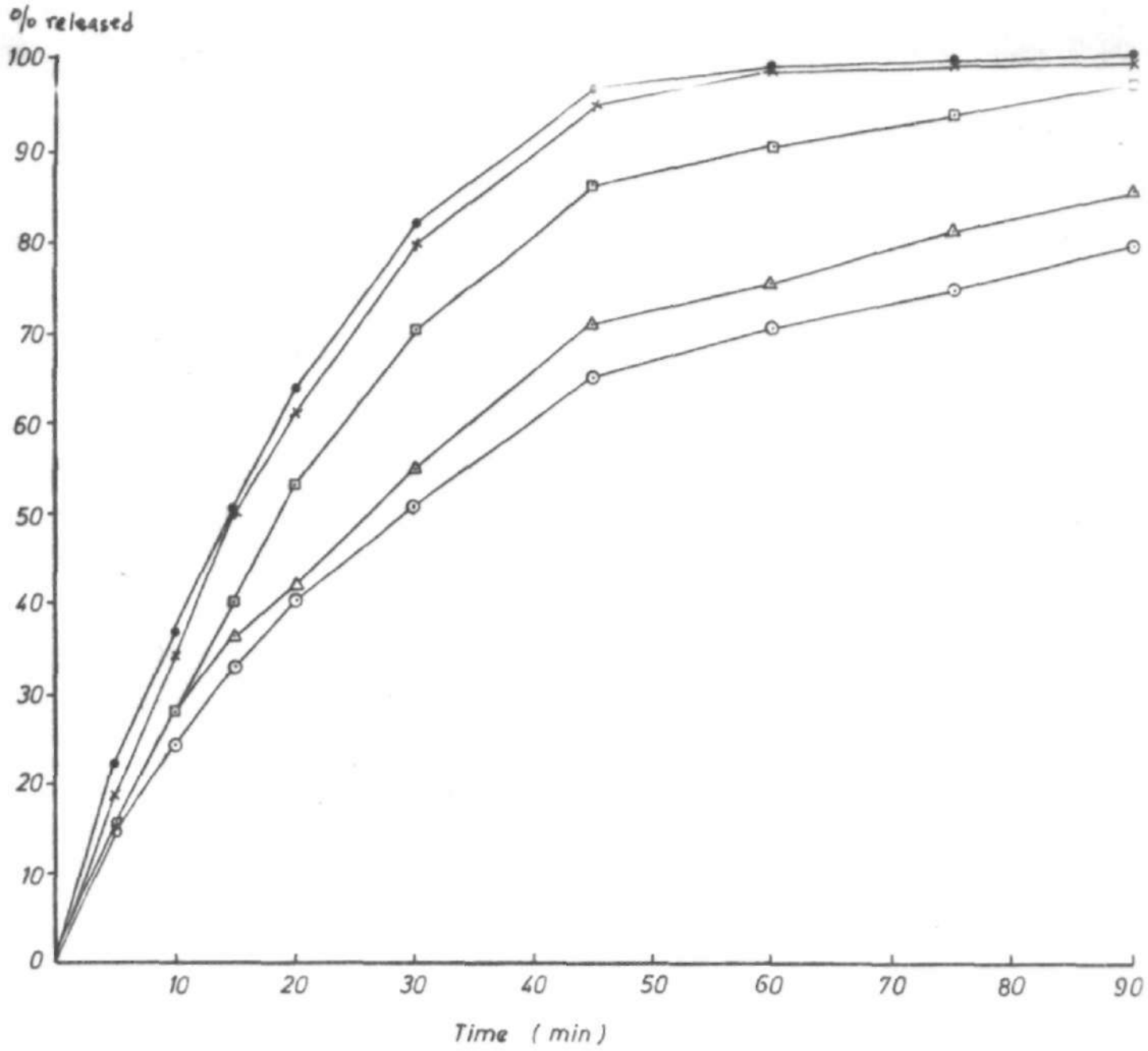


FIG. 5:3 Dissolution profiles of fresh and aged tablets (after storage at various relative humidity conditions for 40 and 105 days) prepared from 30% hydrochlorothiazide - polyvinylpyrrolidone 10 000 coprecipitate in distilled water at 37° C.

x Freshly prepared tablets.

▫ Tablets stored under room conditions for 40 days.

● Tablets stored under room comditions for 150 days.

⊙ Tablets stored under 75% relative humidity for 40 days.

▲ Tablets stored under 75% relative humidity for 105 days.

Table 5.12 Average disintegration times for tablets prepared from pure hydrochlorothiazide and it's coprecipitates with urea and PVP 10,000 in distilled water at 37°C.

Tablet formulation	6 - 30 % R.H.	75 % R.H.	98 % R.H.
Pure hydrochlorothiazide	15.5 min.	13.0 min.	-
Hydrochlorothiazide-urea coprecipitate	0.2 min.	-	-
Hydrochlorothiazide-PVP 10,000 coprecipitate	25.9 min.	30 min.	-

to solubilization of the drug in the tablet prior to exposure to the dissolution medium; a consequence of the significant amount of moisture absorbed into the tablet. This is attested by the increasing initial dissolution rates with increasing relative humidity and time of storage. Increased storage time allows for more moisture absorption. This claim is demonstrated by the dissolution rate data for tablets from hydrochlorothiazide-urea coprecipitates stored under 6 to 30 % R.H. for 40 and 105 days with the latter having a superior dissolution profile. Moreover the disintegration times of these tablets were reduced implying that more surface is exposed faster to the dissolution medium during the test. Similar increase in the dissolution rate with age have been reported for

coprecipitates of chlorpropamide with urea (Ford and Rubeinstein, 1977).

Tablets prepared from hydrochlorothiazide-PVP 10,000 showed a general decrease in the dissolution rate after storage under all the experimental conditions. This could be attributed to the hardening characteristic of these products with age. Furthermore, depending on the nature in which hydrochlorothiazide exist in the PVP, one or a combination of the following changes may be contributory factors to the observed decrease in dissolution rates. Such changes include, precipitation of hydrochlorothiazide from solid solutions and glass solutions, increased crystallinity with age or transformation into a more stable crystalline form such as that observed for sulfathiazole dispersed in urea after storage at 105°C for about one hour (Chiou and Niazi, 1971). Other possible changes may be increased particle size of the drug or coarsening of eutectics. Decreased dissolution rate with age have been reported for indomethacin in dispersion with polyethylene glycol (Allen and Kwan, 1969; Ford and Rubeinstein, 1980). However, investigations into the exact nature of interaction between hydrochlorothiazide and urea or PVP was not carried out.

From figure 5.1, the tablets prepared from pure hydrochlorothiazide showed the least variability in the dissolution rates after storage under all the experimental conditions. This observation further supports the claim that decreased dissolution rates of tablets prepared from hydrochlorothiazide-PVP may significantly be dependant on changes that may have occured in the physical nature of hydrochlorothiazide in these two substances. The average disintegration time of these tablets were also not significantly altered especially when compared to those prepared from hydrochlorothiazide coprecipitates with urea and PVP 10,000. Such apparently indifferent disintegration time should lead to similar dissolution profiles with all parameters being equal.

Summarily, one would say that while exposure of tablets prepared from hydrochlorothiazide-PVP coprecipitate showed a definite decrease in dissolution rates after storage, the dissolution rates of tablets prepared from hydrochlorothiazide-urea coprecipitate were increased. The changes in dissolution rates were also found to be dependent on the R.H.(moisture content of the atmosphere and the time for which the tablets are exposed.

However, the very serious disadvantage associated with tablets from hydrochlorothiazide-urea coprecipitate, which may affect the practical applicability of the solid dispersion technique, is that on prolonged exposure to the atmosphere, the tablets may get too soft to resist reasonable rigours of handling and transportation thereby loosing its potential qualities as a good pharmaceutical product.

GENERAL SUMMARY AND CONCLUSION

Hydrochlorothiazide, a poorly water soluble diuretic, has been found to be stable when coprecipitated with readily water soluble carriers; PVP 10,000, 44,000 and urea.

Aqueous solubility studies indicated a resasonable evidence of interaction between hydrochlorothiazide and these carriers in solution. This is evident by increase in the solubility of hydrochlorothiazide in the presence of the carriers. However, the infrared spectra showed no evidence of interaction in the solid state.

There was a general increase in the dissolution rate of hydrochlorothiazide from the physical mixtures and coprecipitates when compared to the pure drug alone. While increases from the physical mixture was accredited to local solubilization of hydrochlorothiazide by the readily soluble carriers, that from the coprecipitates may be due to one or a combination of the following; particle size reduction, precipitation of hydrochlorothiazide in a thermodynamically unstable armophous form which usually has better solubility than the crystalline form. Improved wettability and dispersibility of the drug particles coupled with a possible reduction of electrostatic attractive forces may be contributory factors.

The dissolution rate of hydrochlorothiazide from compressed tablets prepared from its coprecipitates with PVP 10,000 and urea were similarly increased when compared to those from the pure drug.

On storage humidity has a significant influence on the dissolution profile of those tablets prepared from the solid dispersions. While a definite increase in dissolution rate was observed with the urea coprecipitate, those from the PVP coprecipite showed a decrease. Additionally, tablets prepared from the dispersion with urea absorbed so much moisture that the desired mechanical strength of a good product were lost. This implies that when such area products are likely to be stored for a long period before use (particularly solid dosage forms), they must be adequately protected from moisture so as to preserve the good physical characteristics of the product.

In conclusion, while the solid dispersion technique has been demonstrated to be of biopharmaceutical significance, the choice of carrier is critical in attaining reasonable increase in the dissolution rate of poorly soluble drugs and in maintaining the qualities of a good pharmaceutical product.

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