PREPARATION AND DISSOLUTION STUDIES OF SOLID.. DISPERSIONS OF POORLY SOLUBLE HYPQGLYCAEMIC AGENT- ACETOHEXAMIDE

By

OGABOR OCHIGBOR FRANCIS

A THESIS SUBMITTED TO THE POSTGRADUATE SCHOOL, AHMADU BELLO UNIVERSITY, IN" "PARTIAL" FULFILMENT OF THE DEGREE

OF

. ..**MASTER OF SCIENCE (IN** PHARMACEUTICAL TECHNOLOGY)

DEPARTMENT OF PHARMACEUTICS
FACULTY OF PHARMACEUTICAL SCIENCES
AHMADU BELLO UNIVERSITY, ZARIA

FEBRUARY, 1983

COPY-RIGHT RESERVED

.'"

i

. . . . .; / .

A P P R O V A L

This thesis submitted by Ogabor Ochigbor Francis meets the regulations governing the award of the degree of Master of Science (Pharmacy) of the Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, and it is approved for its contribution to Sciences and literary presentation.

1. Internal Examiner .....
Dr. D. K. Agrawal (B.Pharm, Dr. Sc. Nat Zurich)
Department of Pharmaceutics,
Faculty of Pharmaceutical Sciences,
Ahmadu Bello University, Zaria.

2. External Examiner .....
Professor H. C. Mital B.Pharm. M.Pharm, Ph.D.
Professor of Pharmaceutics, University of Nigeria, Nsukka.

D E C L A R A T I O N

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 applicati n f r a higher degree. All quotations are distinguished by qu tation marks and the sources of information are specifically acknowledged by means of references.

OGABOR OCHIGBOR FRANCIS

A C K N O W L E D G E M E N T

My sincere thanks to Dr. D. K. Agrawal for suggesting this topic and for his continuous supervision of this research work.

My thanks to Mr. A. V. Deshpande for his very useful advise and support.

I take this opportunity to express my indebtedness to Dr. Jonathan Gbefwi for housing me during my studies.

I also gratefully acknowledge the help of Mr. S. A. E. Ejigonojo, Mr. Bartholomew Oche, Mr. Audu Ogbe and Mr. Clement Onate in my struggle for sponsorship.
My deep appreciation to Lilly Laboratories for supplying Acetohexamide powder and finally to Mr. Boniface Ochefu for typing the thesis.

C O N T E N T S

Page

CHAPTER 1 - INTRODUCTION

1.1. General Introduction 1

1.2. Solid dispersion 5

1.2.1. Method of preparation of solid dispersion 5

1.2.2. Types of solid dispersions 8

1.3. Solid solutions 9

1.4. Simple eutectic mixtures 16

1.4.1. Components completely soluble in liquid state, partially soluble in solid state. 19

1.4.2. Drug release from solid solutions and simple eutectics 21

1.5. The aims and the scope of this work ... 23

1.6. Literature review 25

CHAPTER 2 - CHEMICALS AND MATERIALS

2.1 Carriers tried 37

2.2. The drug 41

2.3. Equipment 42

2.3.1. Spectrophotometers 42

2.3.2. Dissolution rate apparatus used 42

2.4. Problems and precautions of the dissolution rate methods 45

CONTENTS (Contd')

Page

CHAPTER 3 - EXPERIMENTAL STUDIES: PRELIMINARY INVESTIGATION

3.1. Introduction 50

3.1.1. Selection of drug 50

3.1.2. Selection of carriers 51

3.1.3. Screening procedure 51

3.1.4. Results and discussion 53

3.2. Determination of the wavelength of maximum absorbance (λmax.) of acetohexamide 58

3.2.1. Results and discussion 59

3.3. Plotting a standard curve 62

3.3.1. Results and discussion ... 63

3.4. Determination of the solubility of pure acetohexamide in water 65

3.4.1. Results and discussion ... 66

CHAPTER 4 - EXPERIMENTAL STUDIES

Preparation and stability studies of the dispersion 68

4.1. Introduction 68

4.2. Preparation of the dispersion 69

4.2.1. Solid dispersion by melt method ... 69

4.2.2. Solid dispersion by coprecipitate method 69

4.2.3. Preparation of the physical mixtures 73

CONTENTS (Contd')

		Page
4.3.	Stability determination of acetohexamide in the dispersions	74
	4.3.1. Stability determination by thin-layer chromatography ...	74
	4.3.2. Preparation of plates	75
	4.3.3. Method	76
	4.3.4. Results and discussion	77
	4.3.5. Stability determination by spectrophotometry	78
	4.3.6. Method	78
4.4.	The infrared studies (I.R.)	80
	4.4.1 Results and discussion	80
4.5.	The phase diagram	81
	4.5.1. Method	81
	4.5.2 Results	82
	4.5.3. Discussion	83
4.6.	Solubility studies	84
	4.6.1. Method	84
	4.6.2. Results and discussion ...	85
CHAPTER 5 - IN-VITRO DISSOLUTION RATE STUDIES		
5.1.	Introduction	86
5.2.	Comparism of the bag method and the tape method	87
	5.2.1. Method	87
	5.2.2. Calculations	88
	5.2.3. Results and discussion	88
	5.2.4. Conclusion	92

CONTENTS (Contd')

		Page
5.3.	In vitro dissolution rate studies using the tape method	95
5.3.2.	Comparism of results	96
5.3.3.	Discussion of results	122
5.3.4.	Conclusion	131
CHAPTER 6 -	TABLET FORMULATION	
6.1.	Introduction	133
6.2.	The direct compression vehicle	136
6.2.1.	Microcrystalline cellulose PH 101 (Avicel)	138
6.2.2.	Calculations	138
6.2.3.	Method	139
6.3.	Evaluation of tablets	142
6.3.1.	Tablet hardness	142
6.3.2.	Results and discussion ...	142
6.3.3.	Friability test	144
6.3.4.	Results and discussion ...	144
6.3.5.	Tablet disintegration times	146
6.3.6.	Tablet dissolution rate studies ...	148
6.3.7.	Results and discussion	148.
6.4.	General Summary and Conclusion	154
	References	156

CHAPTER I

INTRODUCTION

1.1 GENERAL:

With the evolvement of physical pharmacy, the Pharmaceutical Scientists found that size and hence, surface area of a particle, can be related in a significant way to the physical, chemical and pharmacological properties of a drug. Absorption usually occurs only after solution. The intensity of the pharmacological effect elicited by a drug is usually some function of the concentration of this drug at its site of action which depends on the efficiency and rate of absorption at its route of administration and its diffusion from the blood into the various body fluids and compartments.(19) The drug particle size is of utmost importance in all these processes. For solid drugs of poor water solubility whose gastrointesinal absorption is rate-limited by dissolution, reduction of the drug particle size generally increases dissolution rate.(27) And, increasing the dissolution rate at the absorption site necessarily increases the rate and efficiency of absorption and/or bioavailability which ensures more drug into the body at the site of action before metabolism and excretion eliminate the active form of the drug from the body. For drugs that are passively

absorbed, their absorption rate depends on the concentration gradient at the absorption site.

Numerous attempts have been made to modify the dissolution characteristics of certain drugs in an effort to attain more rapid and more complete absorption. Since dissolution rate is directly preportional to the surface area, the dissolution rate may be increased by decreasing the particle size of the drug. The utilization of finely subdivided or micronized particles as a means of increasing the rate of dissolution of a drug has been frequently considered. For example, the increased dissolution rate of the otherwise insoluble griseofulvin by micronization resulted in reduction of its therapeutic dose by 50%[8, 90]. The particle size reduction is achieved in different ways depending on the characteristics of the pharmaceutical materials, the initial particle size and the degree of size reduction. Pharmaceutical materials differ considerably in melting point, brittleness, hardness and moisture content, all of which affect the ease of particle size reduction and dictate the choice of the method.

The existence of many pharmaceutical substances which have only a limited solubility in water has presented formidable problems to the formulator of acceptable dosage forms. A lot of research work has

been conducted in an effort to not only learn of the effects of "Particle Size" in physical systems but also to gain insight into its influence in biological systems. Fincher[19] (1968) has extensively disoussed particle size generally and its relationship to absorption and activity.

Although particle size-reduction may easily be achieved by mechanical means, the resultant fine [illegible] particles may not produce the expected fast dissolution and absorption rates. In a series of in-vitro experiments by Lin et al[43] (1968) it was noted that the reduction of particle size through micronization may not necessarily increase the in vitro dissolution rate. An explanation to the data to support this statement was given as probably due to the development of electrostatic charges on the solid particles after milling, resulting in aggregates which can be larger in particle size than the unmilled drug. Another inherent disadvantage of these pure fine powders of poorly soluble drugs produced mechanically is their poor wetability in water. Hiestand[35] (1966) has extensively talked about factors involved in particle - particle interactions in powder materials. Lachman and Lin[40] (1968) have mentioned the possible existence of static electrostatic charges in common pharmaceutical [illegible] processing operations, such as mixing, micronizing, milling, sieving, compressing, spray drying, coating etc.

The poor wetability in water and the development of electrostatic charges on solid particles are serious problems in attempts to increase the dissolution rates and gastrointestinal absorption of drugs by particle size reduction using the mechanical methods.

Consequently attempts have been made to evolve a possibility of producing increased dissolution by particle size reduction which may be free of these problems. Many authors, Goldberg et al[28],(1965), Chiou and Riegelman[9], 1971, Allen Jr. et al, [1](1977) etc. have attributed the development of a unique method of particle size reduction by solid dispersion to [illegible] Sekiguchi and Obi in 1961, and later applied by many workers. This process involves the dispersion of the water insoluble or poorly soluble drug in a water-soluble, physiologically inert carrier so that upon exposure to aqueous fluids the active drug would be released as fine, dispersed particles. The formation of a eutectic mixture was proposed but later others proposed the possibility of existence of solid solution. Since then, many research workers have approached this unique technique with a view to increasing the dissolution and absorption rates of poorly water-soluble drugs. In a review article Chiou and Riegelman[9](1971) have described methods of preparation of the solid dispersions.

In this research work an attempt has been made to contribute to the development of increasing dissolution rates of poorly water soluble or insoluble drug (acetoheramide) by the

(a) Melting method:

This method is also called the fusion method. It involves the direct heating of known quantities of physical mixture of a drug and a water soluble carrier or physiologically inert material until the physical mixture melts. The melted mixture is stirred and then cooled rapidly. Rapid cooling can be effected either in an ice bath or by pouring the melt thinly on a flat stainless, highly heat conductive metal plate and cooled by blowing ordinary air, cold air, cold water at the opposite side of the plate. The solidified drug-carrier mass may be kept in a dessicator to dry and harden and then powder and sieve if so desired.

The advantage of this method is its simplicity and economy and the fact that a supersaturation of a solute drug in a system can easily be prepared by rapid quenching from a high temperature. The main disadvantage is that either the drug or the carrier may decompose or evaporate during the fusion process at that high temperature of melting. Therefore, thermolabile substances cannot be used.

(b) Solvent method

In this method[9] known weights of the drug and the carrier are dissolved together in a common solvent and then the solvent is evaporated, leaving a crystal

solid of the dispersion. The main advantages of this method is that thermolabile drugs and carriers can be used because their decomposition can be prevented as a result of low temperature required for evaporation of organic solvents. The main disadvantages include the high cost of preparation, the difficulty in completely removing the liquid solvent, the possible adverse effect the supposedly negligible residue solvent may have on the chemical stability of the drug, the selection of a common volatile solvent, the difficulty in reproducing crystals and the fact that supersaturation of the solute in the solid system may not readily be obtained.

(c) Melting solvent method[9]

The method involves first dissolving the drug in the suitable solvent and incorporating the drug solution into the melt of the carrier followed by vigorous stirring and quenching the melt dispersion. This method will be better with easily melting carriers such as polyethylene glycol 6000. This method has not been used in this work and will not be talked about anymore.

1.2.2 TYPES OF SOLID DISPERSIONS

Chiou and Riegelman[9] (1971) have classified solid dispersions into different groups according to their drug release mechanisms.

1) Simple Eutectic mixtures
2) Solid solutions
3) Glass solutions and glass suspensions
4) Amorphous precipitations in crystalline carrier.
5) Compound or complex formations
6) Combinations and miscellaneous mechanisms.

It must be noted that solid dispersion systems may include more than two components. In this work only a binary system has been considered.

1.3 SOLID SOLUTIONS

The idea of solid solution originated from the study of the interrelation of phases in alloy systems in metallurgy[9,12] and it is believed that this idea can also be applied to other chemical systems. Solid solution may better be explained by the use of equilibrium or phase diagram, which gives the interrelation and composition of coexisting phases at all temperatures in a chemical system at equilibrium conditions.

Clark and Varney[12](1962) have defined an equilibrium diagram as a plot of the composition of phases as a function of temperature in a chemical or alloy system under equilibrium conditions. They have classified equilibrium diagrams according to the relation of the components in the liquid and solid states as follows:

1) Components completely soluble in the liquid state
   a) Completele soluble in the solid state
   b) Partly soluble in the solid state
   c) Insoluble in the solid state

2) Components partially soluble in the liquid state.
   a) Completely soluble in the solid state.
   b) Partly soluble in the solid state.

3) Components completely insoluble in the liquid state.

a) Completely insoluble in the solid state

Only the first type of equilibrium diagram is common in pharmaceutical systems and will be discussed. The cooling curve method is employed in determining these phase diagrams.

Consider Fig. 1.1 taken from reference[12]. By heating substances A and B until they melt, forming a one phase liquid system, a series of solid systems containing different amounts of A and B can be obtained from their cooling curve. (Fig. 1.1).

Consider first the cooling of pure A from its molten state, (a). A hold occurs at x and ends at y as solidification begins at x and ends at y_A at a constant temperature T_A. The temperature remains constant during the solidication process because of the liberation of the heat of fusion.

Also consider the cooling of pure B from its molten state [(e) in Fig. 1.1]. In this case a hold indicating solidification begins at x and ends at y at a temperature lower than that in pure A. As can be noted the rate of cooling changes in each case as solidification is completed.

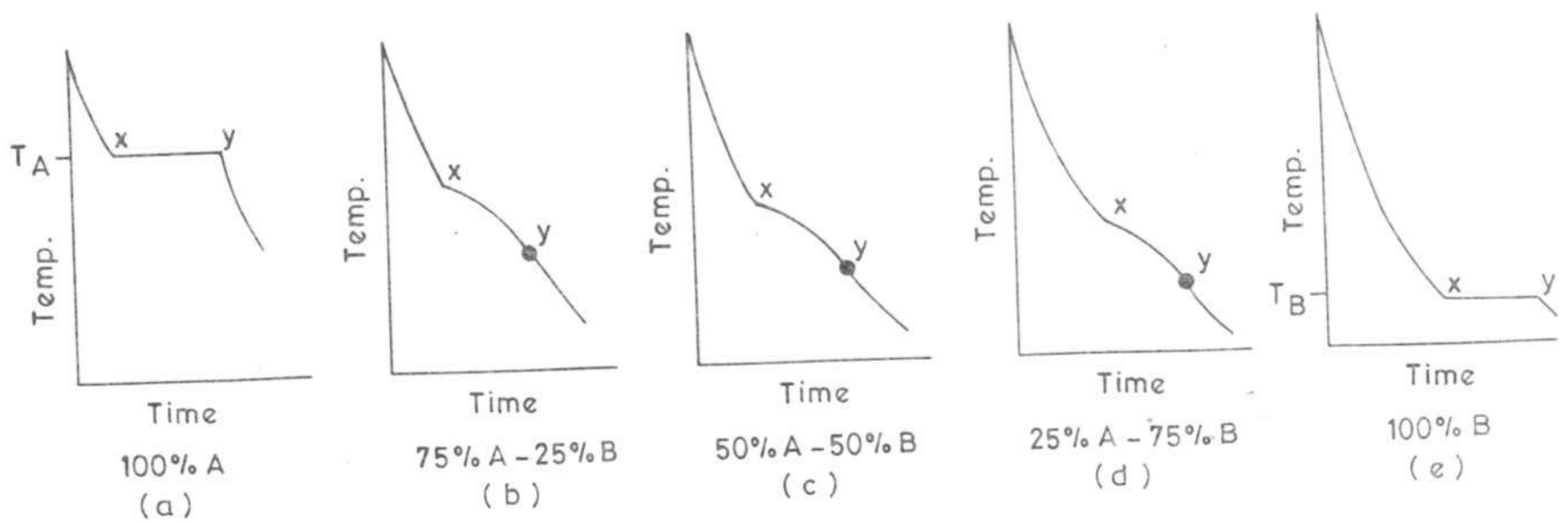


Fig. 1.1 Cooling curves for A and B system.

Now consider the cooling curve of different proportions of A and B shown in the diagram. Their cooling curves indicate a break instead of a hold as in the pure substances at x when solidification starts. The rate of cooling decreases from x to y when solidification is completed and then the cooling rate changes again at y. Point x is designated a break while y is designated recovery. In this case solidification occurs over a range of temperature as against constant temperature exhibited in pure substances. It may be noted from the diagrams that solidification starts at a lower temperature from A to B as the composition of A decreases in the system.

The structure of the solidified mass in all the various compositions of A and B consists of homogeneous one phase system, a solid solution of A and B.

From the above discussion it may be concluded that pure substances soldify at constant temperature and their cooling curve exhibit only a hold, whereas the cooling curves of solid solutions exhibit a break and a recovery.

The results obtained from the cooling curves may now be plotted in the phase diagram shown in Fig. 1.2. The temperature at which solidification begins, x in the cooling curves, form the liquidus Curve, OPR, while

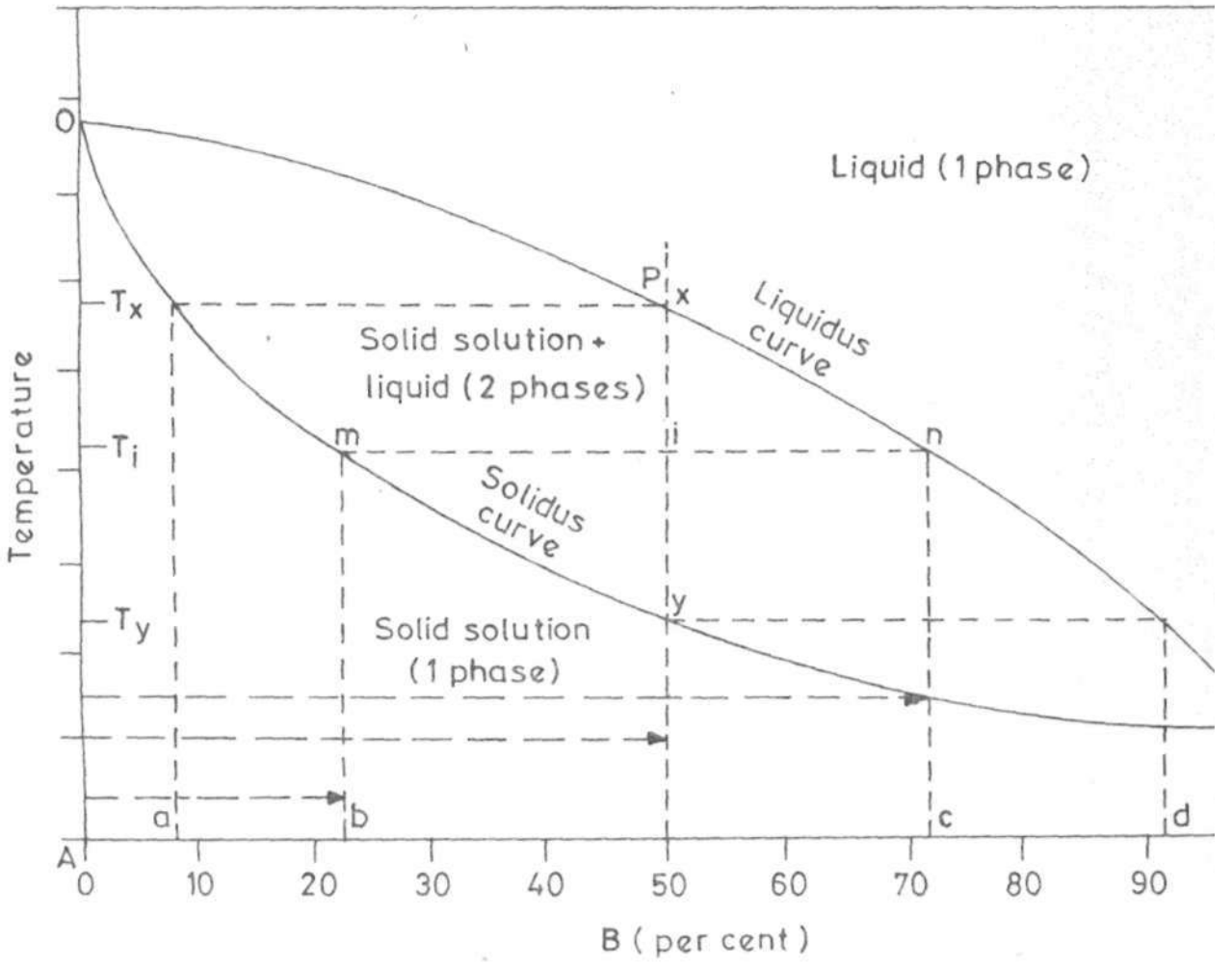


Fig. 1.2 Eqilibrium diagram of A and B.

the temperature at which solidification is completed y, form the solidus curve, OQR, of the phase diagram.

Consider a system containing 50% A and 50% B in which A and B are completely soluble in liquid and solid states. As cooling of the system occurs from a high temperature, solidification will begin when the temperature reaches the liquids curve at x. The composition of the first formed solid may be determined from the intersection of a horizontal line from x through the two phase region to the solidus curve. This corresponds to a solid solution containing 91% A and 9% B. At a temperature corresponding to point i the composition of the solid in equilibrium with the liquid can be found by the intersection of a horizontal line from it to the solidus curve at m. This corresponds to composition b of the solid. Equally the composition of the liquid at this same temperature is determined by the intersection of a horizontal line from i to the liquids curve at n. This corresponds to composition c of the liquid. At equilibrium all of solid solution are of composition b and all of the liquid are of composition c. Since these compositions are different from those of high temperatures it means that an adjustment in the solid and liquid compsotions has occured during cooling from Tx to Ti. The composition adjustment takes place by the process of

diffusion[12]. The adjustment in composition depends on the rate of cooling. If cooling is rapid adjustment will not take place in the composition[12].

Solidification continues as cooling progresses until Ty when solidification is completed. At Ty the composition of the liquid corresponds to d while the composition of the solid corresponds to that of the system being studied.

In systems that posses this kind of phase-diagram all substances that exist below the solidus curve will consist of homogeneous solid solutions. These kind of binary systems exist in alloys e.g. nickel-copper, gold-silver, etc.[12]

From the above discussion it can be observed that a solid solution is made up of a solid solute dissolved in a solid solvent. Since the dissolution of the solid solute takes place prior to exposure to liquid medium a fast dissolution rate of such a solute is expected if the solute is a poorly soluble drug presented to a liquid medium as a solid solution in a rapidly [illegible] liquid soluble carrier.

Chiou and Riegelman[9] have calssified solid solutions according to the extent of miscibility between the two components and according to the crystalline structure of the solid solution. Based on the extent of miscibility between the two components they have identified:

1) Continuous solid solutions in which the two components are soluble or miscible at solid state in all proportions. They have said that no established solid solution of this kind has been known to exhibit fast-release dissolution properties except if one component (the drug) is present as a minor component.

2) Discontinuous solid solution, in which there is only a limited solubility of a solute in a solid solvent at solid state.

These authors[9] have stated that some degree of solid-state solubility can be expected for all two component systems but such a degree of solubility may be small enough to be considered negligible.

Based on the crystalline structure of the solid solution Chiou and Riegelman[9] (1971) have identified.

1) Substitutional solid solution in which the solute molecules substitute for the solvent molecules in the crystal lattice of the solid solvent as shown in Fig. 1.3.

2) Interstitial solid solution in which the solute molecule occupies the interstitial space of the solvent lattice as shown in Fig. 1.3.

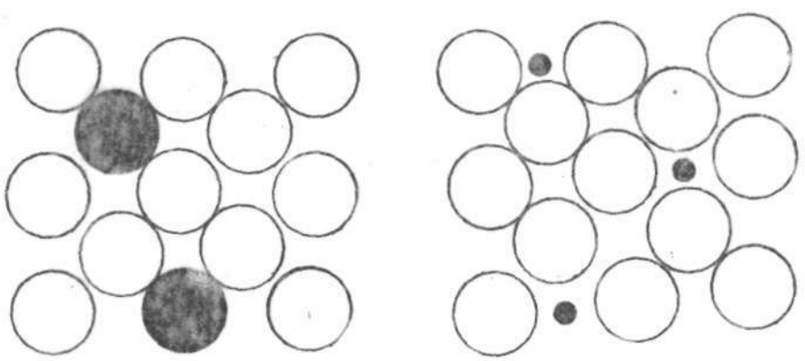


Fig. 1.3 — Right diagram shows the formation of an interstitial solid solution, and left diagram shows the formation of a substitutional solid solution. Dark circles indicate solute atoms or molecules, while open circles indicate solvent atoms or molecules.

While the substitutional solid solution is said to be capable of forming a continuous or discontinuous solid solution the interstitial solid solution is said to form only a discontinuous solid solution. The size and steric factors of both solute and solvent are known to be critical to the formation of solid solution[5]. It is usually desirable that the solid solute be smaller in size than the solid solvent.

1.4 SIMPLE EUTECTIC MIXTURES

The simple eutectic mixtures are usually obtained from the rapid solidification of the fused liquid of two components completely soluble in the liquid state but partially soluble or Completely insoluble in the solid state. This condition may better be illustrated with phase diagrams obtained by the cooling curve method.

Consider the binary mixture of pure substances A and B in Fig. 1.4 (12). (a) and (e) are the cooling curves of the pure substances A and B respectively. Solidification begins at the temperature coressponding to x and is completed at the same temperature y exhibiting a hold at x-y. The cooling curve of a system containing 20% B and 80% A, (b), shows a break at x at a temperature lower than the solidification temperature of pure A. The cooling rate slows down up to point y where cooling occurs at a constant temperature, exhibiting a hold at y-z, and cooling is finally completed at z. The structure of the cooled solid will consist of large grains of pure A formed during the cooling from x to y and, in addition, an intimate mechanical mixture (not a solid solution) of crystals of A and B which formed at the constant temperature y-z. The intimate mechanical mixture is a eutectic(12). Unlike the solid solution where a homogeneous single phase is observed, the simple eutectic mixture exhibits two phases(9).

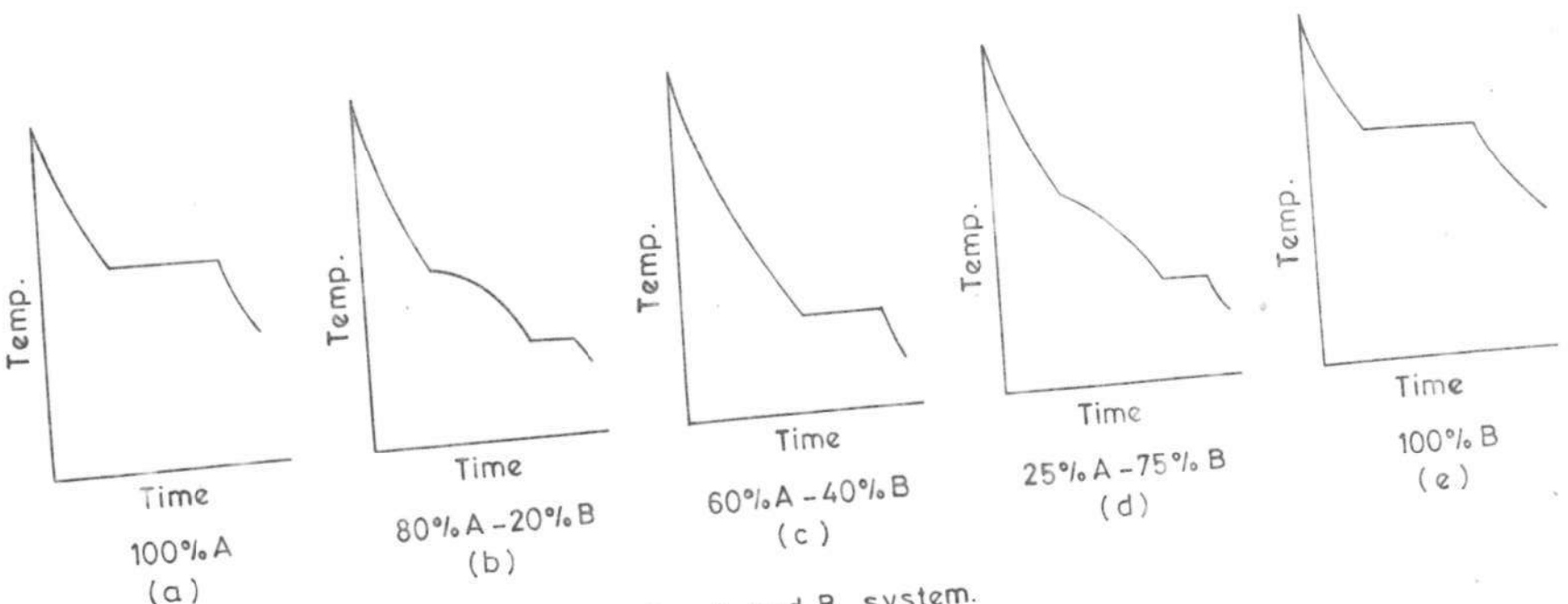


Fig. 1.4 Cooling curves for A and B system.

The cooling curve of the system containing 40% B and 60% A, (c), is unique, in that it has only a hold at x-y and at the lowest temperature of the different compositions where solidification starts. The cooled solid is composed entirely of an intimate mechanical mixture of grains of A and B forming the eutectic. This is the simple eutectic mixture of this binary system. The temperature at which the two crystals of A and B simultaneously crystallize out is the eutectic tempertature of this system.

The cooling curve of the system containing 75% B and 25% A, (d), shows a break at x where solidification starts and the rate of cooling changes up to y where eutectic formation begins at constant temperature y-z and completed at z. The cooled solid will consist of large grains of B and the eutectic mixture of AB.

These cooling curves may now be plotted out into a phase diagram as shown in Fig. 1.5.

This phase diagram indicates an absolute case in which there is no solubility between A and B at solid state. The phase regions of this AB system is as follows.

Above curve ONP - homogenous liquid solution - One phase

Area ONR - Solid A + liquid - two phases.

Area PNS - Solid B + liquid - two phases

Below RNS - Solid A + Solid B - two phases.

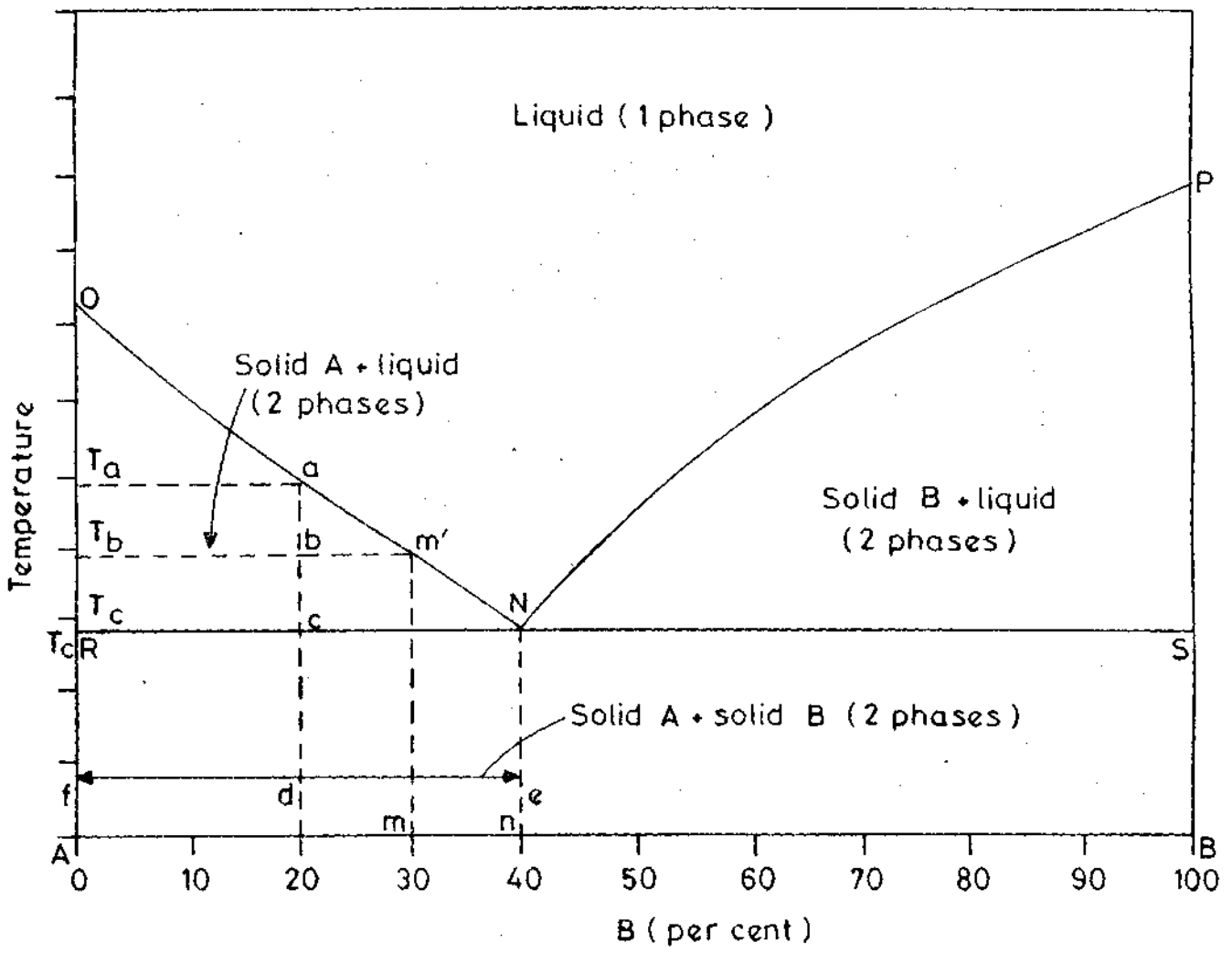


Fig. 1.5 Equilibrium diagram of A and B system.

In the solid state, all mixtures below the line RN will consist of solid A plus eutectic, and all mixtures below the line NS will consist of solid B plus eutectic.

As cooling starts in the system solidification of A starts at the temperature at point O and progresses as cooling progresses down.until the temperature Tc at R is reached. The solid formed at any temperature between OR will be in equilibrium with the liquid at a corresponding point on ON and the composition of the liquid in equilibrium with the solid at the said point can be calculated.

When the temperature Tc at point N is reached, however, the system will be composed of crystals of A in equilibrium with liquid of composition n. Solidification of this liquid at composition n and at temperature Tc (point N) will form an intimate mechanical mixture of crystals of A and B which make up the eutectic. Point N is the eutectic point where crystals of A and B can be in equilibrium with liquid mixture of A and B. This point has a very definite composition of A and B (point n) and at a very definite temperature (Tc).

The above discussion has been based on an absolute case in which there is no solubility of one substance in the other at solid state. It has been stated that

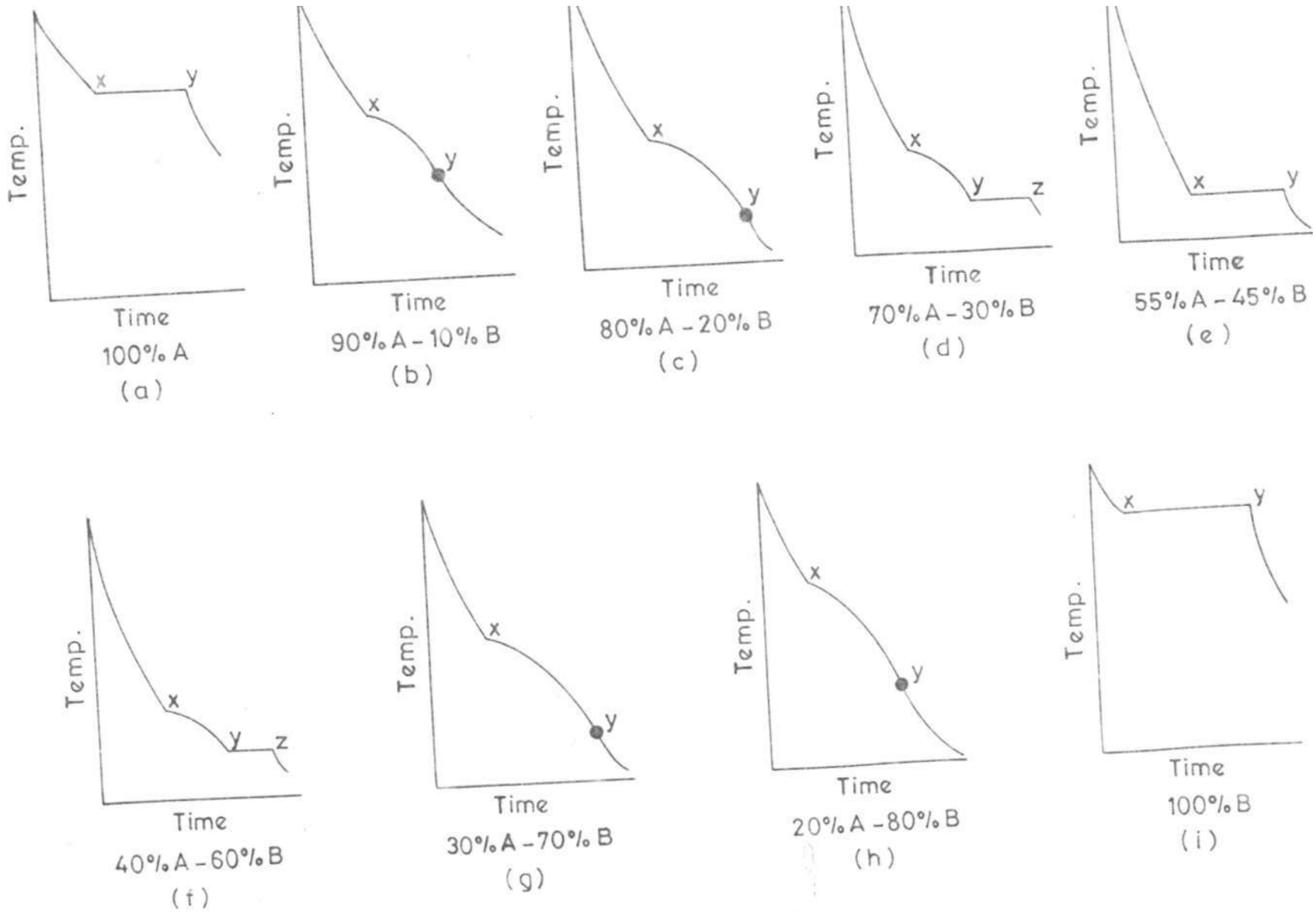


Fig. 1.6 Cooling curves for A-B system.

there is probably no case in which there is not at least some slight solubility of one element in another (9, 12). The solubility may be so slight as to be considered negligible. To better explain the difference between a solid solution and a simple eutectic, it may be necessary to consider components completely soluble in the liquid state but partially soluble in the solid state.

1.4.1 Components completely soluble in liquid state, partially soluble in solid state

This kind of system is the commonest and most important in pharmaceutical systems.

Consider a hypothetical case of substances A abd B in a system. The cooling curves for the pure components and a series of fractional mixtures of them are shown in Fig. 1.6. The cooling curves shown at b, c, g and h in the figure are of the type observed in Fig. 1.1 in which solid solutions were formed. The cooling curves shown at (d), (e) and (f) are similar to those in Fig. 1.4 in which a eutectic was formed. The cooling curve (e) is a characteristic eutectic formation. It is, therefore, expected that the phase diagram of this system will indicate areas of solid solution as well as eutectic formation. The phase diagram of this is shown in Fig. 1.7. The phase regions are as follows.

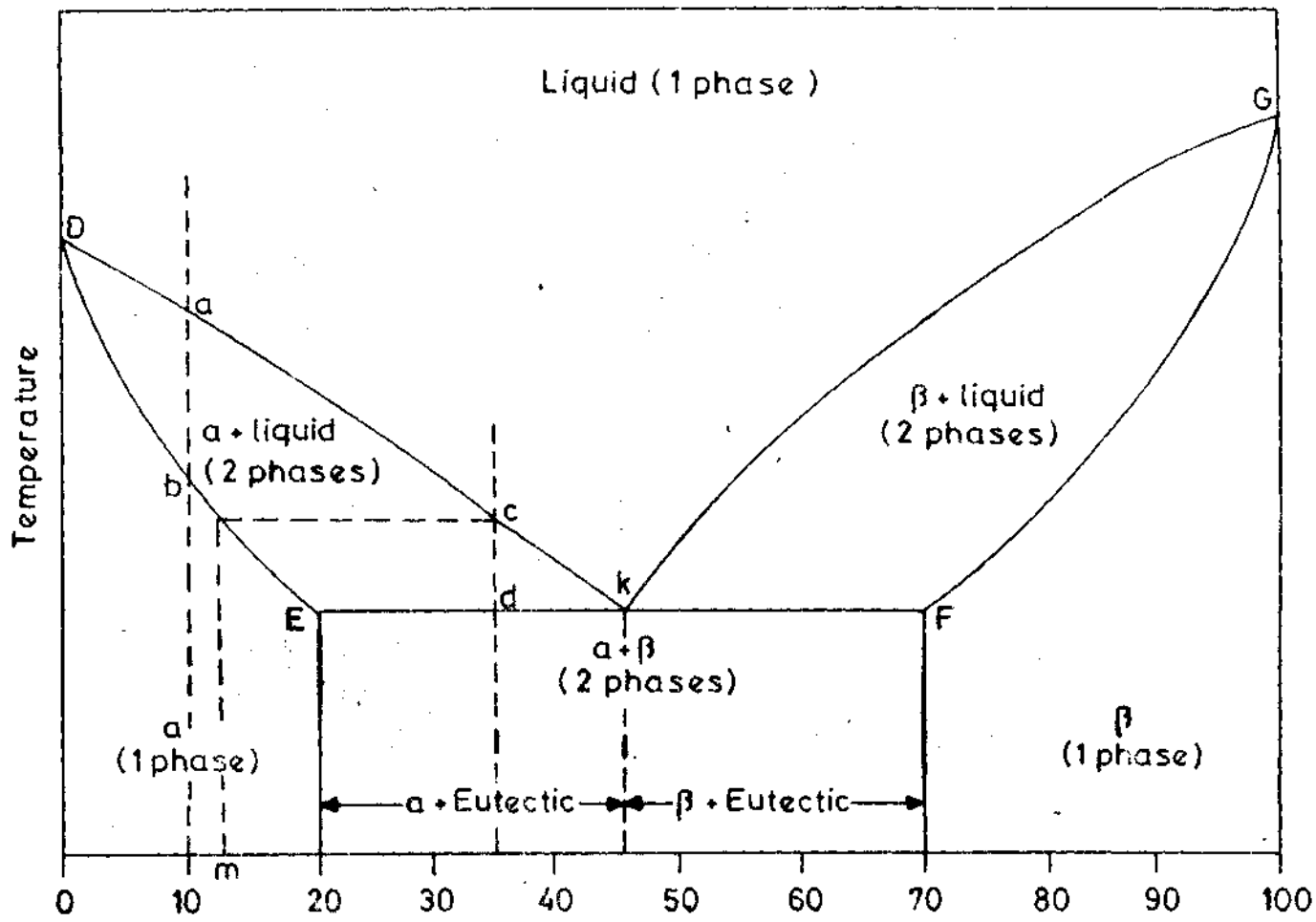


Fig. 1.7 Eqilibrium diagram of A and B.

Above DKG - homogenous liquid solution - one phase

Region DEK - alpha solid solution + liquid - two phases

Region GKF - beta solid solution + liquid - two phases

Below DE - alpha solid solution - one phase

Below GF - beta solid solution - one phase

Below EKF - alpha solid solution + beta solid solution - two phases.

The regions in which the different constituents exist are indicated in Fig. 1.7. The solidification of this system containing 35% B and 65% A will begin at temperature c with the formation of alpha solid solution of composition m. The alpha solid solution formation continues until the temperature d is reached. During the cooling from c to d the composition of alpha solid solution will change from m and will be richer in B. At d, the system will be composed of alpha solid solution containing 20% B and 80% A in equilibrium with liquid of eutectic composition containing 45% B and 55% A. This liquid will solidify at constant temperature to form the eutectic containing grains of alpha solid solution and grains of beta solid solution.

1.4.2 DRUG RELEASE FROM SOLID SOLUTION AND SIMPLE EUTECTICS

In addition to particle size reduction other factors may contribute to the faster dissolution of drugs dispersed in solid solution and perhaps[31] in eutectic mixtures[9].

1) Increased drug solubility may occur if majority of its crystallites are extremely small, since dissolution rate is a function of the surface area available to the dissolution medium.

2) The carriers may possibly effect solubilization in the microenvironment (diffusion layer)[17, 62] immediately surrounding the drug particle at the initial stages of dissolution as the carrier quickly dissolves[17]. This is more applicable in eutectic mixtures as the solid solution is already in molecular dimensions in the carrier at solid state.

3) The absence of aggregation and agglomeration between the crystallites of the pure hydrophobic drug in solid solutions and eutectics, which would have otherwise been present in particle size

reduction by mechanical means[9] may play an important role in increasing dissolution rates and absorption of drugs.

4) Because each crystallite of the drug dispersed in a water soluble carrier as a solid solution or eutectic mixture is intimately encircled by the soluble carrier, excellent wetability and dispersibility results in increased dissolution rate of the drug.

5) An increased dissolution rate may be observed in a eutectic mixture if the drug crystallizes in a metastable polymorphic form after solidification if the polymorphic metastable form has a higher solubility[34].

1.5 THE AIMS AND THE SCOPE OF THIS WORK

In recent years Pharmaceutical Scientists and the Pharmaceutical Industries have been giving increasing attention to the development of solid dispersion with a view to increasing the dissolution rates of poorly water soluble or insoluble drugs. The anticipated advantages of solid dispersion include increased rate and efficiency of absorption and/or bioavailability which ensures more drug at its site of action before metabolism and excretion eliminates the active form of the drug from the body. By increasing the rate and efficiency of absorption and bioavailability a reduced quantity of drug per unit dosage form would be required to attain the same objective and may be even better. By so doing some money is saved on very expensive drugs (raw materials). By reducing the drug content per dosage form undesirable side effects of the unabsorbed drug in the gastrointestinal tract may be minimised.

In addition to increased absorption and bioavailability the solid dispersion technique may have numerous Pharmaceutical applications such as obtaining a homogenous distribution of a small amount of drug at solid state, stabilization of unstable drugs, dispersing of liquid compounds, formulation of sustained - release or prolonged release regimens of soluble drugs by using poorly soluble or insoluble

carriers etc. The main disadvantage however is that systemic toxicity of the drug may result as a result of increased absorption and bioavailability.

In this research work the dissolution rates of different concentrations of Acetohexamide, (a hypoglycemic agent) dispersed in polyethylene glycol 6000 (the physiologically inert carrier) by the melt dispersion technique and various concentrations of Acetohexamide dispersed in polyvinypyrrolidone 44000 (another inert carrier) were studied and compared, with their physical mixtures. Stability of the drug in the dispersions were studied by Spectrophotometry and Thin-layer Chromatography. phase diagram of the melt dispersion was also studied. Tablet formulation of 60% dispersion of Acetohexamide in polyethylene glycol 6000 by the melt method was compared with the formulation of an equivalent physical dispersion in polyethylene glycol 6000.

1.6. Literature Review

Many workers (9, 28) have attributed the initial development of solid dispersions via eutectic formation to Sekiguchi and Obi[9, 28]. Since then a lot of other research workers have made various contributions.

In a review article Chiou and Riegelman[9] (1971) have given the pharmaceutical application of solid dispersion systems. These authors[8] have given the historical background of solid dispersion, methods of preparation, classification, methods of determination of the various classes, aging effects, review of in vivo studies and miscellaneous applications of solid dispersions.

In a study, Chiou and Riegelman[8] (1969) have used different grades of polyethylene glycol, pentaerythritol, pentaerythrityl tetracetate, citric acid and succinic acid as carriers for the preparation and dissolution of several fast-release dispersions of griseofulvin. The melt and solvent methods were used. Ultraviolet and infra red spectrophotometry and also thin-layer chromatography were used for stability studies. They observed increased dissolutions over pure griseofulvin and better dissolution rate from wetted pure griseofulvin prior to dissolution study than non wetted pure griseofulvin. This reveals the importance of wetting in dissolution and suggests that

one of the ways in which water soluble carriers increase dissolution rates of poorly water soluble drugs dispersed in them is by increased wetability. These authors also observed superior dissolution rate of the dispersions by the melt method over those by the solvent method. This suggests that it may be easier to have a saturated solid solution of a drug in a carrier by the melt method than by the solvent method. The highest increased dissolution rate was noted in the dispersion in citric acid and this was attributed to glass formation while the lowest increased dissolution was noted in succinic acid.

In another work, Chiou and Riegelman[11] (1971) studied the phase diagram and the dissolution rate of sulfathiazole-urea solid dispersions. They used two polymorphic forms of sulfathiazole and observed differences in their phase diagrams using [illegible] sulfathiazole-urea physical mixtures and solid dispersions. Solid solubilities were found to be dependent on the polymorphic form of sulfathiazole. This suggests that the polymorphism in solid dispersion may affect its dissolution rate. Increased dissolution rate of sulfathiazole in the dispersion was observed, but a change in the dissolution characteristics was observed with aging.

Still in another study Chiou and Riegelman[10] (1971) used polyethylene glycol 6000 to study the increased dissolution rates of water-insoluble cardiac glycosides and steriods in solid dispersions. They used hydrocortisone acetate, 17-methyl testosterons, prednisolone acetate and digitoxin. The melt method was used for the preparation of solid dispersion and the stability determination was by UV. spectrophotometry and thin-layer chromatography. They observed increased dissolution rate in the dispersion and noted that a supersaturation of each drug could be attained when an excess amount of drug was studied. The increased dissolution rate was attributed to the molecular and/or the colloidal dispersion of the drug in the matrix of polyethylene glycol 6000.

In a review article, Goldberg et al[28] (1965) have given the theoretical considerations and the literature discussion of solid solutions and eutectic mixtures in solid dispersions as it applies to increasing dissolution rates and gastrointestinal absorption of drugs in pharmaceutical systems. These authors have considered solid dispersions produced by the fusion method, taken sulfathiazole-urea and chloramphenicol-urea systems as examples and proposed their mechanism of enhancing dissolution rates.

Considering the phase diagrams of these systems (Sulfathiazole-Urea and Chloramphenicol-Urea) they believed that there existed a significant degree of solid-solid solubility rather than the all simple eutexia earlier proposed; and that the increased dissolution was at least equally attributable to the formation of solid solutions rather than eutectic mixtures alone. They concluded by saying that solid solutions and perhaps eutectic mixtures provide a unique approach to increasing dissolution rates; giving limitations of solid dispersions to such factors as thermal degradation, sublimation and polymorphic transitions.

In another paper Goldberg et al[30] (1966) worked on Urea-acetaminophen system in which the dissolution rate of a simple eutectic mixture of this system was compared with the dissolution rate of pure acetaminophen alone. An initial screening procedure was carried out to ensure that the system formed simple eutectic mixture without any solid solution, and to ensure that the drug and carrier possessed such properties necessary for solid dispersion. The fusion method was used for the preparation of solid dispersion. Equilibrium solubility studies in aqueous solution showed that urea strongly interacted with acetaminophen, manifested by a linear increase in solubility of acetaminophen.

For comparative purposes, one of the acetamimophen granules used for dissolution rate studies was classified in 100 - 120 mesh size while all the other granules were classified 50 - 60 mesh size.

It was observed that the number of particles per unit area of tape, exerted an influence on the dissolution process, that particle size reduction by 50% (from 50 - 60 mesh to 100 - 120 mesh) yielded a 20% increase in dissolution rate using pure acetaminophen. A biphasic dissolution curve was obtained when particles of pure acetaminophen were physically mixed with particles of urea, the second phase of the dissolution curve showing a rate constant which was nearly the same as that of pure acetaminophen. The physically mixed sample of acetaminophen and urea corresponding to the eutectic composition showed the same dissolution characteristics. The fused eutectic mixture showed a similar but prolonged enhancement of dissolution rate. It was then concluded that the increased dissolution rate of acetaminophen in the presence of urea was by virtue of a microenvironmental solubilization and that particle size reduction by eutectic formation alone may not be enough to cause increase in dissolution rate in solid dispersion. In another research Goldberg et al[31] (1966) evaluated griseofulvin-succinic acid solid solution. Solubility

studies showed an interaction between griseofulvin and succinic acid in aqueous medium manifested by linear increase in solubility of griseofulvin with increasing concentration of succinic acid in solution up to a certain concentration. The phase diagram for the griseofulvin and succinic acid system showed a eutectic mixture with considerable solid solubility of grieseofulvin n succinic acid. Dissolution rate studies indicated that the solid solution showed such an unusually high dissolution rate over the physical griseofulvin-succinic acid mixture or pure griseofulvin that the increased dissolution could not be attributed to microenvironmental solubilization. Even the fused eutectic composition showed increase dissolution because it contained 60% solid solution. It was then concluded that the observed increased dissolution was due to the presence of solid solution and that the griseofulvin was already dissolved in succinic acid (griseofulvin particle was reduced to molecular size) before being exposed to the dissolution medium.

And yet in another paper, Goldberg et al[32] (1966) worked on chloramphenicol-urea system. The phase diagram of the system showed both alpha and beta solid solutions and the mixture to be 76% chloramphenicol at the eutectic point, present as part of two distinct saturated solid solutions.

Dissolution rate studies showed the alpha solid solution to have the same dissolution rate as the pure chloramphenicol and the eutectic to have only a very slight increase in dissolution rate over the pure chloramphenicol. Urea was found to sigificantly increase the initial dissolution rate of chloramphenicol-Urea physical mixture. Dissolution rate of the alpha solid solution of chloramphenicol in urea was found to be largely increased over chloramphenicol-urea physical mixture.

The results of these experiments show the importance of solid dispersion in increasing the dissolution rates of poorly water soluble drugs dispersed in readily water soluble carriers. These experiments go further to show that rather than simple eutectic mixtures alone, it is more of solid solutions that are responsible for the increased dissolution rates observed in solid dispersions although factors such as microenvironmental solubilization may also contribute to increased dissolution rates. Similar study was carried out by Block et al[5] (1982) using solid dispersion of chlorthalidone in urea. Increased dissolution rates were observed from prepared discs of the dispersion which did not change after eight weeks of preparation. Simonelli et al[54] (1969) have studied the dissolution rates of high energy polyvinylpyrrolidone (PVP) - Sulfathiazole coprecipitates. They have given a theoretical

consideration of the mechanism of drug release from the coprecipitates. They observed increased dissolution rate of drug from the coprecipitates.

Ford and Rubiastein[23] (1980) have prepared tablets from indomethacin-polyethylene glycol 6000 melt solid dispersions and studied ageing effects on the tablets. Tablets prepared from melts were shown to have shorter disintegration times and better dissolution rates tor the tradinally prepared tablets. Ageing effects were noted to be variable, on tablets prepared from the dispersion.

Geneidi et al[25](1980) studied the dispersion of glibenclamide in mannitol, sorbitol and polyethylene glycols. Increased isssolution rate was observed in the dispersions, but the degree of enhancement of dissolution rate was highest in mannitol/sorbitol systems and least in polytethylene glycols. The degree of enhancement of dissolution rate by polyethylene glycols was independent of their molecular weight.

In another paper Geneidi et al[25](1980) studied enhanced dissolution rates of the dispersion of glibenclamide in oxyethylene-oxypropylene copolymers and polyvinylpyrrolidone Increased dissolution rate was observed in 0.1N HCl. Complex formation was observed between glibenclamide and

polyvinylpyrrolidone. Deshpande and Agrawal[13](1982) observed increased dissolution rates of chlorothiazide, hydrochlorothiazide, fluemiazide and cyclopenthiazide which were solid dispersed in polyethylene glycol.

In another paper Deshpande and Agrawal[14](1982) studied the influence of various dispersing agents on the dissolution rate of hydrochlorothiazide. They observed drug decomposition with dextrose and superior drug release in urea as compared to the other carriers, sorbitol and tartaric acid.

Sulphonylurea hypoglycaemic agents.

Balant[4](1981) has reviewed the clinical Pharmacokinetics of some of the suphonylurea hypoglycaemic agents, including acetohexamide.

Strickland[55](1966) worked on separation and detection of oral hypoglycaemic agents including acetohexamide using thin-layer chromatography.

Said et al[50](1974) observed complex formation between tolbutamide and polyvinylpyrrolidone 40,000 in tolbutamide PVP coprecipitate but could not detect any interaction between tolbutamide and macrogol 6000 in tolbutamido-macrogol fusion mixtures. Increased dissolution rate of tolbutamide was observed in both its coprecipitate with PVP and its fusion with macrogol.

In another paper Said and Saad[51] (1975) noted increased rate and quantity of absorption of tolbutamide from its coprecipitation with PVP and its melt dispersion in macrogol using blood glucose concentration of adult male albino rats.

Ford and Rubinstein[21] (1977), in their study of the effect of composition and ageing on the dissolution rates of chlorpropamide-urea solid dispersions noted increased dissolution rates from melt dispersions over the physical mixtures. The optimum dissolution rate was observed in 30% w/w dispersion. Dissolution rate was also found to increase with age for most melt dispersions.

Chlorpropamide in solid dispersion with urea was found to decompose during the fusion process, Ford et al [22] (1979). Urea was also found to decompose during fusion.

Deshpande and Agrawal[15] (1981) tried the dispersion of chlorpropamide in different carriers by fusion and melt methods and noted that the drug was stable in polyethylene glycol 6000 and ly- polyvinylpyrrolidone 44000 but unstable in citric acid, succinic acid sorbitol and urea. Increased dissolution rate of chlorpropamide was observed from the dispersions. In another paper, Deshpande and Agrawal[16] (1982) noted that out of three different grades of polyvinylpyrrolidone (PVP 10000, 44000 and 70000) PVP 44000 was a better combination with

chlorpropamide which was reflected by superior dissolution rate and better chlorpropamide absorption in the rat stomach. In the study of polymorphism in sulphonylurea hypoglycaemic agents Al-Saieq and Riley[2, 3] prepared five polymorphic forms of chlorpropamide and three polymorphic forms of acetohexamide. Four of the five polymorphic forms of the chlorpropamide were found to be metastable but showed superior dissolution rate over the stable form. All of the acetohexamide were found to be stable but one form showed a better dissolution rate.

Ford and Rubinstein[24] (1981) have prepared tablets from chlorpropamide urea solid dispersions and studied its properties and ageing effects. Increased dissolution rates were observed from tablets prepared from the dispersions. Disintegration times and dissolution rates decreased in the first two months of storage but increased thereafter. Kaur et al[38] have compared polyethylene glycol and polyoxyethylene stearate as excipients for solid dispersion systems using the phase equilibriumof griseofulvin and tolbutamide dispersed in these carriers. The phase diagrams were found to be independent of the method of dispersion preparation. Solid solution of tolbutamide was found in the eutectic in polyoxyethylene 40 stearate which showed a greater solubility of tolbutamide than in polyethylene glycol 2000 which showed no solid Solution. No solid solution of griseofulvin was dected in any of the dispersions.

In another paper comparing polyethylene glycol and polyoxyethylene Kaur et al[38] (1980) compared the dissolution and solubility properties of dispersions of griseofulvin and tolbutamide in these carriers. The rate and extent of drug release were found to be greater from polyoxyethylene than from polyethylene glycol dispersion.

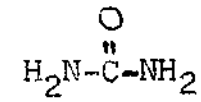
CHAPTER 2

CHEMICALS AND MATERIALS

The following chemicals and materials were used.

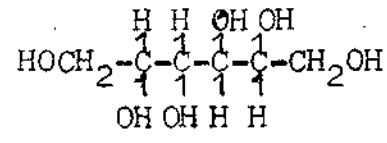
2.1 CARRIERS TRIED.

(a) UREA: - A white crystalline powder, nearby odourless and with a slight saline taste. Urea is carbonyldiamide with the structure



and the molecular weight 60.06. Its melting point range is 132°C - 134°C and is very soluble in water. At high doses (up to a maximum of 1.5 g/kg body weight per day given by infusion as a 30% w/v solution) urea is used as an osmotic diuretic because it is non-metabolised and it is passively filtered through Bowmans Capsule into the renal tubules where it is not reabsorbed. It has been used by many researchers as an inert carrier in solid dispersion (11, 24, 30).

(b) Mannitol - A hexahydric alcohol with the structure



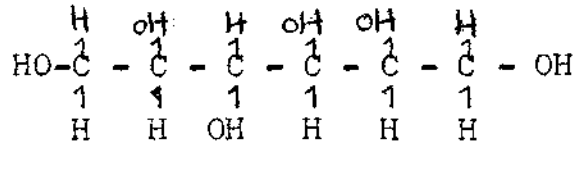
and molecular weight 182.17. It is a white odourless crystalline powder with a sweat taste. Its melting

point range is 165°C - 169°C and solubility 1 in 6 of water, 1 in 18 of glycerol, slightly soluble in alcohol and pyridine but insoluble in ether.

Mannitol is used as an osmotic diuretic in high doses (up to 200 g. daily) as an intravenous infusion. It is also used as a diagnostic agent for kidney function. (25, 46, 59, 61)

(c) Sorbitol: -

It is a white hygroscopic powder with a sweet sugar taste having the structure



It melts at about 96°C, solubility 1 in 0.5 water, 1 in 25 alcohol but insoluble in chloroform and ether. Given intravenously in 50% w/v solution sorbitol is used as an osmotic diuretic. It is also used as a laxative, sweetener and a pharmaceutical vehicle. Sorbitol does not produce a rise in blood sugar when taken by mouth probably because it is poorly absorbed from the gastrointestinal tract. It can therefore be used by diabetic patients in formulations of hypoglycemic agents. (25, 59, 61)

(d) Polyethylene glycol (PEG) 6000 -

This is a mixture of condensation polymer of ethylene oxide and water with an average molecular weight of 6000. It is a creamy-white, wax-like

flakes with a faint odour, soluble 1 in 2 of water, 1 in 2 of chloroform, slightly soluble in alcohol but insoluble in ether.

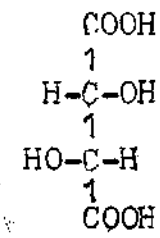
Polyethylene glycol is consistently stable under adverse condtions and therefore used in many pharmaceutical preparations, such as ointment bases, suppository bases, creams etc. It melts between 57°C and 63°C. It has been used as a carrier in the pharmaceutical preparation of solid dispersions (8, 9,10). A probable limitation to using polyethylene glycol as a carrier for solid dispersion is the possible tendency of the ether group in the polymer to form stable and insoluble complexes[8].

(e) Polyvinylpyrrolidone (PVP 44000 - Povidone

A creamy white odourless, tasteless powder, soluble soluble in water alcohol and chloroform but insoluble in Acetone and ether. Polyvinyprrolidine is not known to be metabolised in the body. It is used as a suspending agent, a binding agent in tablet granulation, etc. Some research workers have used polyvinylpyrrolidone as a carrier in solid state dispersion by coprecipitation [50, 51, 54].

(f) TARTARIC ACID

A white crystalline powder, almost odourless with an acid taste and having the structure

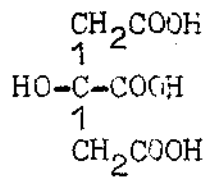


It is soluble 1 in 9.8 ml water, 9.5 ml hot water, 2 ml alcohol and about 250 ml water.

Tartaric Acid is absorbed from the gastrointestinal tract but excreted through the urine unchange (46, 59, 61). It could be used as a carrier in pharmaceutical dosage forms.

(g) Citric Acid:

An odourless, white crystalline powder with the structure:



It is soluble, 1 in 0.5 ml. water, 2 ml. alcohol and about 30 ml. ether. It has been used in the preparation of anticoagulant. It has been used as a water-soluble carrier in solid dispersions(8, 57)

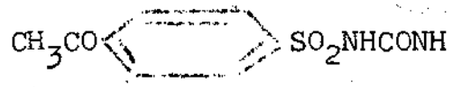
(h) Succinic Acid -

Has also been used as a carrier in solid dispersion(8, 31).

2.2 THE DRUG

The drug used for dispersion in this experiment is Acetohexamide. The drug is the solute while the carrier acts as the solvent.

Acetohexamide is a sulfonyl urea oral hypoglycemic agent with the following structure and known by the following names:



Acetohexamide

(i) 4-acetyl-N- [(cyclohexylamino)-carbonyl] benzene sulfonamide

(ii) 3-cyclohexyl-1-(p-acetylphenyl sulfonyl)-urea.

(iii) 1-[(P-acetylphenyl) sulfonyl]-3-cyclohexyl urea.

(iv) N-(P-acetylbenzene sulfonyl)-N-cyclohexyl urea.

(v) Benzene sulfonamide, 4-acetyl-N-[(cyclohexylamino) carbonyl]-urea

Acetohexamide is an odoureless, light, white, fine powder that melts between 182°C and 187°C. It id insoluble in water and ether, slightly soluble in alcohol and chloroform, soluble in pyridine and dilute solutions of alkali hydroxides (46, 61).

2.3 EQUIPMENT

2.3.1 SPECTROPHOTOMETERS

(a) Visible/Ultraviolet Spectrophotometer S.P.30 (Pye Unicam)

(b) Visible/Ultraviolet spectrophotometer S.P. 8 - 100 (Pye Unicam).

(c) Infrared spectrophotometer.

2.3.2 DISSOLUTION RATE APPARATUS USED

(a) THE BAG METHOD

As shown in plate I

The Assembly consist of a 600.0ml. beaker which contains the dissolution medium immersed in a constant temperature water bath maintained at 37°C.

Cellophane paper (Whatman 105)[2] was cut to size and folded. Using araldit to seal the open edges, and leaving one end through which to admit the test sample, a rectangular flat bag of 4.5 cm x 5.0 cm. was formed. The araldit was allowed to dry for 24 hours and when the folded bag was opened up a nearly cylindrical bag representing the cylindrical stainless-steel basket of a conventional USP dissolution rate apparatus, but flanged at the base was formed. On admitting the test substance through the opening into the bag, the bag plus the contents

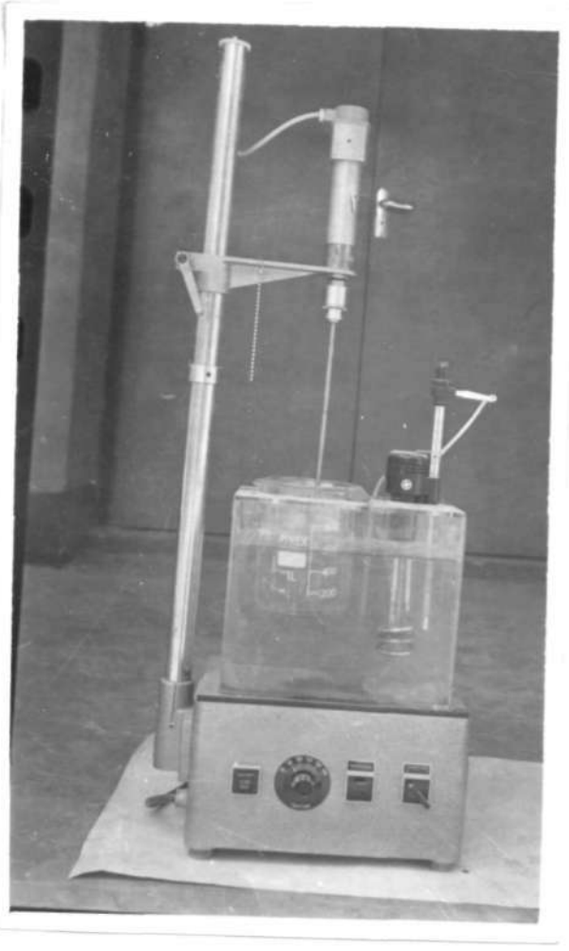


PLATE I — THE BAG METHOD

were firmly attached through the same opening using a rubber band to the round end (with a groove) of a long metal shaft so modified for the purpose. The shaft was attached to a motor fitted with a speed-regulating device that allows the motor speed to be varied between 25 r.p.m. and 200 r.p.m.

METHOD

The test substance was weighed into the prepared bag. The bag was firmly atta hed as earlier described and immersed in the dissolution medium which is 400 ml. distilled water maintained at 37°C. The bag containing the test substance was rotated at 50 r.p.m. in the dissolution medium. At appropriate time intervals 5.0 ml. of the dissolution medium was withdrawn using a 5 ml. pipette into a 25 ml. volumetric flask and used for analysis. The 5 ml. of the fluid withdrawn from the dissolution medium was replaced with another 5 ml. distilled water to keep the dissolution medium constant. Absorbance readings of the the withdrawn quantities of the dissolution medium at given time intervals were taken on the ultraviolet spectrophotometer. From the absorbance readings, the quantities and percentages of Acetohexamide released with time were calculated.

(b) THE TAPE METHOD

The tape method as recommended by Goldberg et al (29) (30) was used.

Apparatus: -

As shown in plate II

The basic parts of the Apparatus consists of:

1) 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 mounting an adhesive tape (selotape)

2) A piece of adhesive tape that holds particles of the test substance.

3) A 600 ml - beaker to contain the dissolution medium and runners to position the frame in contact with the dissolution medium.

4) A paddle acting as a stirrer in the dissolution medium being attached to a motor fitted with a Speed - regulating device that allows the motor speed to be varied between 25 r.p.m. and 200 rpm. (Plate)

The 600 ml-beaker with its contents is immersed in a litre beaker containing water at 37°C and the whole apparatus is immersed in a constant temperature water bath maintained at 37°C by a heater fitted with

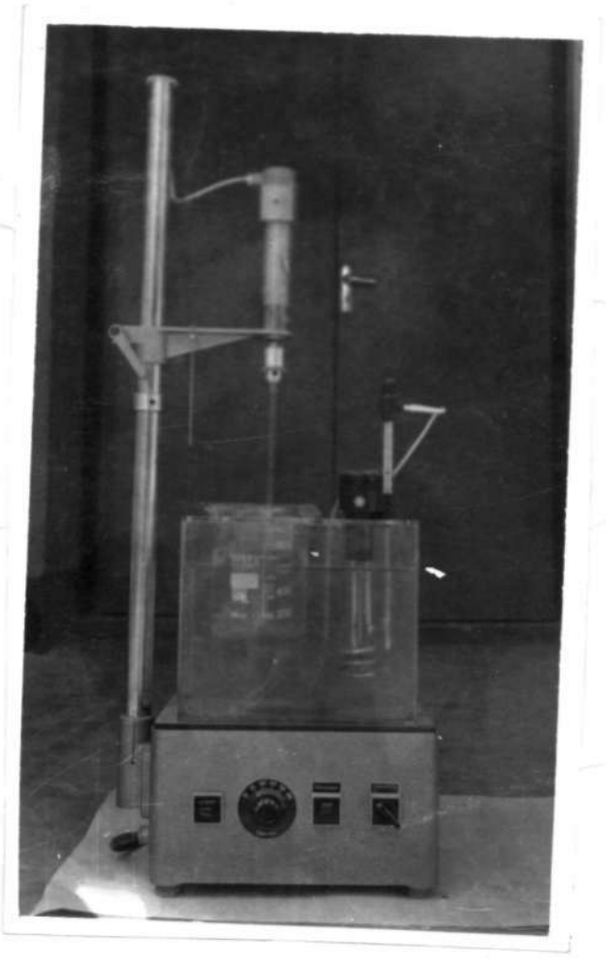


PLATE 2 — THE TAPE METHOD

METHOD

A strip of the adhesive tape 3 cm. wide, was fastened to the frame to present an adhesive surface onto which the weighed amount of the test granules were uniformly sprayed to form a monolayer. The frame was positioned in the frame holder already placed in the dissolution medium with the paddle always at a constant distance from the tape and rotated at 50 rpm. The dissolution medium is distilled water preheated to 37°C and maintained at that temperature in the constant temperature water bath. The rest of the procedure was the same as that for the Bag method.

2.4. PROBLEMS AND PRECAUTIONS OF THE DISSOLUTION RATE METHODS

According to the Noyes-Whitney[62] equation the dissolution rate of a solid is a function of the surface area presented to the dissolution medium as well as the concentration gradient existing between the Solid-liquid interphase and the bulk of the dissolution medium. In particulate dissolution where only the concentration gradient is kept constant by keeping the dissolution medium sufficiently dilute the dissolution rate is proportional to the surface area[39]. The film theory has it that the dissolution process involves the formation of a thin layer or film of saturated solution at the solid-liquid interphase and the diffusion of molecules from this layer to the

(a) The bag method

In the bag method two interphases now exist during the dissolution rate studies; the solid-liquid interphase inside the bag itself and the bag-liquid interphase in the dissolution medium. This may, to a certain extent, interface with the observed dissolution rate using the bag method.

Another set back in the bag method is the orientation of the particulate material in the bag during the dissolution rate studies. In the bag the particles are packed so close together that they touch one another. Light particles that would normally float in the dissolution medium may be closely packed on one side of the bag as the pressure of the bag forces the particles immersed in the dissolution medium. Stirring may not even correct this particulate packing effect.

If the particulate density in the bag is such that the diffusion layer of each particle "Overlaps" with that of its neighbouring particle the observed dissolution rate may be affected.

The defects not withstanding, the bag method could still be used for comparative dissolution rate studies. Certain precautions must, however, be taken.

1) The material (celophane paper or any other material) used for the formation of the bag must not be too thick, otherwise the dissolved test substance may not easily get out of the barrier formed into the dissolution medium to indicate dissolution rate effect. However, the material must be strong enough to withstand the time, so that it can be taken out of the dissolution medium at the end of the dissolution test without breaking.

2) The pores of the material used for the bag formation must not be too large, otherwise particles of colloidal dimensions will pass through it into the dissolution medium causing inconsistencies in the dissolution rate studies.

3) The hight of the bag containing the test particles must be maintained constant in the dissolution medium.

(b) <u>The tape method</u>

The major problem of the tape method is the fact that not all the functional surface area of the particle is available to the dissolution medium at the start of the experiment. That part of the particle attached to the adhesive part of the tape is not immediately available and depending on the geometry

and the orientation of the granules in the tape the unavailable part could be significant. It may, however, later become available to the dissolution medium as the experiment progresses.

Inspite of this draw back the tape method could still be used for dissolution rate studies. Certain precautions must, however, be taken.

1) It is important that the components of the tape do not react or interfer with the assay or dissolution process in anyway.

2) It is also important for the particles to form a monolayer on the adhesive part of the tape. To this effect the particles to be used should not be too fine or too large. Too fine a particle may dissolve in the tape or become very difficult to form a monolayer of it on the tape. Other fine powder particles not attached to the tape could easily get out into solution and be picked up when withdrawing alliquots for assay. This Could cause inconsistent results.

3) The length of the stir paddle must at least equal the length of the tape and the paddle must be vertically positioned so that no part of the tape extends beyond the length of the paddle. This will ensure that all particles on the tape are equally

stirred and will minimise errors arising as a result of particle position or particle density on the tape in the dissolution medium.

4) The distance between the stir paddle and the tape must be maintained constant throughout subsequent experiments.

5) It is possible that particle might be swept off the tape during the experiment producing a source of error. This can be corrected by filtering the alliquots withdrawn for analysis.

CHAPTER 3.

EXPERIMENTAL STUDIES

PRELIMINARY INVESTIGATION

3.1 INTRODUCTION

The object of this investigation is mainly standardisation of the working procedure, such as, the wavelength of maximum absorbance of the drug, a standard plot to determine up to what extent Beer's law is obeyed and the specific absorption constant, K, The solubility in water of the drug and its stability after dispersion were determined. A study was carried out to find a poorly soluble drug that would easily be dispersed in a water soluble carrier.

3.1.1. Selection of the drug.

A literature sur ey was undertaken to find out that the drug employed met the following criteria as recommended by Goldberg et al[30].(1966)

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°

The sulfonyl urea hypoglycemic agents were considered based on the fact that they are practically insoluble in water, are given in low doses for a long time and because of their gastrointestinal side effects such as heart burn, upper abdominal discomfort, nausea, lower abdominal cramps and diarrhoea.

3.1.2. Selection of the carriers

A literature survey was also undertaken to find out that the carriers investigated met the following criteria [30]:-

a) soluble in water
b) physiologically inert
c) a melting point of not more than 200°
(only for carriers used in fusion dispersion).
d) thermal stability up to its melting point.
e) a relatively low vapour pressure.

3.1.3. SCREENING PROCEDURE

In order to select drug-carrier combinations which would be used for more detailed investigation an initial screening procedure was developed to permit rapid evaluation.

(1) (i) MELT METHOD

5.0 gm. quantities of 5% dispersion of each drug in each carrier were prepared. 0.25 gm. of the drug and 4.75 gm. of the carrier were weighed into a stainless steel crucible, heated over an oil bath and with a thermometer and a glass stirrer to stir the mixture in the crucible. On melting (if any) the following observations were made:-(table 3.2)

a) Temperature at which melting started

b) Temperature at which there was a colour change, gas evolved or any other physical changes.

c) Temperature at which melting was completed.

d) The number of phases on melting.

When melting was completed the melted mixture was poured on a flat stainless steel plate to effect fast cooling and solidification at room temperature. The following observations were again made.(table 3.3)

a) time taken for the melt to solidify

b) the physical state of the solidified mixture.

c) time taken for the soldified mixture to dry.

(ii) Coprecipitate method.

5.0 gm. quantities of 5% dispersion of each drug in each carrier were prepared. The common solvent used for preparing the solution is acetone/methanol

mixture in 1:1 ratio. 0.25 gm . of the drug and 4.75 gm. of the carrier were each weighed separately into a porcelain evaporating dish and the solvent added with stirring until solution was formed. The solvent was then evaporated over a water bath at a temperature not exceeding 50°C. The following observations were made:- (table 3.4)

a) the volume of the solvent added before solution was formed.
b) the nature of the solution and
c) the physical appearance of the coprecipitate after solvent evaporation.

3.1.4. RESULTS AND DISCUSSION

On the basis of results obtained in the screening procedure, acetohexamide was chosen from the other hypoglycemic agents as a drug to be used. Acetohexamide is relatively stable on melting, forms dispersion with various carriers and was readily available. Also the melting point of acetohexamide (182° - 187°C) is below 250°C which is reasonable for fusion melt dispersion.

Also on the basis of the same results polyethylene glycol 6000 was chosen as the water soluble inert carrier for the melt dispersion and polyvinylpyrrolidine was chosen as the water soluble inert carrier for coprecipitate dispersion.

TABLE 3.1

Trying The Dispersion of Some Hypoglycaemic Agents

1) Melt Dispersion

Drug (0.25g)	Carrier (4.75g)	No. of Phases of the comelt	Fusion Formed or not formed
Acetohexamide	Polyethylene Glycol 6000	One	Formed
	Urea	One	Formed
Chlorpropamide	Polyethylene Glycol 6000	One	Formed
	Urea	One	Formed
Tolazamide	Polyethylene Glycol 6000	One	Formed
	Urea	One	Formed
Tolbutamide	Polyethylene Glycol 6000	One	Formed
	Urea	One	Formed

2) Coprecipitate Dispersion

Drug (0.25g)	Carrier (4.75g)	Volume of Solvent (Acetone/ Methanol)	Solution formed	Coprecipitate Formed
Acetohexamide	Polyvinypyrrolidone 44000	73.0ml	Pale yellow	Pale yellow
	Citric acid	145.0ml	Colourless	White
Chlorpropamide	Polyvinylpyrrolidone 44000	75.0ml	Pale yellow	Pale yellow
	Citric acid	150.0ml	Colourless	White
Tolazamide	Polyvinylpyrrolidone 44000	75.0ml	Pale yellow	Pale yellow
	Citric acid	147.0ml	Colourless	White
Tolbutamide	Polyvinylpyrrolidone 44000	77.0ml	Pale yellow	Pale yellow
	Citric acid	148.0ml	Colourless	White

TABLE 3.2

Acetohexamide/Carrier Dispersions

Fusion Method

295836

Carrier (4.75g)	Temperature melting started °C	Temperature discoloration Gas Evolved °C	Temperature melting complete °C	Number and Discription of phases
Polyethylene Glycol 6000	58	-	112	A Clear pale Yellow single Phase
Urea	102	-	126	A Clear colourless single phase
Mannitol	140	132 Browning of the Carrier 148 Gas	156	Greyish Single phase with scattering Brwon particles floating (Charring?)
Sorbitol	88°C	104 Gas 135 Browning of the paste	95	No clear phase A milky thick melt with scattered acetohexamide particles
Tartaric Acid	120	130 Foaming of the mass	140	No clear phase thick milky foaming paste
Succinic Acid	155	115 Browing of the	188	A Brownish Single phase
Citric acid	120	130 Bubbles formed	130	Foamy, yellow viscous phase
Polyvinyl pyrrolidone (PVP) 44000	195 No melt	No Change	Heated to was no sign	195°C But their of any melt.

TABLE 3.3

Characteristics Of The Dispersion Produced.

Fusion Method

Carrier	Time Taken for Crystal Formation	Physical State of mass (Crystalline or Amorphous)	Time Taken for Crystal to dry
Polyethylene Glycol 6000	Under 10 minutes	Oily Crystalline mass	Under 10 minutes
Urea	Immediately	Pale yellow Needle shaped glass crystals	Immediately
Mannitol	Under Two (2) minutes	Gleyish-yellow with Brownish particles scattered in the crystal	
Sorbitol	Over 10 hours	A Brownish thick paste - Amorphous	Over 10 Hours
Tartaric acid	Under 5 minutes	Foamy Amorphous grey solid	Below 5 minutes
Succinic Acid	Immediately	Crystalline	Under 3 minutes
Citric Acid	Above 10 minutes	Pale yellow Foamy viscous Amorphous	Over 15 minutes

TABLE 3.4

Dispersion of Acetohexamide in Different Carriers By The Liquid Dispersion Technique

Carrier Sample (4.75g)	Volume of Solvent added (ml)	Description of Solution	Description Coprecipitate
Urea	126.0	Colourless	White
Tartaric Acid	70.0	Colourless	White
Polyvinylpyrrolidone 44000	75.0	A pale yellow gummy substance on initial addition of solvent forming a pale yellow solution on continuous addition	Pale yellow shinny crystals
Succinic acid	130.0ml	Colourless	White
Citric acid	150.00	Colourless	White
Mannitol	up to 200.00	No solution formed even at this high volume	-
Polyethylene glycol 6000	580.0	No solution	-
Lactose	200.00	No solution	-
Sorbitol	200.00	No solution	-

3.2. DETERMINATION OF THE WAVELENGTH OF MAXIMUM ABSORBANCE (λ MAX) OF ACETOHEXAMIDE

In this study the wavelength of maximum absorbance (λmax) of acetohexamide has been determined.

Because of the insolubility of pure acetohexamide in water, no solution of acetohexamide can be prepared in this medium. Rather, solutions are prepared in 50% methanol.

METHOD

100 ml. solution of acetohexamide of concentration 1mg/ml. was prepared in 100% methanol by weighing 100mg. acetohexamide and dissolving it in some quantity of 100% methanol in a 100 ml volumetric flask, making up the volume with 100% methanol. 50ml. of this solution was diluted with an equal volume of distilled water to provide a solution of 0.5mg/ml. acetohexamide in 50% methanol. A separate 50% methanol was prepared and used for dilution to prepare the concentration of acetohexamide in 50% methanol from the above solution.

A little quantity of each of the 20 µg/ml.) concentrations was taken in a 10mm silica cell (PyeUnicam) and using 50% methanol as blank, absorbance readings of wavelength curves between 200 - 300 nm were taken on the S.P.30 UV

Spectrophotometer (Tables 3.5 and 3.6). Further, 10 ug/ml and 25 µg/ml pure acetohexamide solution in 50% methanol were scanned on the spectrophotometer and the wavelength of maximum absorbance calculated (Fig. 3.1)

3.2.1 RESULTS AND DISCUSSION

The results of the above experiments are shown in Tables 3.5 and 3.6 and Fig. 3.1. Table 3.6 shows λ_{max} of acetohexamide to be between 251 nm and 252 nm. The automatic spectrophotometer, SP8-100 UV (Pye Unicam) has given λ_{max} as 249 nm (Fig. 3.1) and from standard text books λ_{max} for acetohexamide is said to be 248 nm.

However, 251 nm shown on the SP.30 UV Spectrophotometer (Pye Unicam) as λ_{max} for acetohexamide has been chosen as the wavelength of maximum absorbance for acetohexamide.

TABLE 3.5

DETERMINATION OF THE WAVELENGTH OF MAXIMUM ABSORBANCE FOR ACETOHEXAMIDE, (UV RANGE 200 - 380 nm)

WAVELENGTH (nm)	ABSORBANCES 20 ug/ml in 50% METHANOL
200	0.545
205	1.098
210	0.820
215	0.414
220	0.204
225	0.183
230	0.274
235	0.420
240	0.598
245	0.762
250	0.857
255	0.828
260	0.673
265	0.451
270	0.255
275	0.142
280	0.092
285	0.065
290	0.042
295	0.012
300	-
305	-

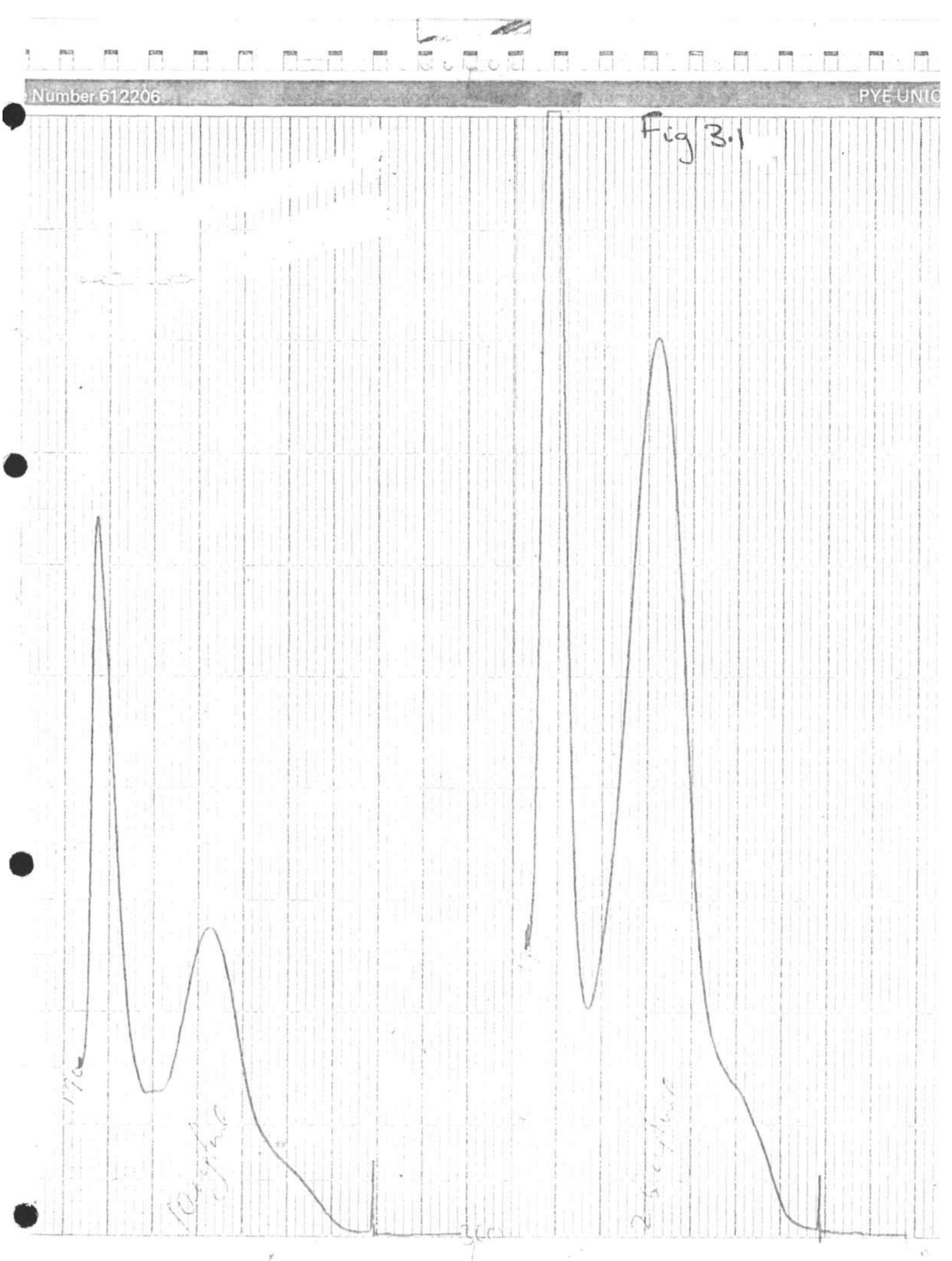

Number 612206
PYE UNIC
Fig 3.1

TABLE 3.6

DETERMINATION OF THE WAVELENGTH OF MAXIMUM ABSORBANCE (λ_{max}) FOR ACETOHEXAMIDE

(UV RANGE = 200 nm - 380 nm)

WAVELENGTH (nm)	ABSORBANCE 20 ug/ml in 50% methanol
201	0.644
202	0.770
203	0.917
204	1.045
205	1.101
206	1.109
207	1.094
208	1.035
209	0.932
210	0.828
246	0.785
247	0.802
248	0.824
249	0.846
250	0.857
251	0.861
252	0.861
253	0.858
254	0.842

3.3 PLOTTING A STANDARD CURVE

A plot of absorbance of acetohexamide against its concentration at the wavelength of maximum absorbance will reveal up to what concentration Beer's law is obeyed. The same plot will also give the limit of concentration range whose reading on the instrument can be relied on and therefore act as a guide on what concentration range to prepare to obtain reliable readings.

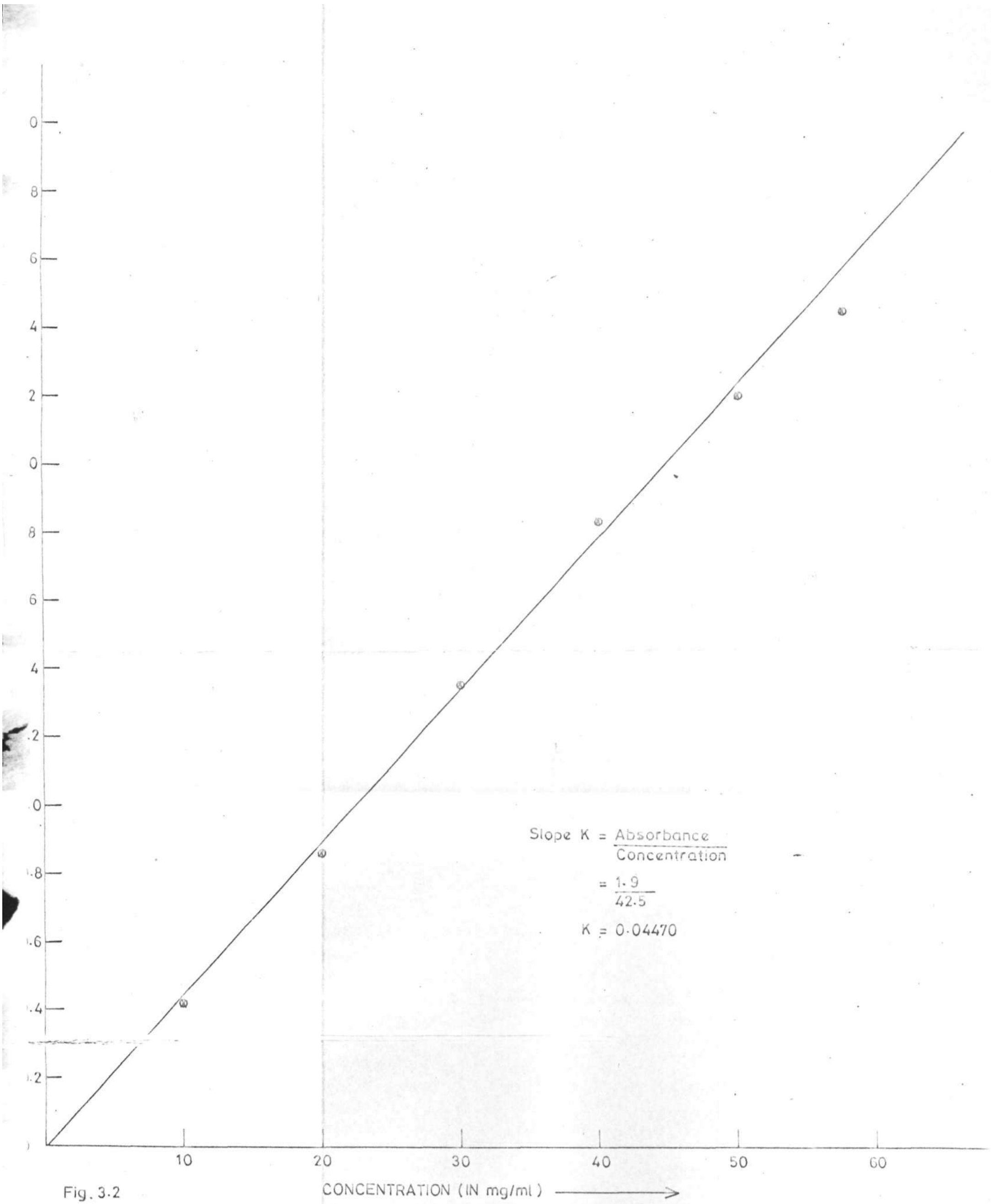
The slope of the plot will provide the specific absorbance, K, where.

$$\text{Slope } K = \frac{\text{Absorbance}}{\text{Concentration}}$$

METHOD

100 mg. pure acetohexamide was dissolved in 100ml., 100% methanol to provide 1mg/ml acetohexamide solution in 100% methanol. 20 ml. of this solution was diluted to 40 ml. with distilled water to provide the solution in 50% methanol and further diluted to 200 ml. with an already prepared 50% methanol. This provided a solution of 100 µg/ml. Acetohexamide in 50% methano. From this stock solution dilutions were carried out to provide the different concentrations for plotting a standard curve.

Using the UV Spectrophotometer the absorbance of each concentration was recorded against the concentration.



Slope K = $\frac{\text{Absorbance}}{\text{Concentration}}$

$= \frac{1.9}{42.5}$

K = 0.04470

Fig. 3.2

A plot of absorbance against concentration was constructed and the slope calculated.

TABLE 3.7

READING FOR PLOTTING A STANDARD CURVE

CONCENTRATION (µg/ml)	ABSORBANCES (AT 250nm) I	II	III	AVERAGE
2	0.089	0.092	0.090	0.090
5	0.230	0.221	0.224	0.225
10	0.424	0.417	0.407	0.416
20	0.875	0.869	0.839	0.861
30	1.375	1.345	1.325	1.348
40	1.858	1.781	1.829	1.835
50	2.235	2.204	2.203	2.214
60	2.460	2.450	2.455	2.455

3.3.1 RESULTS AND DISCUSSION

Table 3.7 and Fig. 3.2 show the results. Fig. 3.3 is a plot of the readings in Table 3.7. Fig. 3.2 shows that up to about 45 µg/ml, Beer's law is obeyed. Concentration readings on the spectrophotometer within this range may reasonably be relied on. Above this range, a gradual deviation from the straight line may be noted in the plot.

This gives an indication of what concentration range to prepare before taking absorbance readings on the Spectrophotometer.

The slope of the curve is given by

$$\text{Slope } K = \frac{\text{absorbance}}{\text{concentration}}$$

$$= \frac{1.9}{42.5}$$

$$= 0.04470$$

K is the specific absorbance for acetohexamide in this experiment.

3.4 DETERMINATION OF THE SOLUBILITY OF PURE ACETOHEXAMIDE IN WATER

The ultimate object of this research work is to find out the increased solubility of acetohexamide by certain carriers. United States Pharmacopeia (USP XIX) 19th Revision states that acetohexamide is practically insoluble in water. It is, however, believed that at least, a negligible amount of acetohexamide be soluble in water. Before a comparative increase in solubility is observed this negligible amount of acetohexamide soluble in water must be determined.

METHOD

Two different samples were prepared and the process repeated three times for each sample.

In sample one, 50mg weight of acetohexamide was taken in a 100 ml. volumetric flask and 50 ml. volume of distilled water added.

These two samples were each shaken on a Griffin flask shaker for 48 hours. The samples were then filtered through a millipore filter membrane, of 5 µm porosity. The absorbance of the filtrate was determined on the U.V. Spectrophotometer at 251nm using distilled water as reference standard.

TABLE 3.8

DETERMINATION OF THE SOLUBILITY OF PURE ACETOHEXAMIDE IN WATER.

SAMPLE	FILTERATE					
	I		II		III	
	ABSORBANCE AT 251nm	CONCENTRATION (ug/ml)	ABSORBANCE AT 251nm	CONCENTRATION (ug/ml)	ABSRBANCE AT 251nm	CONCENTRATION (ug/ml)
50mg Acetohexamide in 50ml. WATER	0.961	21.500	0,783	16.5	0.859	18.0
125mg ACETOHEXAMIDE IN 25ML. WATER	1.006	22.5	0.809	17.0	1.126	23.0
AVERAGE		22.0		17.0		20.5

GROSS AVERAGE = 0.0198 ug/ml

= 0.02mg/ml.

3.4.1 RESULTS AND DISCUSSION

The results are shown in table 3.8. Sample one is 50mg/50ml. Acetohexamide in water, which is apparently 1mg/ml. Sample two is 125mg/25ml Acetohexamide, apparently showing 5mg/ml. Sample two is therefore 5 times more than sample one. But

the results after shaking is not showing a corresponding increase. This shows that shaking the two samples for 48 hours brought the acetohexamide in equilibrium with water.

The concentrations were calculated by using K (Fig 3-2) determined from the standard curve. This shows that the maximum solubility of acetohexamide is 0.02mg/ml or 20 ug/ml. at room temperature.

CHAPTER 4

EXPERIMENTAL STUDIES

PREPARATION AND STABILITY STUDIES OF THE DISPERSION

4.1 INTRODUCTION

The object of this study is to prepare the solid dispersion of acetohexamide in various concentrations by the melt method and the coprecipitate method and subject these dispersions to stability and standardisation tests. The solid dispersion of acetohexamide in polyethylene glycol (PEG) 6000 was prepared by the melt method while the dispersion of acetohexamide in polyvinylpyrrolidone (PVP) 44000 was prepared by the coprecipitate technique. The stability of acetohexamide in these dispersions were studied by the thin layer chromatography and the ultraviolet spectrophotometric methods. The infrared (I.R.) spectrum of the dispersion was taken and the phase diagram of the dispersion of acetohexamide in PEG was plotted.

4.2 PREPARATION OF THE DISPERSION

4.2.1 Solid dispersion by melt method

Various concentrations ranging from 5% to 80% of acetohexamide/polyethylene glycol 6000 dispersions were prepared by the melt method as already described. The same observations were taken as earlier described, and shown in tables 4.1 and 4.2. The different dispersion concentrations prepared were dried at room temperature over phosphorous pentoxide P_2O_5 in a dessicator. The dispersions were powdered, sieved through 355/250 µm sieve and stored at room temperature in a dissicator containing phosphorous pentoxide.

4.2.2. Solid dispersion by coprecipitate method

Different concentrations ranging from 5% to 60% of acetohexamide/polyvinylpyrrolidone 44000 were prepared by the coprecipitate method as earlier described. The same observation as earlier described were made as shown in table 4.3. The solvent liquid was methanol/acetone in 1:1 ratio. The solvent was evaporated at a temperature not exceeding about 50° over a water bath. The solid dispersion was dried in a dessicator at room temperature over phosphorous pentoxide. The dried coprecipitate was powdered, sieved through 355/250 um sieve size and stored in the dessicator containing phosphorous pentoxide.

TABLE 4.1

DIFFERENT CONCENTRATIONS OF ACETOHEXAMIDE/PEG. 6000 FUSION MELT DISPERSIONS

Sample concentrations	Temp. Melting started (°C)	Temp. Discolouration, Gas Evolved °C	Temp. Melting completed °C	Number and description of phases
5%	58° carrier melting	-	112°	a pale yellow single phase
10%	58 carrier melting	-	120°	a pale yellow single phase
20%	59 melting melting	127 Gas Evolved 130 foaming	133 foam clears	a pale yello single phase
30%	60 carrier melting	130 Gas Evolved 135 foaming	138 foaming clears	a pale yellow single phase
40%	60 carrier melting	130 Gas evolved foaming	138 foaming	a pale yellow single phase
50%	60 carrier melting	132 Gas evolved 136 foaming	140 foaming clears	a pale yellow single phase
60%	61 carrier melting	133 Gas evolved 138 foaming	142 foaming cleare	a pale yellow single phase
70%	61 carrier melting	133 Gas evolved 138 foaming	144 foaming clears	a pale yellow single phase
80%	61 carrier melting	133 Gas evolved 138 foaming	145 foaming clears	a pale yellow single phase.

TABLE 4.2

DIFFERENT CONCENTRATIONS OF ACETOHEXAMIDE/PEG. 6000 FUSION MELT DISPERSIONS DESCRIPTION OF THE FUSION MELT DISPERSION.

DISPERSION CONCENTRATION	TIME TAKEN FOR THE MELT TO SOLIDIFY	PHYSICAL STATE OF THE MASS	TIME TAKEN FOR THE MASS TO DRY
5%	Less than 5 minutes	Pale yellow oily mass	Less than one day
10%	Over 5 minutes	"	Less than one day
20%	Between 5 - 10 minutes	pale yellow	about one day
30%	5 - 10 minutes	dark yellow	Over one day
40%	5 - 10 minutes	dark yellow	2 - 5 days
50%	About 10 minutes	Brownish	3 - 5 days
60%	10 - 15 minutes	Brownish	5 - 6 days
70%	10 - 15 minutes	Brownish	Over one week
80%	10 - 15 minutes	Brownish mass	Over 8 days

TABLE 4.3

DIFFERENT CONCENTRATIONS OF ACETOHEXAMIDE DISPERSED IN POLYVINYLPYRROLIDONE BY COPRECIPITATION

10g. Samples	Volume of solvent added (ml)	Description solution	Coprecipitate
5%	70	Pale yellow and Gumy substance initially with a resultant pale yellow solution same	Pale yellow shiny crystals
10%	80	Same as above	ligh pale yellow
20%	155	Becomes ligh lighter	slight pale yellow almost colourless
30%	175	colourless	
40%	400	colourless	white
60%	730	colourless	white

TABLE 4.4

ACETOHEXAMIDE STABILITY IN THE COPRECIPITATE BY ULTRAVIOLET SPECTROPHOTOMETRY

Percentage sample dispersion	Theoretical Concentration of acetohexamide in sample (ug/ml)	Absorbance AT 251nm	Calculated concentration of acetohexamide in the samle (ug/ml)	Percentate difference
5%	25.0	1.117	24.99	-0.04
10%	25.0	1.115	24.94	-0.24
20%	25.0	1.118	25.01	+0.04
30%	25.0	1.116	24.97	-0.12
40%	25.0	1.118	25.01	+0.04
60%	25.0	1.116	24.97	-0.12

4.2.3 PREPARATION OF THE PHYSICAL MIXTURES:

a) With the carrier, polyethylene glycol 6000

Ideally the acetohexamide and the polyethylene glycol 6000 supplied should have been sieved through 355/250 um sieve before mixing and using the mixture for dissolution rate studies. The acetohexamide supplied was in very fine powder. No attempt was made to recrystallise it before preparing the physical mixture with polyethylene glycol 6000.

On the other hand, the polyethylene glycol 6000 supplied was in the form of flakes. The PEG. was, therefore, powdered and screened through 125 um sieve to provide as fine powder as the acetohexamide before preparing their physical mixtures.

The physical dispersions of acetohexamide in the carrier were prepared in different concentrations by weighing the required amount of acetohexamide and the carrier into a glass mortar and physically mixing them using a glass pestle.

b) With the carrier polyvinylpyrrolidone 44000

The physical mixture of acetohexamide and polyvinylpyrrolidone 44000 were prepared only in different concentrations ranging from 5% to 30%. The required amounts of acetohexamide and the carrier were weighed into a glass mortar and physically mixed using a glass pestle.

4.3 STABILITY DETERMINATION OF ACETOHEXAMIDE IN THE DISPERSIONS

Two methods have been employed for the stability determination of acetohexamide in the carriers.

a) Thin layer chromatography

b) Spectrophotometric method.

4.3.1 Stability determination by thin-layer chromatography

The thin-layer chromatography was used by Strickland[55] (1966) for the detection of oral hypoglycaemic agents. Chiou and Riegelman[10, 8] (1969) have also used this method for stability studies of drugs in solid dispersions.

The thin-layer chromatography uses the principle of adsorption. Certain materials have the ability to adsorb some other substances; e.g. carbon has the ability to adsorb certain gases. The adsorbed materials form a "bond" with the surface of the adsorbent resulting in a layer of the adsorbed material being attached to the surface of the adsorbent. The type of bond various from Van der Waals forces to chemical bonds. For any two given materials there is a difference between their forces of attraction for the surface of the adsorbent. This difference can be used as a means of separating chemical materials. If

two compounds are adsorbed by a solid and a solvent is passed over them the one less tightly held will be washed away first. It will then pass on to a new portion of the surface and reform its bond. By a repeated series of adsorptions and desorptions, separation of chemical materials can be carried out [7]. Separation will depend on the strength of the bond between the solid and the chemical compound to be separated, on the solubility of the compound in the solvent (or mobile phase) and on the rate of flow of the solvent.

4.3.2 Preparation of Plates

i) PLATES: 20cm x 20 cm size of glass plates were used

ii) Adsorbent: Silica gel $G.F._{254}$ (type 60) E. Merck.

The plate was prepared by weighing 40gm. silica gel, adding 80ml. distilled water and shaking vigorously until a slurry was formed (shaking for approximately 95 seconds). The slurry was poured into the trough of the applicator head adjusted to 250 um on the glass plate. The trough was gently run on the plates to form uniformly 250 um thick layer of the adsorbent on the glass plates already arranged on the applicator. The plates were allowed to dry for about 12 hours and activated by heating at 110° in an oven for one hour. Activated plates were used the same day.

iii) Solvent System: Acetone-benzene-water mixture in the ratio 65:30:5.

iv) VISUALIZATION: 3mg/ml ninhydrin in n-butanol (Ninhydrin spray) and then 5% Vanillin in concentrated sulphuric acid reagent.

v) STANDARD: Acetohexamide solution - 1% prepared by weighing 500 mg. acetohexamide powder and dissolving in 50 ml. acetone-methanol mixture in the ratio 1:1.

4.3.3. METHOD: A 1% solution of the dispersion was prepared in acetone-methanol mixture in 1:1 ratio.

Using glass micropipettes a spot of each solution of the dispersions was applied to two points on the plates each point being 10cm apart. A spot of the reference standard (1% acetohexamide solution in acetone-methanol mixture) was applied in between the two points, 5cm. from each point of application of the substance under investigation. The mobile phase (solvent front) was allowed to advance 10cm. in a previously saturated paper lined tank. The plates were removed and after air-evaporation of the solvent they were observed under ultraviolet light. The plates were then heated for 20 minutes at 110°C sprayed with ninhydrin spray, heated for a further ten minutes at the same temperature and then sprayed with 5% vanillin

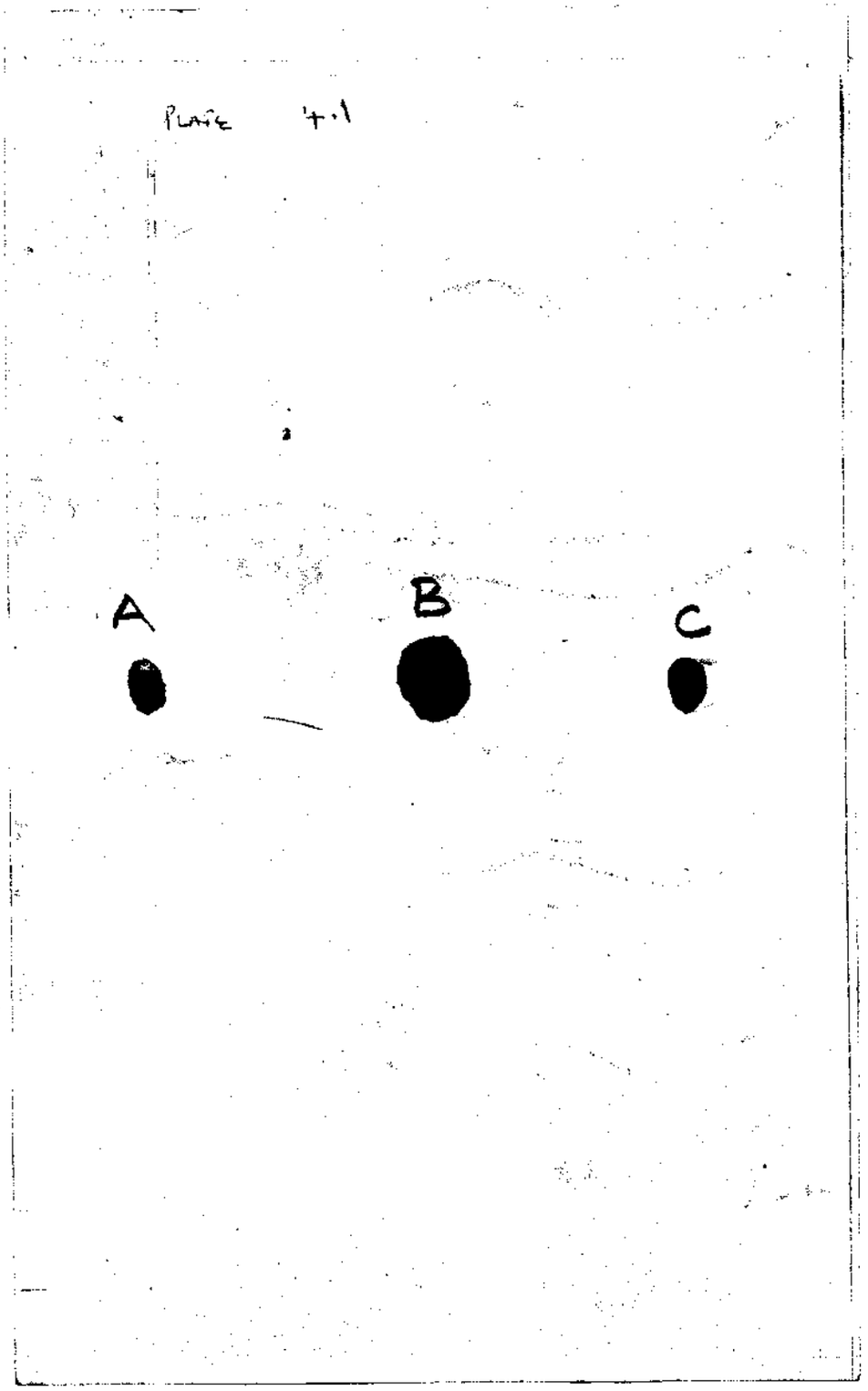


Fig. 4.1 - T.L.C. PLATE

in concentrated sulphuric acid already prepared. The plates were warmed for two minutes and acetohexamide appeared immediately as red spots. These spots were traced as the spots did not clearly show when the photograph was taken. One such result is shown in Fig. 4.1.

4.3.4. Results and discussion

This experiment was carried out in anticipation that if acetohexamide decomposed on heating with the carrier, a new compound would be formed. There would be a difference in the forces of attraction for the surface of the adsorbent between acetohexamide and the new compound formed. On running the T.L.C. there will be separation and the new compound should be observed at a point on the chromatogram [illegible] different from the point of acetohexamide either by using the ultraviolet light or during spraying with ninhydrin or vanillin in conc. H_2SO_4. No such point of a new compound has been observed in this experiment. Acetohexamide clearly shows as red spots. At least the R.F. was expected to be affected but no clear effect is observed.

This does not mean that acetohexamide has not undergone alteration in the carriers. Since the presence of acetohexamide in the dispersion is seen just as red spot after spraying the chromatoplate

with Vanillin in Con. H_2SO_4, it does not indicate the concentration of acetohexamide in the dispersion and therefore, can not show partial decomposition of acetohexamide in the dispersion. Another method must be employed to show partial decomposition.

4.3.5 Stability determination by spectrophotometry

An initial experiment was conducted to see if the carriers used (polyethylene glycol 6000 and polyvinypyrroldione 44000) has any absorbance at the wavelength of maximum absorbance of acetohexamide. The experiment showed that since the carriers did not show any evidence of absorbance at the working wavelength the carriers would not interfere with the determination of acetohexamide at that wavelength.

The spectrophotometric method compares actual readings on the spectrophotometer to theoretical, calculated results. A reasonable deviation indicates instability.

4.3.6 Method

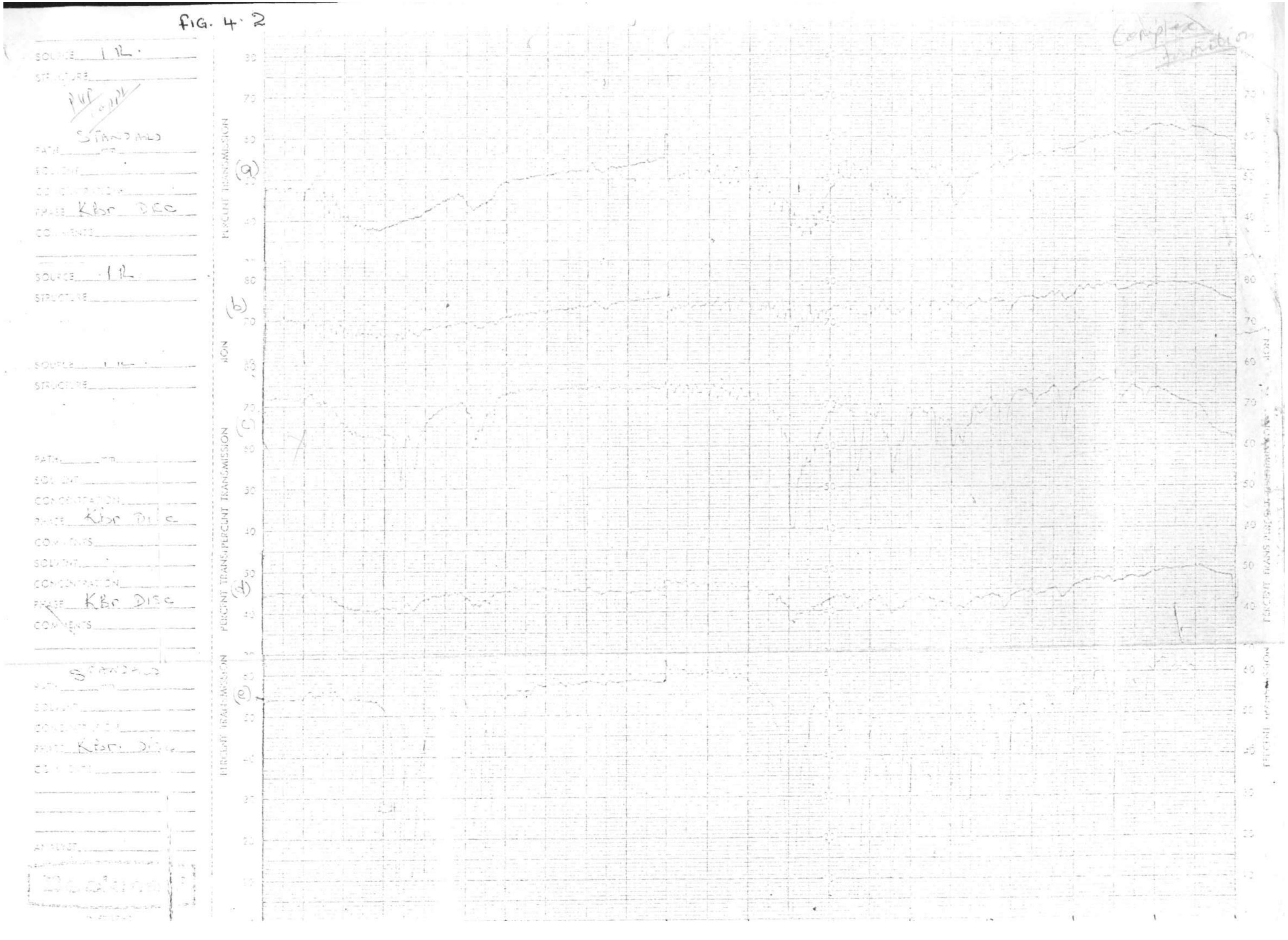
50mg. of each dispersion was dissolved in a 100ml. volume of 100% methanol. 50 ml. portion of this solution was diluted to 100ml. with distilled water to provide a solution in 50% methanol. With an already prepared 50% methanol serial dilutions were carried out for each dispersion concentration so that the solutions gave concentrations in 50% methanol. The absorbance readings of the solutions were taken as earlier described.

TABLE 4.5

STABILITY DETERMINATION OF ACETOHEXAMIDE IN THE DIFFERENT CONCENTRATIONS OF THE FUSION MELT DISPERSION BY THE ULTRAVIOLET SPECTROPHOTOMETER

Dispersion concentration	Theoretical acetohexamide concentration in the sample	Absorbance AT 251nm	Calculated concentration of acetohexamide in the sample ug/ml	Percentage difference
5%	25ug/ml	1.112	24.877	-0.49
10%	25ug/ml	1.114	24.922	-0.31
20%	20ug/ml	0.894	20.00	-0.00
30%	30ug/ml	1.340	29.978	-0.07
40%	20ug/ml	0.893	19.978	-0.11
50%	25ug/ml	1.117	24.989	-0.04
60%	30ug/ml	1.339	29.955	-0.15
70%	25ug/ml	1.118	25.011	+0.04
80%	20ug/ml	0.893	19.978	-0.11

FIG. 4.2



SOURCE IR.
STRUCTURE
PUP COPPL
STANDARD
PATH mm
SOLVENT
CONCENTRATION
PHASE KBr DISC
COMMENTS
SOURCE IR
STRUCTURE
SOURCE IR
STRUCTURE
PATH mm
SOLVENT
CONCENTRATION
PHASE KBr DISC
COMMENTS
SOLVENT
CONCENTRATION
PHASE KBr DISC
COMMENTS
STANDARD
PATH mm
SOLVENT
CONCENTRATION
PHASE KBr DISC
COMMENTS
ANALYST
PERCENT TRANSMISSION
(a)
(b)
(c)
(d)
(e)
Complex formation

FIG. 4·3

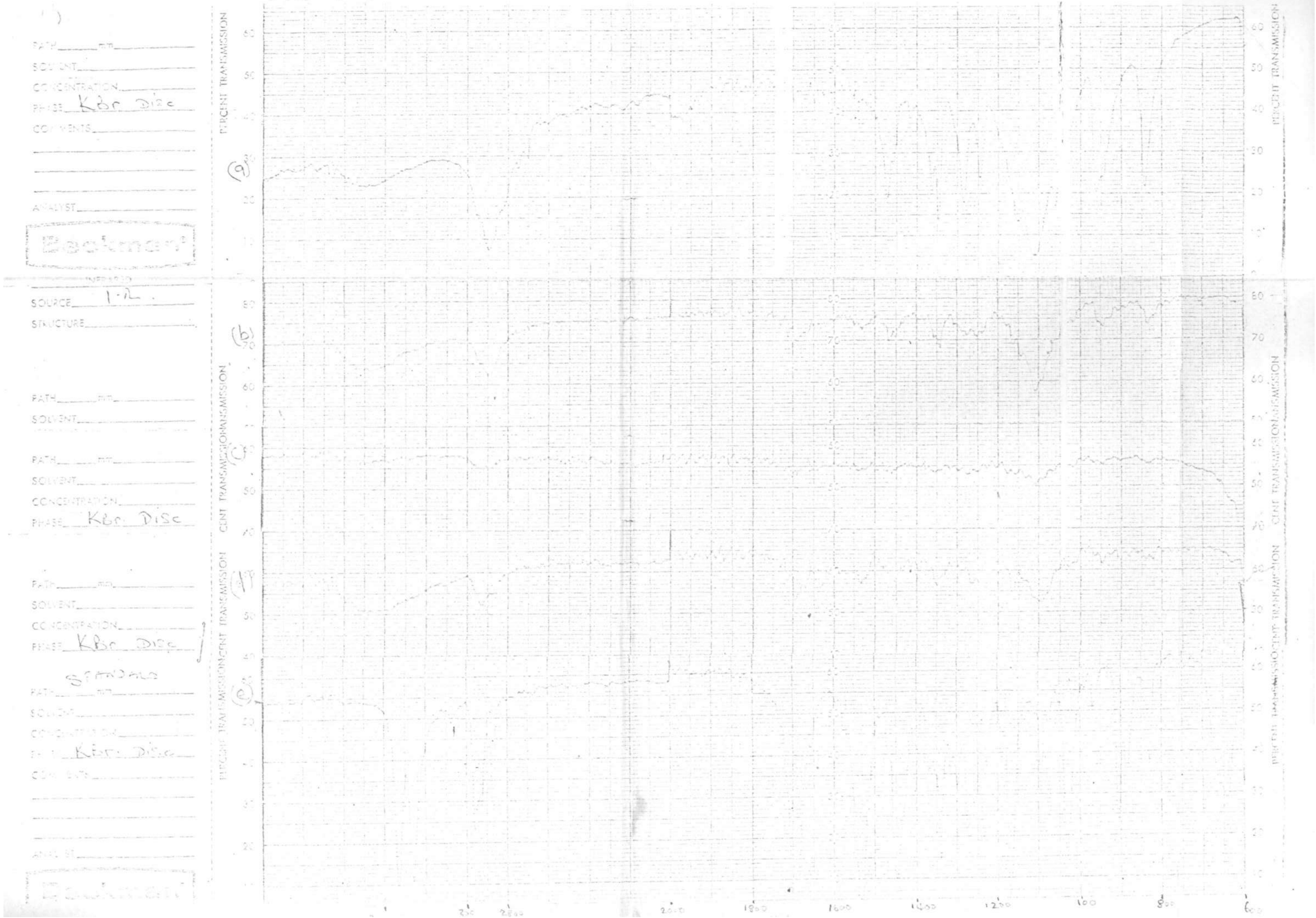

PATH mm
SOLVENT
CONCENTRATION
PHASE KBr Disc
COMMENTS
ANALYST
Beckman
INFRARED
SOURCE 1·2
STRUCTURE
PATH mm
SOLVENT
PATH mm
SOLVENT
CONCENTRATION
PHASE KBr Disc
PATH mm
SOLVENT
CONCENTRATION
PHASE KBr Disc
SPANDALO
PATH mm
SOLVENT
CONCENTRATION
PHASE KBr Disc
COMMENTS
ANALYST
Beckman
PERCENT TRANSMISSION
(a)
(b)
(c)
(d)
(e)
2800
2000
1800
1600
1400
1200
1000
800
600

Fig. 4.2

(a) Pure polyvinylpyrrolidone (PVP) 44000

(b) acetohexamide/PVP. 44000
20% coprecipitate dispersion

(c) 30% acetohexamide/PVP. 44000
physical mixture

(d) 30% acetohexamide/PVP. 44000
Coprecipitate dispersion

(e) Pure acetohexamide

Fig. 4.3

(a) Pure polyethylene glycol (PEG) 6000

(b) 20% acetohexamide/PEG. 6000 melt dispersion

(c) 50% acetohexamide/PEG. 6000
melt dispersion

(d) 60% acetohexamide/PEG 6000

(e) Pure acetohexamide

4.4 The Infra-red studies (I.R.)

The KBr method was used for the infra red determination of some of the dispersions.

4.4.1 Results and discussion.

The infra red spectrum of some of the dispersions are shown in Fig. 4.2 and 4.3. Fig. 4.2 shows the I.R. spectrum of the dispersions in polyvinylpyrrolidone 44000 with those of pure PVP and pure acetohexamide while Fig. 4.3 shows the dispersion in PEG. 6000 with pure PEG and pure acetohexamide. The spectrum shows some interaction between the drug and the carriers. In Fig. 4.2 these interactions can be noted between 2800cm^{-1} wave number and 3400cm^{-1} wave number between 600 and 1750 wave number (the finger print region). In Fig. 4.3, these interactions can be noted in the same areas as in Fig. 4.2. These interactions cannot be said to have resulted in acetohexamide decomposition in the carriers since such decomposition has not been observed either by the thin-layer chromatography or the UV. spectrophotometry. The type of interaction remains to be investigated.

The spectrum shows that some differences may exist in the nature of the interaction between acetohexamide and polyethylene glycol 6000 and the interaction between acetohexamide and polyvinylpyrrolidone 44000.

4.5 The Phase diagram

The purpose of the phase diagram is to correlate the extent of interaction between the drug and the carrier at solid state, if any and to see if the interaction results in the formation of solid solution or a simple eutectic mixture. The formation of a eutectic or solid solution helps to explain the characteristic of the dissolution rate. Goldberg et al (1965) (28, 30, 31, 32) have used the phase diagram to identify the formation of eutectic mixtures and solid solutions in a dispersion and have explained the increased dissolution rate of the dispersion as a function of solid solution formation rather than the simple eutectic formation. Block et al (5) (1982) have also used the phase diagram. Because of inadequate chemicals and equipment the phase diagram of only the dispersion of acetohexamide in polyethylene glycol 6000 by the melt method has been attempted.

4.5.1 Method

The thermomicroscopic method as used by Goldberg et al (30) (1966) was used. Different concentrations of acetohexamide in polyethylen glycol 6000 ranging from 10% to 90% was prepared by the melt method. The melt dispersion was allowed to dry and then powdered. A polarised microscopy with a hot stage was used. The fine powder of the dispersion was placed on a cover slip and covered with another cover slip. The mounted

Table 4.6 - Melting temperature of different dispersion concentrations.

Sample Disp.	1st temp. Range C°	Average
Pure PEG. 6000 =	59 - 63° -	61
10% =	57 - 60 -	58.5
20% =	56.5 - 60 -	58
30% =	55 - 59 -	57
40% =	53 - 56 -	54.5
50% =	54 - 60 -	57
60% =	95 - 105 -	100
70% =	115 - 120 -	117.5
80% =	118 - 127 -	122.5
90% =	139 - 148 -	143.5
Pure acetohexamide =	185 - 188 -	186.5

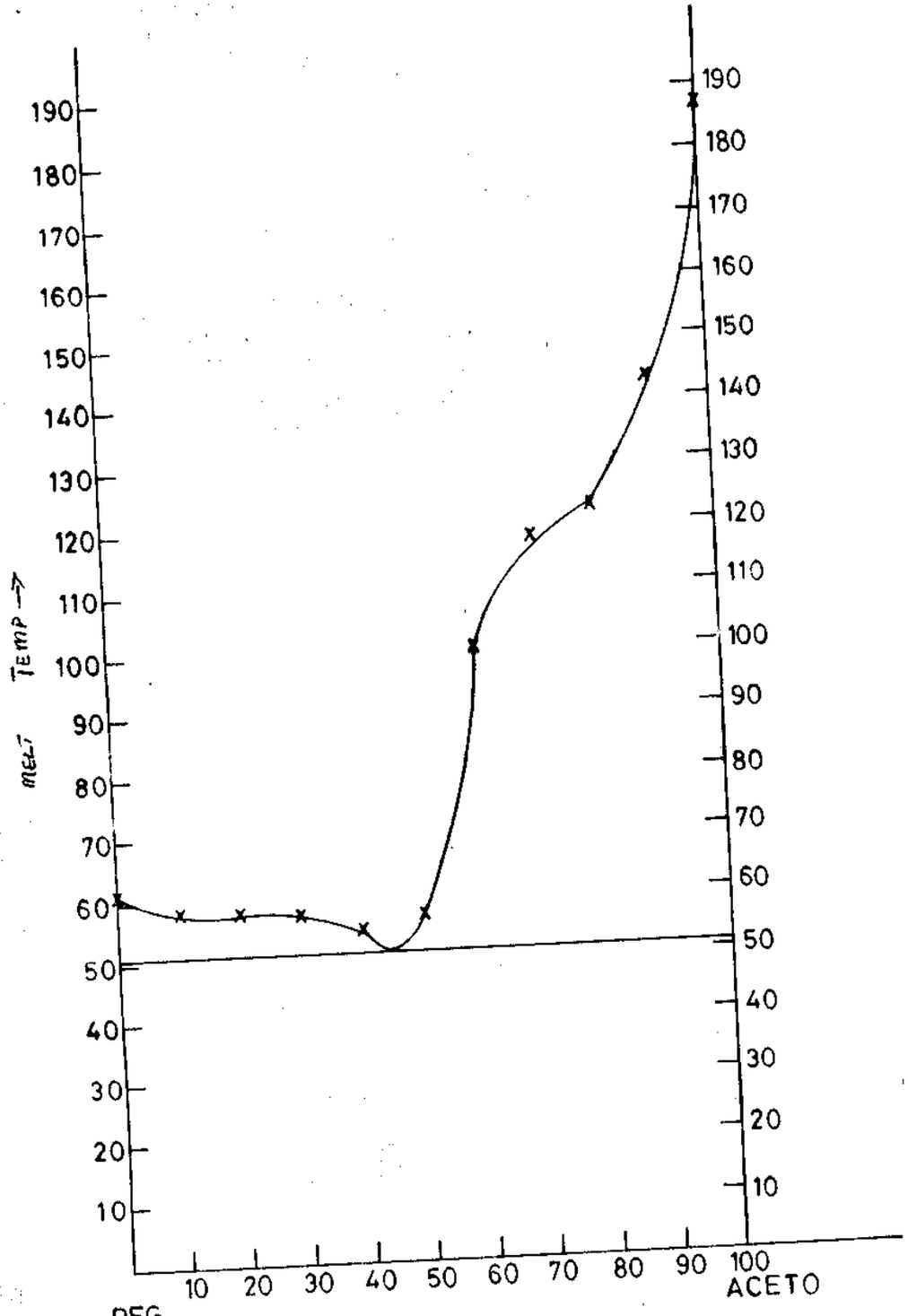


Fig. 4.4 Phase digram - Acetohexamide polyethylene glycol 6000

powder in the cover slip was placed in the heating part of the hot stage microscope and covered with a modified glass so provided as to minimise the amount of heat escaping from the hot area of the microscope. With a thermometer in place the powdered dispersion was electrically heated and observed under the high power magnification of the microscope. Initially the heating was rapid in order to make a rough estimate of the melting point range. When the melting point range was approximated heating was done with a fresh sample at a rate not more than 3° per minute near the estimated melting point. This was repeated for all the dispersions prepared and also for both pure acetohexamide and pure polyethylene glycol 6000.

4.5.2 Results

Table 4.6 is the melting temperature of different concentrations of acetohexamide/polyethylene glycol 6000 dispersion by the melt method. As each dispersion concentration was heated the melting point was a range as can be observed in the table. When the first melt was completed there were some particle-like substances (not crystal like) that appeared to float on the melt. On continued heating these particles gradually disappeared. A plot of the result is shown in Fig. 4.4. Fig. 4.4 is a plot of the average of the range of temperature.

4.5.3 Discusssion

From Fig. 4.4 One would be tempted to predict a eutectic formation with 45% acetohexamide 65% polyethylene glycol 6000 and with a eutectic temperature at about 52°C. The thermal microscopic method cannot be reliably used for determining the phase diagram of the acetohexamide/polyethylene glycol 6000 dispersion(9). This becomes more obvious when one notes from table 4.6 that even the melting points of the pure substances, acetohexamide and polyethylene glycol 6000, show ranges.

The cooling curve method would probably have been better since pure substance would show constant melting temperature as against a range observed in the thermomicroscopic method.

4.6 Solubility studies

Solubility studies of pure acetohexamide was determined in solutions of polyethylene glycol 6000. The aim of solubility studies is to determine any possible interaction between the drug and the carrier in aqueous solution.

4.6.1 Method

1 gm. polyethylene glycol 6000 was dissolved in 200 ml. distilled wate to prepare a stock solution. From this stock solution the following dilute solutions were prepared;

1mg/100ml

5mg/100ml

10mg/100ml

20mg/100ml

50mg/100ml

100mg/100ml

An excess amount of acetohexamide (500mg) was weighed into 50ml of each of the prepared solutions in a 100 ml volumetric flask. The flasks were sheken for 48 hours using a Giffin flask shaker, and allowed to settle for one hour. The contents were filtered through a filter membrane, 5 um, and the absorbance of the filtrate taken on the U.V. Spectrophotometer at 251nm.

Table 4.7

Solubility of acetohexamide in polyethylene glycol solutions

PEG Concentration		Absorbance of the filtrate at 251nm		Concentration (ug/ml)
2 ug/ml	-	0.823	-	18.412
5 ug/ml	-	0.837	-	18.725
10 ug/ml	-	0.851	-	19.038
20 ug/ml	-	0.927	-	20.805
50 ug/ml	-	0.930	-	20.798
100 ug/ml	-	0.935	-	20.917

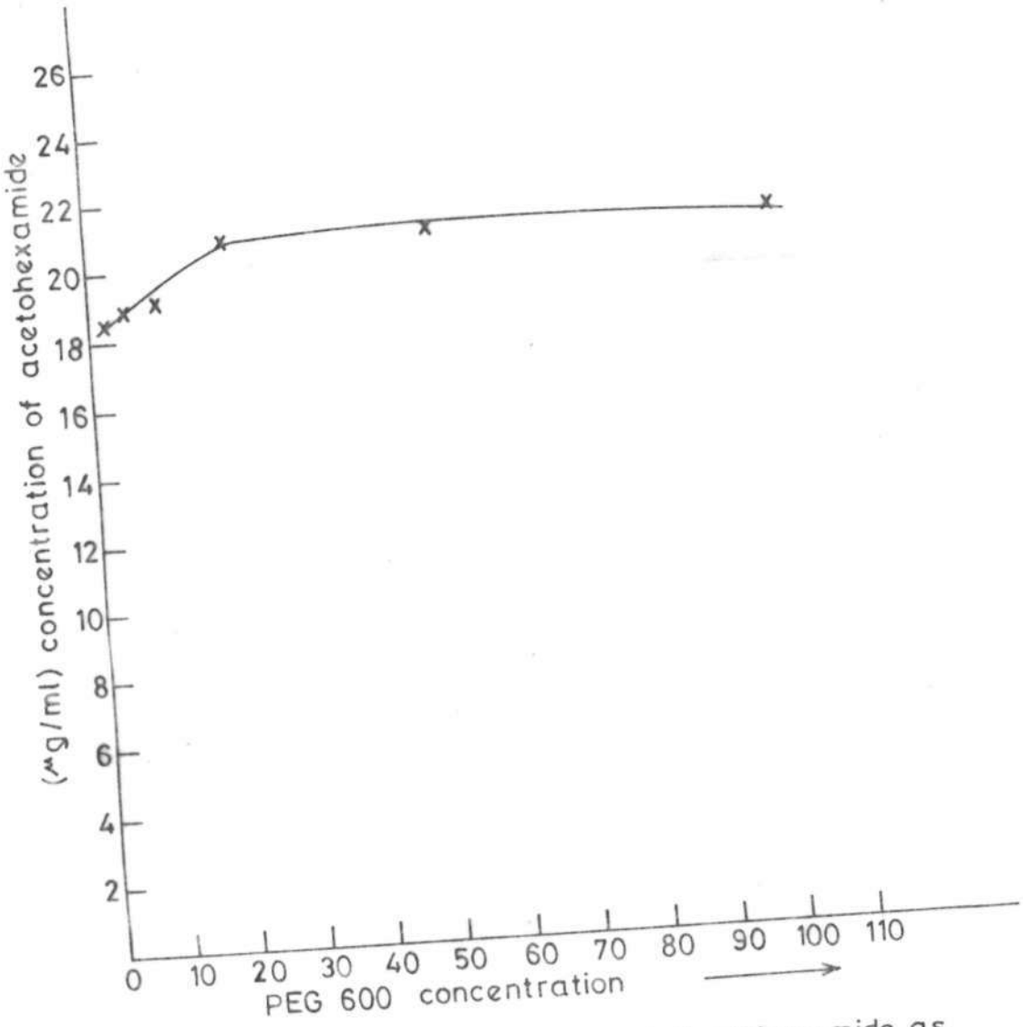


Fig. 4.6 Aqueous Solubility of Acetohexamide as a function of PEG concentration.

CHAPTER 5

IN VITRO DISSOLUTION RATE STUDIES

5.1 INTRODUCTION

In this experiment the two methods of dissolution rate studies earlier mentioned, ie. the tape method and the bag method have been compared and on the basis of the comparison the tape method was chosen and used for further dissolution rate studies. In the dissolution rate studies, the rate and the quantity of acetohexamide released from the dispersions prepared by the fusion melt and the coprecipitate methods were studied and these were compared to their physical mixtures.

5.2 COMPARISON OF THE BAG METHOD AND THE TAPE METHOD

Dissolution rate studies were carried out using the bag method and the tape method as earlier described. Two concentrations, 5% and 20% dispersions of acetohexamide in polyvinylpyrrolidone 44000 were arbitrarily chosen for comparison of the two methods. Both the coprecipitate and the physical dispersions were used.

5.2.1 Method

The prepared dispersions were carefully weighed on an electrical balance and carefully transferred into either the bag or the tape surface as the case may be; care was taken so as not to loose particles of the dispersion during the transfer from the weighing balance. All the precautions already mentioned about the tape and bag methods were taken. Sample containing 4mg. acetohexamide (which is equal to half the determined solubility of acetohexamide in water) were used so as not to saturate the dissolution medium. The dissolution medium was 400ml distilled water in a 600ml beaker maintained at 37°C in a constant temperature water bath. The bag containing the sample in the dissolution was rotated at 50 r.p.m. while the paddle in the tape method was rotated at 50 r.p.m. Each dissolution rate experiment was run for sixty minutes. 5ml. samples of the dissolution medium were withdrawn and immediately replaced with another 5ml water at the given time intervals. These samples were

assayed without dilution at 251nm using the ultraviolet spectrophotometer S.P. 30. Each result is an average of three experiments.

5.2.2 Calculations

It was recognised that at least a little quantity of the drug was taken away from the dissolution medium along with the aliquot of the dissolution medium withdrawn for analysis. Such quantities were considered insignificant and have not been corrected for. So, the results calculated are not cummulative. The formula used for calculations are as follows:

$$\frac{\text{Absorbance} \times \text{dilution factor} \times \text{Vol. of dissolution medium}}{K \times 1000} = \text{Quantity of drug released in milligrams}$$

$$\frac{\text{Drug released in milligrams} \times 100}{\text{Amount of drug (in mg.) in the dispersion used in the dissolution rate test.}} = \text{Percentage of drug released}$$

5.2.3 Results and Discussion

The results are shown in tables 5.1 to 5.8 and Figs. 5.1 and 5.2. The dissolution rate of pure acetohexamide was taken using the tape method.

(a) 5% dispersion

The release of acetohexamide from 5% dispersion is shown in tables 5.1 to 5.4 and Fig. 5.1. From the tables and the graphs it can be observed that acetohexamide release from the dispersions by any method is superior to its release into solution from its pure form. Acetohexamide release from its coprecipitate appears more significant in the tape method than in the bag method. Drug release from the physical mixture appears to be more consistent in the bag method than in the tape method. From the coprecipitate T_{50} (time taken for 50% of the drug to dissolve) is less than two minutes using the method while it is about two minutes using the bag method. From the physical dispersion T_{50} is less than two minutes using the tape method while it is about thirteen minutes using the bag method. So, while the overall drug release in the coprecipitate is more and faster with the tape method than the bag method, the release in the physical mixture is more by the bag method but faster by the tape method.

TABLE 5.1

5% ACETOHEXAMIDE/PVP 44000 COPRECIPITATE

AMOUNT OF DISPERSION - 80.0mg

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 4.0mg
VOLUME OF DISSOLUTION MEDIUM = 400ml.

THE BAG METHOD

TIME (MINUTES)	AVERAGE ABSORBANCE	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE (µg)	% ACETOHEXAMIDE RELEASED
1	0.155	3.47	1387.02	34.68
4	0.280	6.26	2505.59	62.64
8	0.310	6.93	2774.05	69.35
10	0.315	7.05	2818.79	70.47
15	0.320	7.16	2863.53	71.59
20	0.340	7.61	3042.51	76.06
30	0.345	7.72	3087.25	77.18
40	0.370	8.28	3310.96	82.77
50	0.365	8.16	3266.22	81.65
60	0.380	8.50	3400.45	85.01

THE TAPE METHOD — 5.2

TIME (MINUTES	AVERAGE ABSORBANCE AT 252nm	ACETOHEXAMIDE CONCENTRATION (µg/ml)	QUANTITY OF ACETOHEXAMIDE (µg)	% ACETOHEXAMIDE RELEASED
1	0.195	4.36	1744.97	43.62
4	0.445	9.95	3982.10	99.55
8	0.450	10.07	4026.85	100.67
10	0.460	10.29	4116.33	102.91
15	0.460	10.29	4116.33	102.91
20	0.460	10.29	4116.33	102.91
30	0.450	10.07	4026.85	100.67
40	0.455	10.18	4071.59	101.18
50	0.460	10.29	4116.33	102.91
60	0.455	10.18	4071.59	101.18

5% ACETOHEXAMIDE/PVP 44000 PHYSICAL MIXTURE

AMOUNT OF DISPERSION - 80.0mg

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 4.0mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml.

THE BAG METHOD - TABLE 5.3

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	ACETOHEXAMIDE CONCENTRATION (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE RELEASED
1	0.115	2.57	1029.08	25.73
4	0.160	3.58	1431.77	35.79
8	0.195	4.36	1744.97	43.62
10	0.200	4.47	1789.71	44.74
15	0.235	5.26	2102.91	52.57
20	0.240	5.37	2147.65	53.69
30	0.270	6.04	2416.11	60.40
40	0.265	5.92	2371.36	59.28
50	0.285	6.38	2550.34	63.76
60	0.275	6.15	2460.85	61.52

THE TAPE METHOD - TABLE 5.4

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE RELEASED
1	0.105	2.35	939.60	23.49
4	0.265	5,93	2371.36	59,28
8	0.260	5.82	2326.62	58,16
10	0.250	5.59	2237.14	55.93
15	0.255	5.70	2281.88	57.05
20	0.250	5.59	2237.14	55.93
30	0.250	5.59	2237.14	55.93
40	0.240	5.37	2147.65	53.69
50	0.240	5.37	2147.65	53.69
60	0.245	5.48	2192.39	54.81

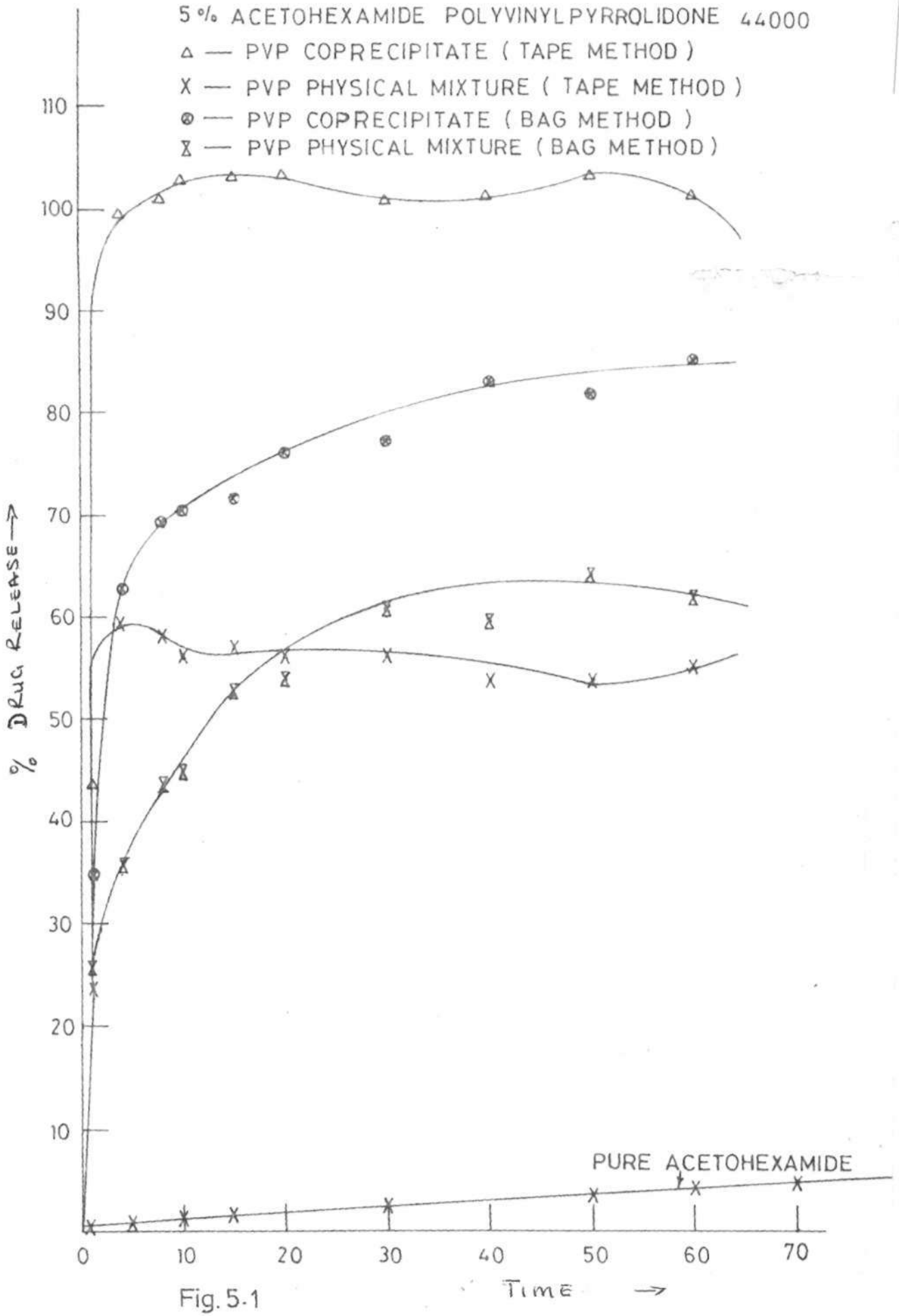

5 % ACETOHEXAMIDE POLYVINYLPYRROLIDONE 44000
△ — PVP COPRECIPITATE (TAPE METHOD)
X — PVP PHYSICAL MIXTURE (TAPE METHOD)
⊗ — PVP COPRECIPITATE (BAG METHOD)
⧖ — PVP PHYSICAL MIXTURE (BAG METHOD)
% DRUG RELEASE →
110
100
90
80
70
60
50
40
30
20
10
PURE ACETOHEXAMIDE
0
10
20
30
40
50
60
70
TIME →

Fig. 5-1

20% dispersion

The drug release from 20% dispersion is shown in tables 5.5 to 5.8 and in Fig. 5.2. The drug release from the coprecipitate appears more consistent in the tape method than in the bag method. The drug release from the physical dispersion using the two methods is nearly the same. T_{50} is not reached at all in the physical mixture and in the coprecipitate T_{50} is about 60 minutes from the coprecipitate dispersion using the tape method.

5.2.4 Conclusion

On the basis of the above studies, it appears that dissolution rate studies using the tape method is more signficant, consistent and may be more reliable than the bag method. The tape method was, therefore, chosen as the method to be used for further dissolution rate studies.

20% ACETOHEXAMIDE/PVP 44000 COPRECIPITATE

AMOUNT OF DISPERSION USED - 20.0mg

QUANTITY OF ACETOHEXAMIDE IN DISPERSION USED - 4.00mg

VOLUME OF DISSOLUTION MEDIUM = 400ml.

THE BAG METHOD - TABLE 5.5

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE RELEASED (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE RELEASED
1	0.160	3.58	1431.77	35.79
4	0.185	4.14	1655.48	41.39
8	0.170	3.80	1521.25	38.03
10	0.145	3.24	1297.54	32.44
20	0.150	3.36	1342.28	35.56
30	0.160	3.58	1431.77	35.79
40	0.175	3.91	1565.99	39.15
50	0.195	4.36	1744.97	43.62
60	0.220	4.92	1968.68	49.22

THE TAPE METHOD TABLE 5.6

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE RELEASED (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE RELEASED
1	0.120	2.68	1073.82	26.85
4	0.160	3.58	1431.77	35.79
8	0.175	3.91	1565.99	39.15
10	0.180	4.03	1610.74	40.27
15	0.190	4.25	1700.22	42.51
20	0.190	4.25	1700.22	42.51
30	0.195	4.36	1744.97	43.62
40	0.205	4.59	1834.45	45.86
50	0.215	4.81	1923.94	48.10
60	0.185	5.14	2058.16	51.45

20% ACETOHEXAMIDE/PVP 44000 PHYSICAL MIXTURE

AMOUNT OF DISPERSION - 20.0mg

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 4.00mg.

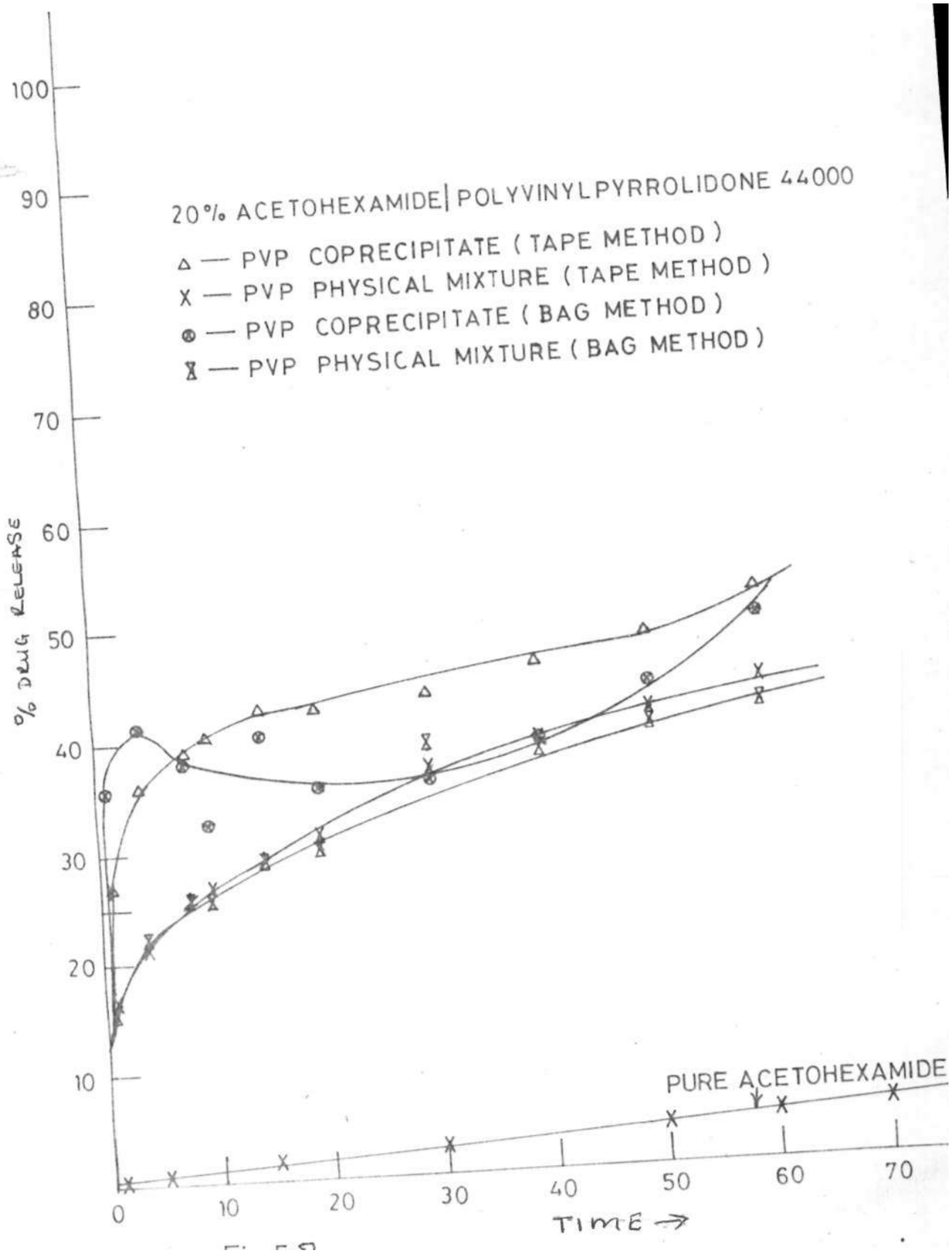
VOLUME OF DISSOLUTION MEDIUM = 400ml.

THE BAG METHOD TABLE 5.7

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg/ml)	% ACETOHEXAMIDE RELEASED
1	0.070	1.57	626.40	15.66
4	0.100	2.24	894.85	22.37
8	0.115	2.57	1029.08	25.73
10	0.115	2.57	1029.08	25.73
15	0.130	2.91	1163.31	29.08
20	0.135	3.02	1208.05	30.20
30	0.175	3.91	1565.99	39.15
40	0.170	3.80	1521.25	38.03
50	0.180	4.03	1610.74	40.26
60	0.185	4.14	1655.48	41.39

THE TAPE METHOD TABLE 5.8

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXAMIDE REEASED (ug)	% ACETOHEXAMIDE RELEASED
1	0.075	1.68	671.14	16.78
4	0.095	2.12	850.11	21.25
8	0.115	2.57	1029.08	25.73
10	0.120	2.68	1973.82	26.84
15	0.130	2.91	1163.31	29.08
20	0.140	3.13	1252.80	31.32
30	0.165	3.69	1476.51	36.91
40	0.175	3.91	1565.99	39.15
50	0.185	4.14	1655.48	41.39
60	0.195	4.36	1744.97	43.62


20% ACETOHEXAMIDE| POLYVINYLPYRROLIDONE 44000
△ — PVP COPRECIPITATE (TAPE METHOD)
X — PVP PHYSICAL MIXTURE (TAPE METHOD)
⊗ — PVP COPRECIPITATE (BAG METHOD)
⧖ — PVP PHYSICAL MIXTURE (BAG METHOD)
% DRUG RELEASE
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
TIME →
PURE ACETOHEXAMIDE

5.3 IN VITRO DISSOLUTION RATE STUDIES USING THE TAPE METHOD

In this study the dissolution rate studies of the following using the tape method were carried out and compared.

1) Pure acetohexamide
2) The dispersion of acetohexamide at different concentrations in polyethylene glycol 6000 by the physical and the fusion melt disperstion technique.
3) The dispersion of acetohexamide at different concentrations in polyvinylpyrrolidone 44000 by both the physical and the coprecipitate dispersion technique,

The process is as earlier described with all the precautions taken. The quantity of the dispersion containing 8mg. of acetohexamide was used for dissolution rate studies in each case. The dissolution medium was 400ml. distilled water in a 600 ml. beaker maintained at 37°C in a constant temperature water bath. Each dissolution rate experiment was run for ninty minutes, 5ml. samples of the dissolution medium were withdrawn and immediately replaced with another 5ml. water at the given time intervals. These samples were assayed without dilution as in the previous case. Again the quantity and percentage of drug release is non cummulative. The results are shown in the tables and the figures. Each result is an average of three experiments at least.

5.3.2 COMPARISON OF RESULTS

(a) 5% DISPERSION

Table 5.9 and Fig. 5.3 show the dissolution rate of pure acetohexamide, while the release of acetohexamide from 5% dispersion in the two carriers, polyethylene glycol (PEG) 6000 and polyvinylpyrrolidone (PVP 44000 are shown in Tables 5.10 - 5.13 and Fig. 5.4.

It was noted that only a negligible amount of acetohexamide is gone into solution, the maximum concentration of acetohexamide in solution after ninety minutes being only about 6.5% of the total quantity used for the dissolution rate studies.

From the melt dispersion in PEG it can be noted that about 30% of acetohexamide is released in the first five minutes, more than 50% in less than thirty minutes and over 75% in the total experimental time of ninety minutes.

The physical dispersion in PEG 6000 shows about 38% acetohexamide release in the first five minutes, 40% in thirty minutes and only about 48% in the experimental time of ninety minutes. Acetohexamide release from the physical mixture is small when compared to its release from an equivalent quantity of the melt dispersion in PEG 6000.

With polyvinylpyrrolidone (PVP) 44000 as carrier about 60% of the acetohexamide content in the dispersion by the coprecipitate method is released in five minutes, nearly 100% is released under thirty minutes and the concentration being reduced to 97% in ninety /minutes/ because of the regular 5ml. withdrawals from the dissolution medium which is not corrected for.

From the physical dispersion of acetohexamide in PVP 44000 about 43% of the total acetohexamide content in the experimental sample is released in five minutes, 51% in thirty minutes and 56% in ninety minutes.

Generally acetohexamide released into solution from its carrier dispersion, be it the dispersion by fusion melt, coprecipitate or even the physical mixture, is greater than the release into solution from its pure form. Acetohexamide released from the physical mixture is less than its release from either its coprecipitate with PVP or its melt dispersion in PEG. The total release of acetohexamide into solution from its physical dispersion in PVP is greater than the release from its physical dispersion in PEG.

The dissolution rate of 5% acetohexamide dispersion in PVP by the coprecipitate method is greater than the same equivalent acetohexamide dispersion in PEG by the melt method.

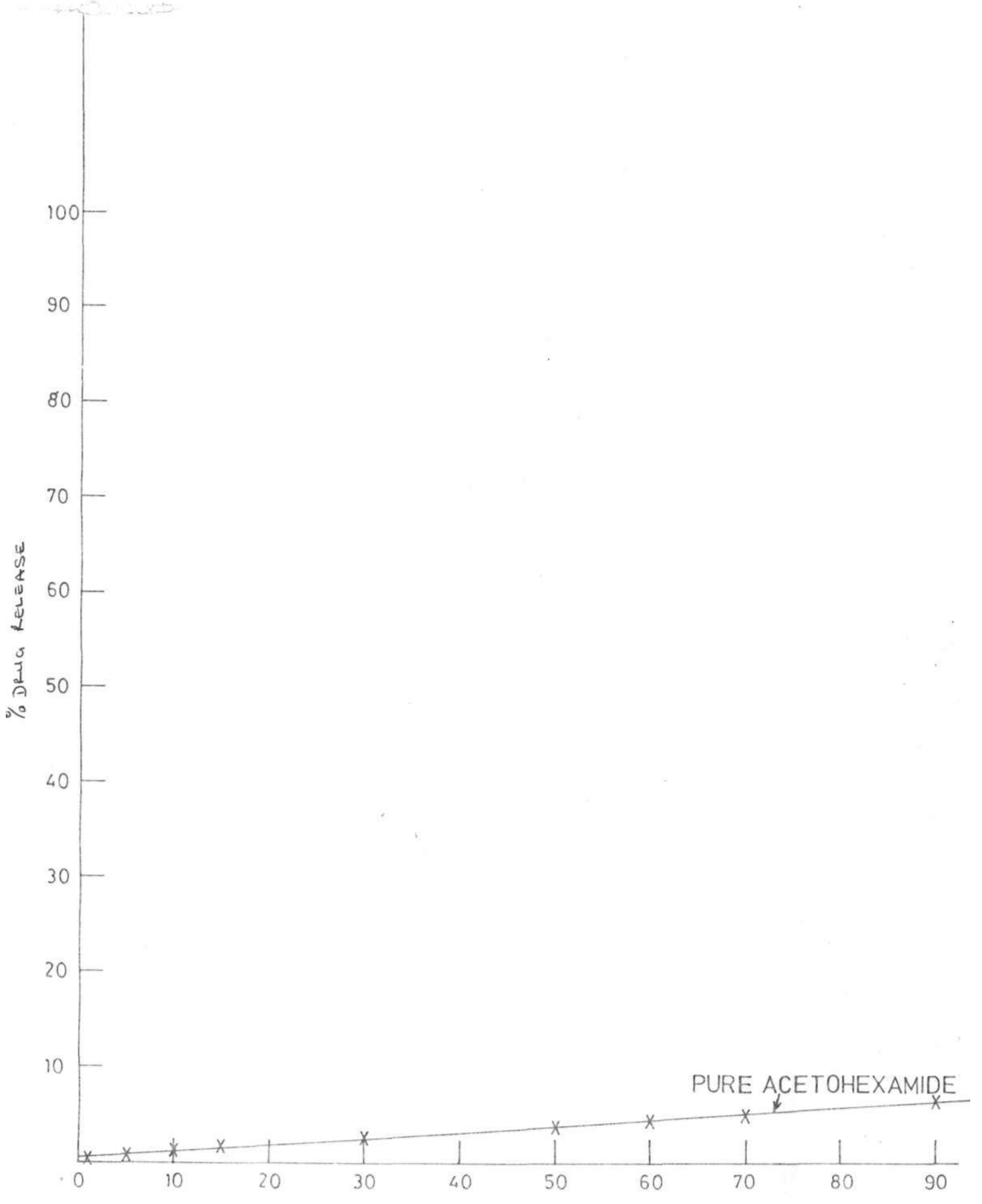

% Drug Release
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
90
Time →
PURE ACETOHEXAMIDE

Fig. 5.3

IN VITRO DISSOLUTION STUDIES

THE TAPE METHOD

TABLE 5.9

QUANTITY OF ACETOHEXAMIDE USED - 8.0mg

VOLUME OF DISSOLUTION MEDIUM - 400.0ml

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE IN SOLUTION (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.005	0.11	44.74	0.56
5	0.008	0.18	71.59	0.89
10	0.012	0.27	107.38	1.34
15	0.016	0.36	143.18	1.79
30	0.024	0.54	214.76	2.68
50	0.034	0.76	304.25	3.80
60	0.041	0.92	366.89	4.59
70	0.045	1.01	402.68	5.03
90	0.058	1.30	519.02	6.49

DISSOLUTION RATE STUDIES

THE TAPE METHOD

TABLE 5.10

5% ACETOHEXAMIDE/POLYETHYLENE GLYOOL 6000

AMOUNT OF DISPERSION - 160.0mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.00mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml.

FUSION MELT

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (ug)	% ACETOHEXAMIDE IN SOLUTION
1	0.103	2.304	921.70	11.52
5	0.271	6.063	2425.06	30.31
10	0.379	8.879	3391.499	42.39
15	0.435	9.731	3892.62	48.66
30	0.526	11.767	4706.93	58.84
50	0.603	13.490	5395.97	67.45
60	0.627	14.028	5610.74	70.13
70	0.642	14.362	5744.97	71.81
90	0.675	15.101	6040.27	75.50

TABLE 5.11 PHYSICAL MIXTURE

TIME (MINUTES)	AVERAGE ABSORBANCE AT 25 nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (ug)	% ACETOHEXAMIDE IN SOLUTION
1	0.189	4.23	1691.27	21.14
5	0.340	7.61	3042.51	38.03
10	0.353	7.90	3158.84	39.48
15	0.359	8.03	3212.53	40.16
30	0.363	8.12	3248.32	40.60
50	0.378	8.46	3382.55	42.28
60	0.400	8.95	3579.42	44.74
70	0.404	9.04	3615.21	45.19
90	0.434	9.71	3883.67	48.55

TABLE 5.12

5% ACETOHEXAMIDE/POLYVINYLPYRROLINDONE 44000

AMOUNT OF DISPERSION = 160.0mg

QUANTITY OF ACETOHEXAMIDE IN DISPERSION = 8.0mg

VOLUME OF DISSOLUTION MEDIUM = 400ml.

COPRECIPITATE

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug)	QUANTITY OF ACETOHEXA-MIDE RELEASED (ug)	% ACETOHEXA- IN SOLUTION
1	0.318	7.07	2826.67	35.33
5	0.864	19.2	7680.00	96.00
10	0.891	19.80	7920.00	99.00
15	0.906	20.13	8053.32	100.67
30	0.941	20.91	8364.44	104.56
50	0.949	21.09	8435.56	105.44
60	0.943	20.96	8382.22	104.77
70	0.933	20.73	8293.33	103.67
90	0.924	20.53	8213.33	97.40

TABLE 5.13

PHYSICAL MIXTURE

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXA-MIDE RELEASED (ug)	% ACETOHEXA-MIDE IN SOLUTION
1	0.085	1.89	755.55	9.44
5	0.389	8.64	3457.78	43.22
10	0.440	9.78	3911.11	48.89
15	0.447	9.93	3973.33	49.67
30	0.459	10.27	4107.38	51.34
50	0.472	10.49	4195.55	52.44
60	0.492	10.93	4373.33	54.67
70	0.505	11.22	4488.89	56.11
90	0.508	11.29	4515.55	56.44

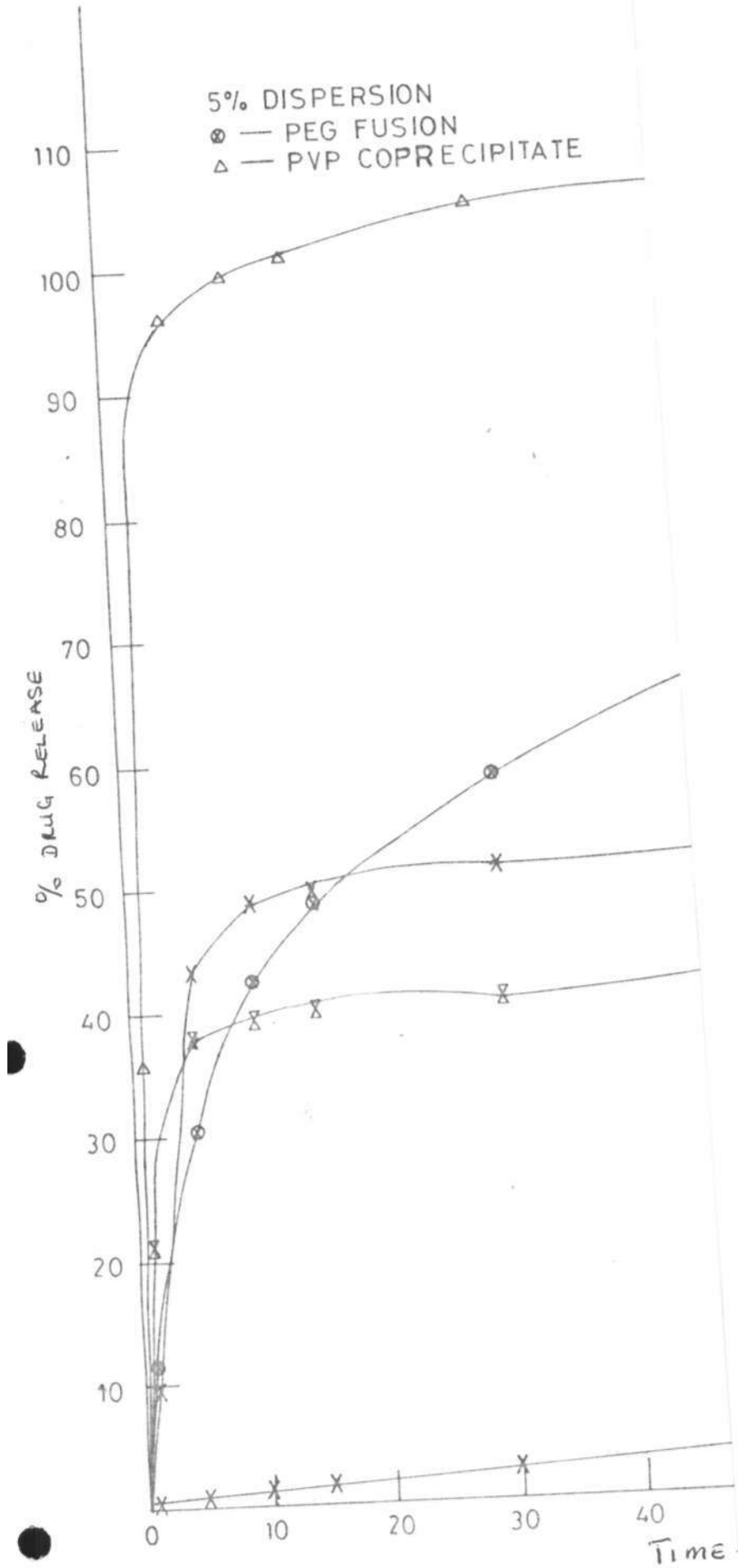

5% DISPERSION
⊗ — PEG FUSION
△ — PVP COPRECIPITATE
% DRUG RELEASE
110
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
Time

Fig. 5.4

b) 10% DISPERSION

Tables 5.14 to 5.17 and Fig. 5.5 show the relsease of acetohexamide from its various 10% dispersions in the two carriers polyethylene glycol 6000 and polyvinylpyrrolidone 44000.

From Fig. 5.5 it can be observed that about 21% of acetohexamide is released from the melt dispersion in PEG (Table 5.14) in five minutes, 37% after thirty minutes and about 59% in the total experimental time of ninety minutes.

From its physical dispersion in PEG (Table 5.15) acetohexamide is shown to be about 25% released in five minutes, 30.8% in thrity minutes and 44% in ninety minutes.

From the acetohexamide dispersion in polyvinylpyrrolidone 44000 by the coprecipitate method (Table 5.16) it can be observed that 53% of acetohexamide content of the experimental sample is released in five minutes, 56% in 30 minutes and 62.6% in ninety minutes.

The physical dispersion of acetohexamide in polyvinylpyrrolidone 44000 shows that about 32% of the acetohexamide content of the used sample is released in five minutes, 39% in thirty minutes and 52% in ninety minutes (Table 5.17).

Generally the rate of acetohexamide release into solution from its physical dispersion in either the

TABLE 5.14

10% ACETOHEXAMIDE/POLYETHYLENE GLYCOL 6000

AMOUNT OF DISPERSION - 80.00mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.00mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml.

FUSION MELT

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXA-MIDE RELEASED (ug)	% ACETOHEXA-MIDE IN SOLUTION
1	0.071	1.503	635.35	7.94
5	0.188	4.206	1682.33	21.03
10	0.230	5.145	2058.16	25..73
15	0.253	5.660	2263.98	28.30
30	0.334	7.472	2988.81	37.36
50	0.416	9.306	3722.59	46.53
60	0.464	10.380	4152.12	51.90
70	0.495	11.074	4429.53	55.37
90	0.530	11.857	4742.73	59.28

PHYSICAL MIXTURE

TABLE 5.15

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXA-MIDE RELEASED (ug)	% ACETOHEXA-MIDE IN SOLUTION
1	0.166	3.71	1485.46	18.57
5	0.224	5.01	2004.47	25.06
10	0.246	5.50	2201.34	27.52
15	0.251	5.61	2246.08	28.08
30	0.276	6.17	2469.80	30.87
50	0.320	7.16	2863.53	35.79
60	0.332	7.43	2970.92	37.14
70	0.353	7.90	3158.84	39.48
90	0.395	8.84	3534.68	44.18

TABLE 5.16

10% ACETOHEXAMIDE/POLYVINYLPYRROLIDONE 44000

AMOUNT OF DISPERION - 80.0mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.0mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml

COPRECIPITATE

TIME (MINUTES)	AVERAGE ABSORBACNE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXA-MIDE RELEASED (ug)	% ACETOHEXA-MIDE IN SOLUTION
1	0.199	4.45	1780.76	22.25
5	0.480	10.74	4295.30	53.69
10	0.489	10.94	4375.84	54.70
15	0.497	11.12	4447.43	55.59
30	0.503	11.25	4505.12	56.26
50	0.528	11.81	4724.83	59.06
60	0.538	12.04	4814.32	60.18
70	0.545	12.19	4876.96	60.96
90	0.560	12.53	5011.19	62.64

PHYSICAL MIXTURE

TABLE 5.17

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXA-MIDE RELEASED (ug)	% ACETOHEXA-MIDE IN SOLUTION
1	0.092	2.06	823.27	10.29
5	0.287	6.42	2568.23	32.10
10	0.325	7.27	2908.28	36.35
15	0.328	7.34	2935.12	36.69
30	0.352	7.87	3149.89	39.37
50	0.398	8.90	3561.52	44.52
60	0.405	9.06	3624.16	45.30
70	0.414	9.26	3704.70	46.31
90	0.468	10.47	4187.92	52.35

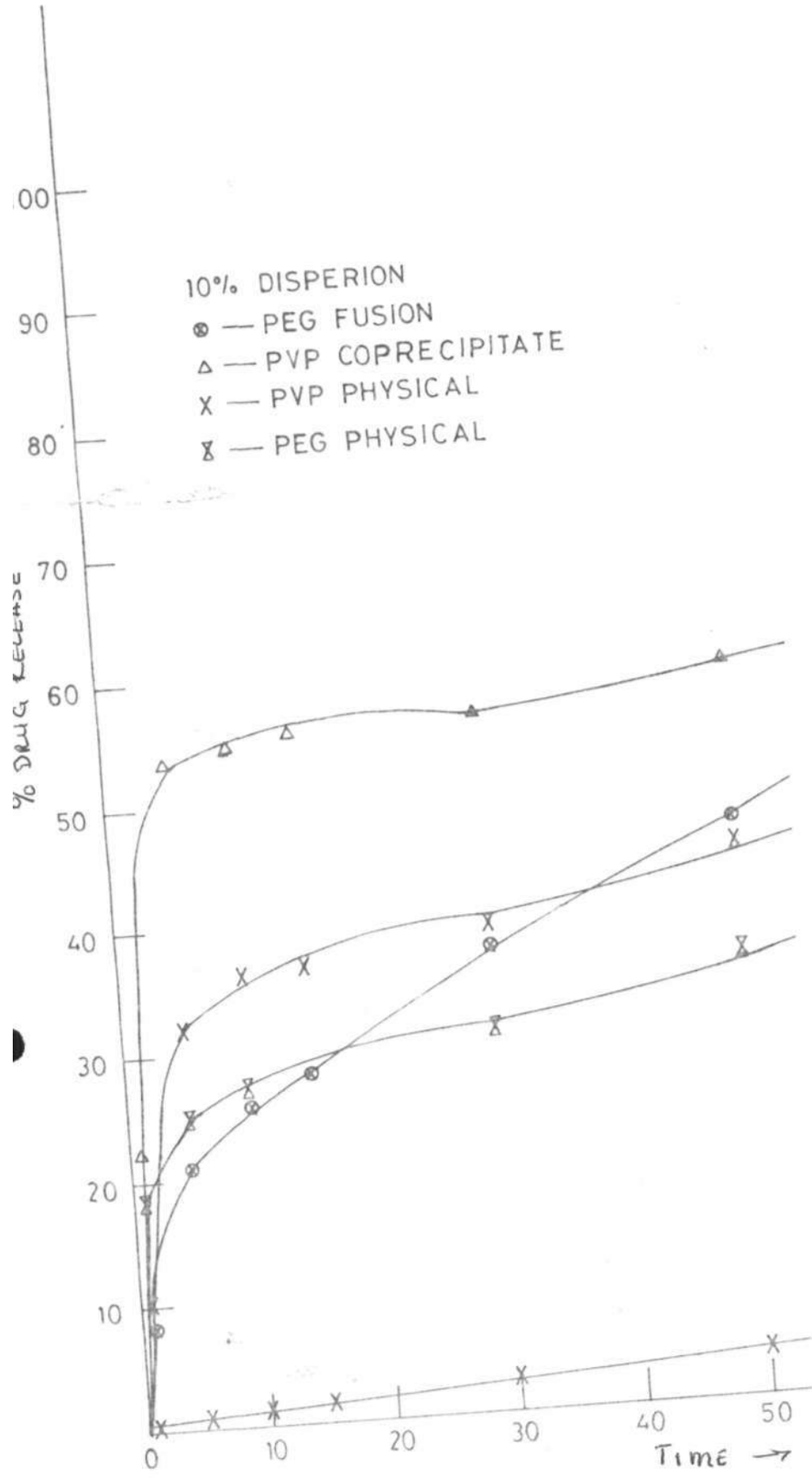

10% DISPERION
⊗ — PEG FUSION
△ — PVP COPRECIPITATE
X — PVP PHYSICAL
⧖ — PEG PHYSICAL
% DRUG RELEASE
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
Time →

Fig. 5.5

PEG 6000 or the PVP 44000 is less than its release rate from its dispersion in both PEG melt method and PVP coprecipitate method.

In the physical mixture the rate of acetohexamide release into solution is only a little more in the PVP dispersion than the PEG dispersion.

The rate of acetohexamide release from the melt dispersion in PEG is only a little less than the equivalent dispersion in PVP coprecipitate dispersion.

c) 20% DISPERSION

Tables 5.18 to 5.21 and Fig. 5.6 are the results of the dissolution rate studies of the 20% acetohexamide dispersion in the carriers, polyethylene glycol 6000 and polyvinylpyrrolidone 44000.

From the melt dispersion of acetohexamide in polyethylene glycol 6000 Fig. 5.6 it can be noted that about 21% of the total acetohexamide contained in the used sample is released in five minutes, 23% in thirty minutes and nearly 38% in ninety minutes. (Table 5.18).

From the physical dispersion of acetohexamide in polyethylene glycol 6000 Fig. 5.3 about 13% of the total acetohexamide content in the sample used is released in five minutes, 25% in thirty minutes and nearly 39% in ninety minutes (Table 5.19).

From the same Fig. 5.6 it can be noted that about 53% of the total acetohexamide content in the sample of the dispersion in polyvinylpyrrolidone 44000 by the coprecipitate method is released in five minutes, 59% in thirty minutes and about 60% in ninety minutes (Table 5.20).

The physical dispersion of acetohexamide in polyvinylpyrrolidone 44000 shows 21% of the total acetohexamide content in the sample used is released in five minutes, 33% in thirty minutes and 48% in ninety minutes (Table 5.21).

TABLE 5.18

20% ACETOHEXAMIDE/POLYETHYLENE GLYCOL 6000

AMOUNT OF DISPERSION - 40.0mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.00mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml.

FUSION MELT

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (ug)	% ACETOHEXAMIDE IN SOLUTION
1	0.083	1.858	742.73	9.28
5	0.187	4.183	1673.38	20.92
10	0.210	4.698	1879.19	23.49
15	0.220	4.922	1968.68	24.61
30	0.256	5.727	2290.83	28.63
50	0.282	6.309	2523.49	31.54
60	0.300	6.711	2684.56	33.56
70	0.316	7.069	2827.74	35.35
90	0.339	7.584	3033.56	37.92

PHYSICAL MIXTURE

TABLE 5.19

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (ug/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (ug)	% ACETOHEXAMIDE IN SOLUTION
1	0.672	1.61	644.29	8.05
5	0.122	2.73	1091.72	13.65
10	0.198	4.43	1771.81	22.15
15	0.204	4.56	1825.50	22.82
30	0.227	5.06	2031.32	25.39
50	0.250	5.59	2237.14	27.96
60	0.260	5.82	2326.62	29.08
70	0.276	6.17	2469.80	30.87
90	0.303	6.78	2711.41	33.89

TABLE 5.20

20% ACETOHEXAMIDE/POLYVINYLPYRROLIDONE 44000

AMOUNT OF DISPERSION - 40.0mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.00mg.
VOLUME OF DISSOLUTION MEDIUM = 400ml.
COPRECIPITATE

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.200	4.44	1777.78	22.22
5	0.480	10.67	4266.67	53.33
10	0.520	11.55	4622.22	57.78
15	0.527	11.67	4666.67	58.33
30	0.530	11.77	4711.11	58.89
50	0.530	11.82	4728.89	59.11
60	0.532	11.84	4737.78	59.22
70	0.534	11.89	4755.55	59.44
90	0.540	12.02	4808.89	60.11

PHYSICAL MIXTURE TABLE 5.21

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg)	QUANTITY OF ACETOHEXAMIDE RELEASE (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.056	1.24	497.78	6.22
5	0.190	4.22	1688.89	21.11
10	0.234	5.20	2080.00	26.00
15	0.251	5.58	2231.11	27.89
30	0.299	6.64	2657.78	33.22
50	0.353	7.84	3137.78	39.22
60	0.361	8.02	3208.89	40.11
70	0.373	8.29	3315.56	41.44
90	0.433	9.62	3848.89	48.11

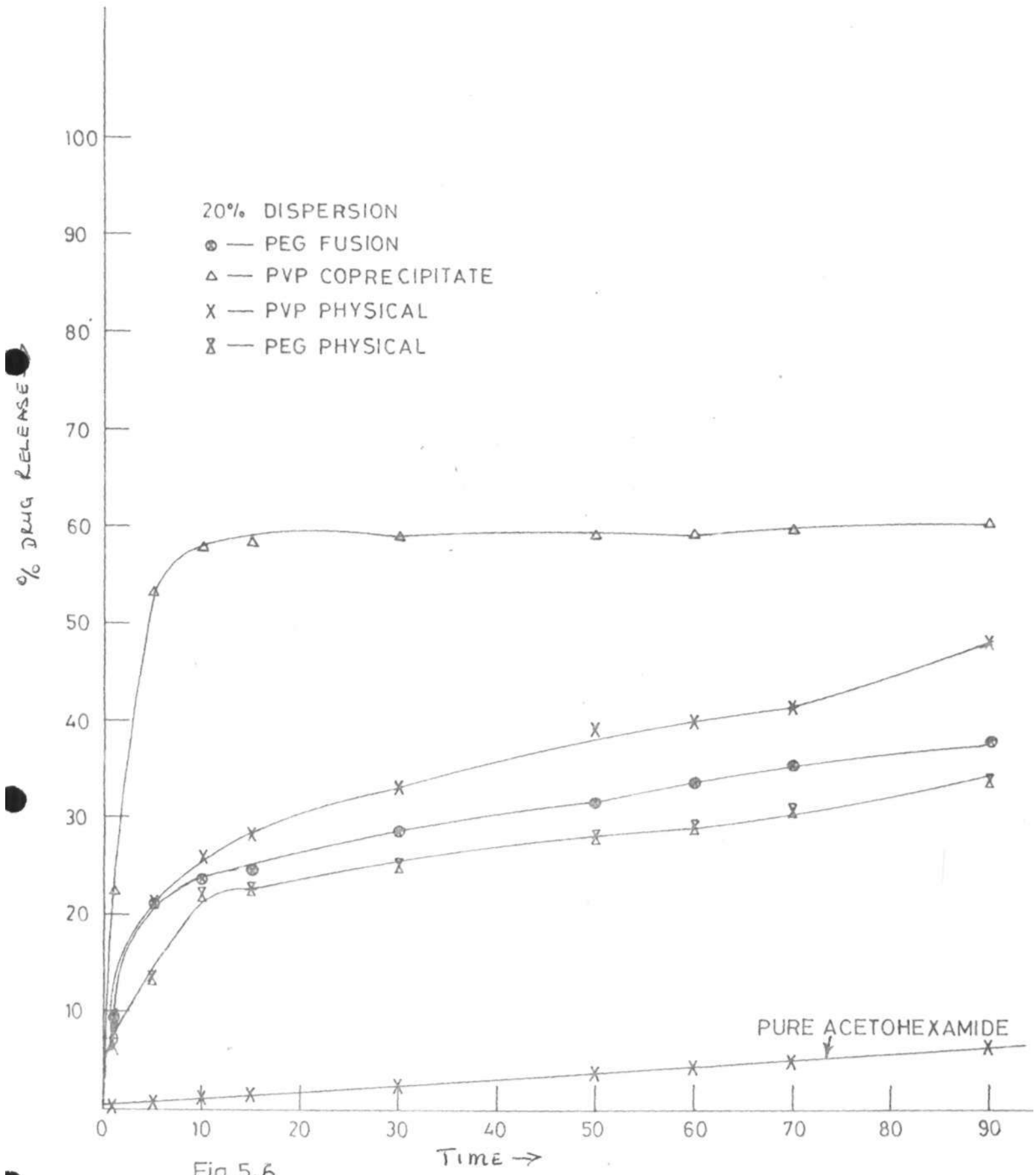

20% DISPERSION
⊗ — PEG FUSION
△ — PVP COPRECIPITATE
X — PVP PHYSICAL
⧖ — PEG PHYSICAL
% DRUG RELEASED
100
90
80
70
60
50
40
30
20
10
PURE ACETOHEXAMIDE
0
10
20
30
40
50
60
70
80
90
TIME →

Fig. 5.6

d) 40% DISPERSION

Fig. 5.7 shows the results of the dissolution rate studies of 40% melt dispersion in polyethylene glycol 6000 and 40% coprecipitate dispersion in polyvinylpyrrolidone 44000.

As can be noted (Table 5.22) about 22% of the total acetohexamide content in the sample of the melt dispersion in polyethylene glycol 6000 is released in five minutes, about 33% in thirty minutes and nearly 37% in ninety minutes.

From the equivalent phhsical dispersion of acetohexamide in PEG 6000 (Table 5.23) about 6% of the total acetohexamide content is released in five minutes, 9% in thirty minutes and about 22% in ninety minutes.

From the acetohexamide dispersion in polyvinylpyrrolidone 44000 by coprecipitation (Table 5.24) about 32% of the total acetohexamide content in the sample used is released in five minutes, 49% in thirty minutes and about 54% in ninety minutes. From an equivalent physical dispersion of acetohexamide in PVP 44000 (Table 5.25) about 8% of the acetohexamide content in the sample used is shown to be released in five minutes, 17% in thirty minutes and about 31% in ninety minutes /

From Fig. 5.7 it can be noted that with polyethylene glycol 6000 as carrier, the rate of acetohexamide release is greater from the fusion melt dispersion than from the physical dispersion.

TABLE 5.22

40% ACETOHEXAMIDE/POLYETHYLENE GLYCOL 6000

AMOUNT OF DISPERSION - 20.00mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.00mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml.

FUSION MELT

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE REEEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.093	2.08	832.21	10.40
5	0.202	4.52	1807.61	22.59
10	0.249	5.57	2228.19	27.85
15	0.277	6.20	2478.75	30.98
30	0.300	6.71	2684.56	33.56
50	0.311	6.96	2783.00	34.79
60	0.314	7.02	2809.84	35.12
70	0.318	7.11	2845.64	35.57
90	0.330	7.38	2953.02	36.91

PHYSICAL MIXTURE TABLE 5.23

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.042	0.94	375.81	4.70
5	0.058	1.30	519.02	6.49
10	0.061	1.36	545.86	6.82
15	0.067	1.50	599.55	7.49
30	0.088	1.97	787.47	9.84
50	0.137	3.06	1225.95	15.32
60	0.165	3.69	1476.51	18.46
70	0.178	3.98	1592.81	19.91
90	0.201	4.50	1798.66	22.48

TABLE 5.24

40% ACETOHEXAMIDE/POLYVINYLPYRROLIDONE 44000

AMOUNT OF DISPERSION - 20.0mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.00mg.
VOLUME OF DISSOLUTION MEDIUM = 400ml.
COPRECIPITATE

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.095	2.11	844.44	10.56
5	0.292	6.49	2595.56	32.44
10	0.359	7.98	3191.11	39.89
15	0.400	8.89	3555.56	44.44
30	0.445	9.89	3955.56	49.44
50	0.462	10.27	4106.67	51.33
60	0.468	10.40	4160.00	52.00
70	0.472	10.49	4195.56	52.44
90	0.491	10.91	4364.44	54.56

PHYSICAL MIXTURE TABLE 5.25

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.034	0.76	302.22	3.78
5	0.077	1.71	684.44	8.56
10	0.102	2.27	906.67	11.33
15	0.114	2.53	1013.33	12.67
30	0.156	3.47	1386.67	17.33
50	0.212	4.71	1884.44	23.56
60	0.222	4.93	1973.33	24.67
70	0.248	5.51	2204.44	27.56
90	0.279	6.20	2480.00	31.00

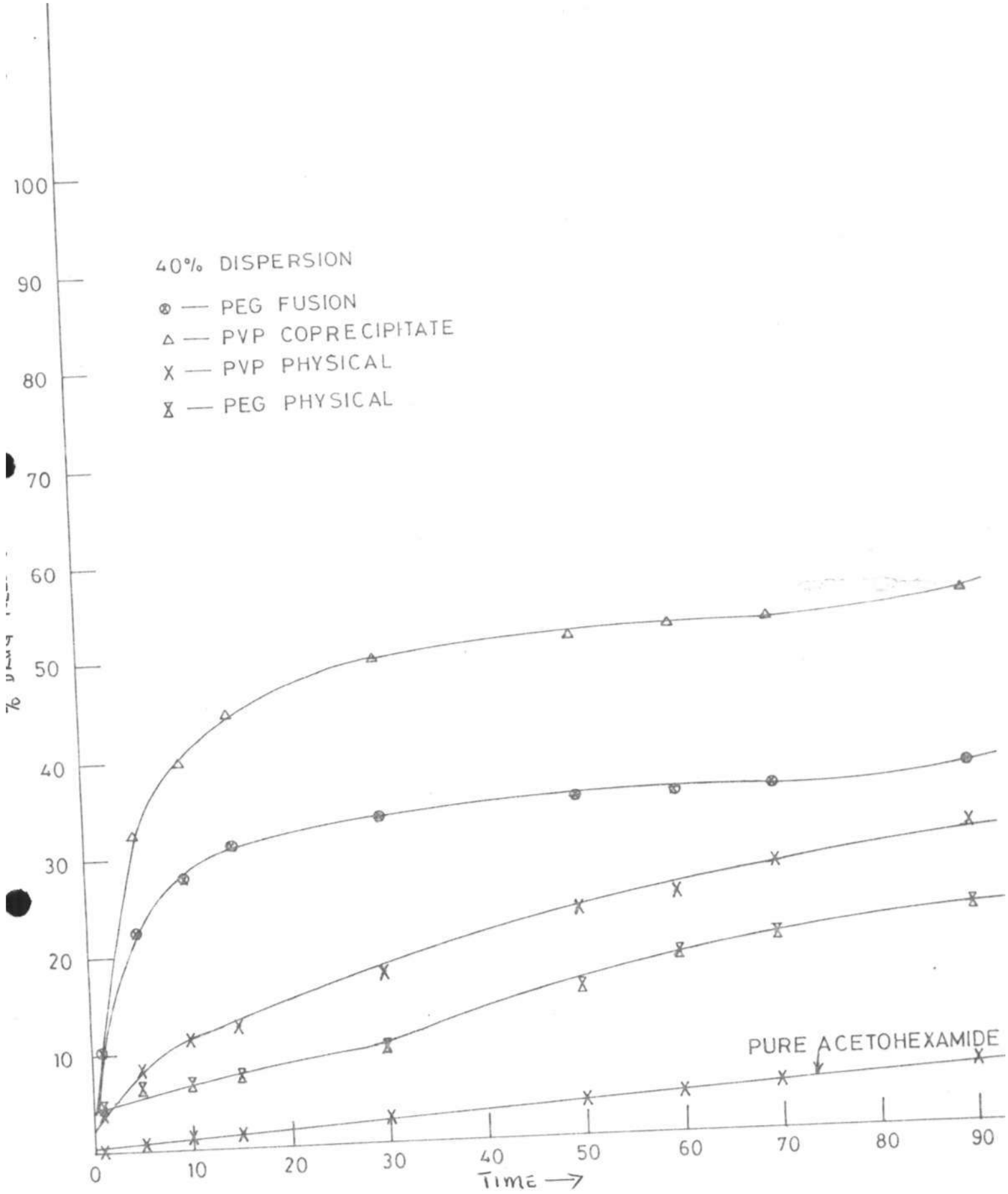

40% DISPERSION
⊗ — PEG FUSION
△ — PVP COPRECIPITATE
X — PVP PHYSICAL
⧖ — PEG PHYSICAL
PURE ACETOHEXAMIDE
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
90
Time →

Fig. 5.7

The rate of acetohexamide release is greater from its physical dispersion in polyvinylpyrrolidone than from its equivalent physical dispersion in polyethylene glycol.

The rate of acetohexamide release is greater from its coprecipitate dispersion in polyvinylpyrrolidone 44000 than from its equivalent fusion melt dispersion in polyethylene glycol 6000.

However, while the rate of acetohexamide release is only slightly greater in the fusion melt dispersion in polyethylene glycol 6000 than in the physical dispersion in polyvinylpyrrolidone, the rate of release is more than two times greater in the PVP coprecipitate than in PEG. Physical dispersion. (Tables 5.22 - 5.23)

60% DISPERSION

Fig. 5.8 shows the result of the dissolution rate studies of 60% dispersion of acetohexamide in the two carriers, polyethylene glycol 6000 and polyvinylpyrrolidone 44000.

Table 5.26 shows the dissolution rate results of the Fusion melt dispersion in PEG. 6000 while (Table 5.27) is the result of the physical dispersion; both results are presented in the graphs in Fig. 5.8.

In the fusion melt, out of the total acetohexamide content in the test sample about 26% is released in solution in five minutes, about 47% in thirty minutes and 54.8% in ninety minutes.

In the physical mixture, only about 3.6% of the total acetohexamide content is released in five minutes, 8.5% in thirty minutes and 14.7% in ninety minutes.

This shows that far less of the acetohexamide content is released into solution in the physical mixture when compared with the dispersion by the fusion melt.

The dissolution rate results is shown in table 5.28 for the coprecipitate dispersion of acetohexamide in PVP 44000 while that of the physical dispersion is shown in table 5.29 both results are presented in the graph in Fig. 5.8.

TABLE 5.26

60% ACETOHEXAMIDE/POLYETHYLENE GLYCOL 6000

AMOUNT OF DISPERSION - 13.33mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.0mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml.

FUSION MELT

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.099	2.21	885.91	11.07
5	0.232	5.19	2076.06	25.95
10	0.305	6.82	2729.31	34.12
15	0.353	7.90	3158.84	39.48
30	0.427	9.55	3821.03	47.76
50	0.468	10.47	4187.92	52.35
60	0.474	10.60	4241.61	53.02
70	0.478	10.69	4277.40	53.47
90	0.490	10.96	4384.79	54.81

PHYSICAL MIXTURE TABLE 5.27

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	%ACETOHEXAMIDE IN SOLUTION
1	0.024	0.54	214.76	2.68
5	0.032	0.72	286.35	3.58
10	0.036	0.80	322.15	4.03
15	0.048	1.07	429.53	5.37
30	0.076	1.70	680.09	8.50
50	0.097	2.17	868.01	10.85
60	0.116	2.59	1038.03	12.97
70	0.122	2.73	1091.72	13.65
90	0.132	2.95	1181.21	14.76

TABLE 5.28

60% ACETOHEXAMIDE/POLYVINYLPYRROLIDONE 44000

AMOUNT OF DISPERSION - 13.33mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.0mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml.

COPRECIPATE

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.174	3.87	1546.67	19.33
5	0.211	4.69	1875.56	23.44
10	0.230	5.11	2044.44	25.56
15	0.235	5.22	2088.89	26.11
30	0.253	5.62	2248.89	28.11
50	0.268	5.96	2382.22	29.78
60	0.279	6.20	2480.00	31.00
70	0.282	6.27	2506.67	31.33
90	0.298	6.62	2648.89	33.11

PHYSICAL MIXTURE TABLE 5.29

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.028	0.62	248.89	3.11
5	0.045	1.0	400.00	5.00
10	0.063	1.4	560.00	7.00
15	0.077	1.71	684.44	8.56
30	0.112	2.49	995.56	12.44
50	0.155	3.44	1377.78	17.22
60	0.170	3.78	1511.11	18.89
70	0.184	4.09	1635.56	20.44
90	0.210	4.67	1866.67	23.33

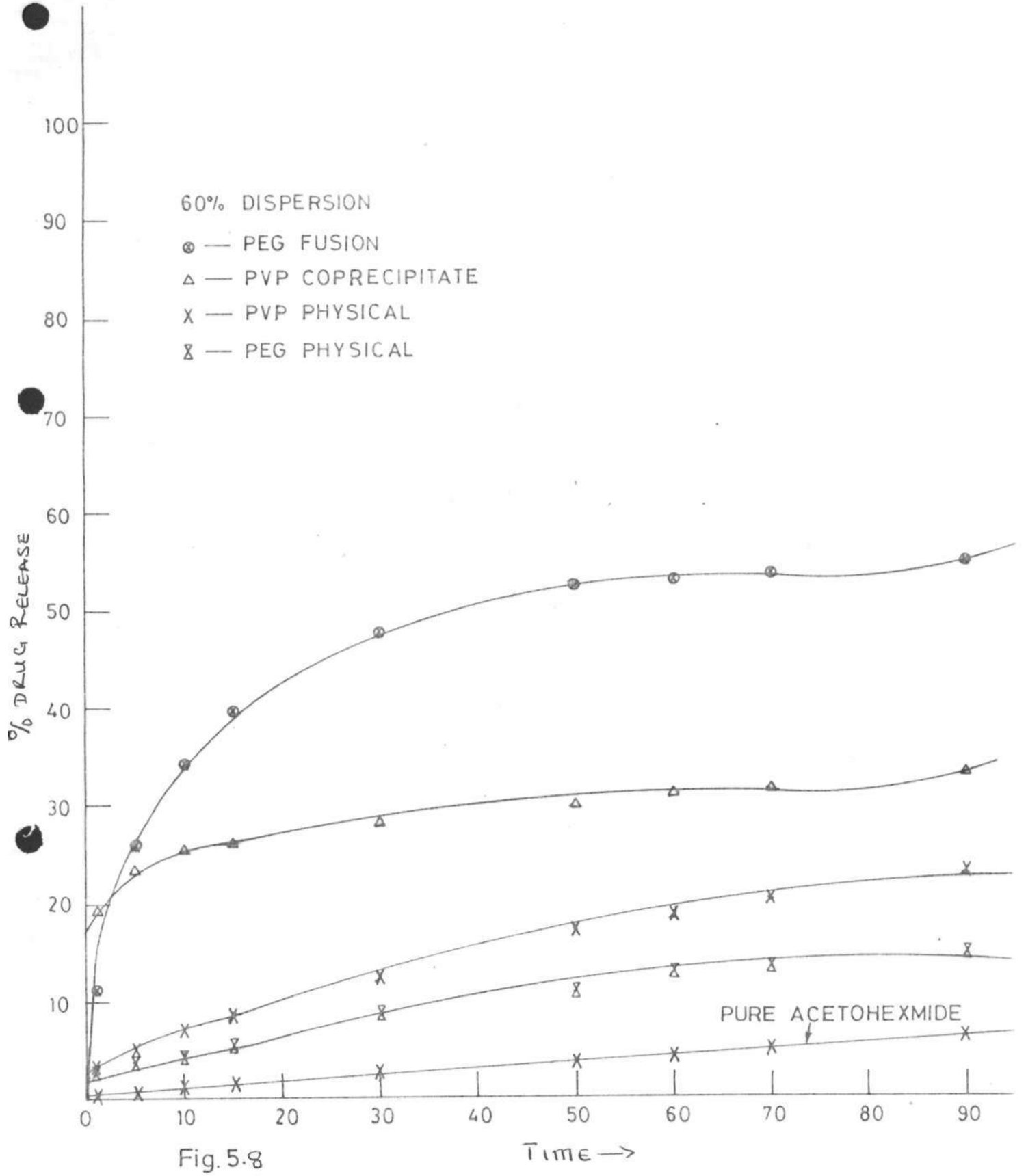

60% DISPERSION
⊗ — PEG FUSION
△ — PVP COPRECIPITATE
X — PVP PHYSICAL
⧖ — PEG PHYSICAL
PURE ACETOHEXMIDE
% DRUG RELEASE
Time →
0
10
20
30
40
50
60
70
80
90
100

Fig. 5.8

Out of the total acetohexamide content of the test sample in the coprecipitate, about 23% is released in five minutes, 28% in thirty minutes and 33% in ninety minutes.

From the same sample quantity in the physical mixture, 5% is released in five minutes, 12% in thirty minutes and about 23% in ninety minutes.

This clearly shows how more of the acetohexamide content of the dispersion is released into solution in the coprecipitate than in the same equivalent in the physical mixture. Hence the rate of acetohexamide release is less from its coprecipitate dispersion in polyvinylpyrrolidone than from its fusion melt dispersion in polyethylene glycol but greater in the coprecipitate than from its physical dispersion in polyethylene glycol.

(f) 70% DISPERSION

The dissolution rate studies of 70% dispersion of acetohexamide in polyethylene glycol 6000 is shown in Fig. 5.9. Table 5.30 shows the dissolution rate of the fusion melt dispersion while table 5.31 shows that of the physical dispersion.

The release rate of acetohexamide from the fusion melt dispersion is more than four times that from the same equivalent of the physical dispersion.

In this fusion melt dispersion while about 17% of the total acetohexamide content in the test sample is released in five minutes, 42.7% in thirty minutes and 59.6% in ninety minutes, the release of acetohexamide from the physical dispersion is about 12.5% in five minutes, 5.9% in thirty minutes and only 14.5% throughout of the total period of ninety minutes.

TABLE 5.30

70% ACETOHEXAMIDE/POLYETHYLENE GLYCOL 6000

AMOUNT OF DISPERSION - 11.43mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION - 8.00mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml.

FUSION MELT

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.057	1.275	510.07	6.38
5	0.157	3.512	1404.92	17.56
10	0.228	5.101	2040.27	25.50
15	0.278	6.22	2487.70	31.10
30	0.382	8.55	3418.34	42.73
50	0.460	10.29	4116.33	51.45
60	0.485	10.85	4340.04	54.25
70	0.508	11.36	4545.86	56.82
90	0.533	11.92	4769.57	59.62

PHYSICAL MIXTURE TABLE 5.31

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.019	0.42	170.02	2.12
5	0.023	0.51	205.82	2.57
10	0.028	0.63	250.56	3.13
15	0.034	0.76	304.25	3.80
30	0.053	1.19	474.27	5.93
50	0.072	1.61	644.29	8.05
60	0.084	1.88	751.68	9.40
70	0.095	2.12	850.11	10.63
90	0.130	2.91	1163.31	14.54

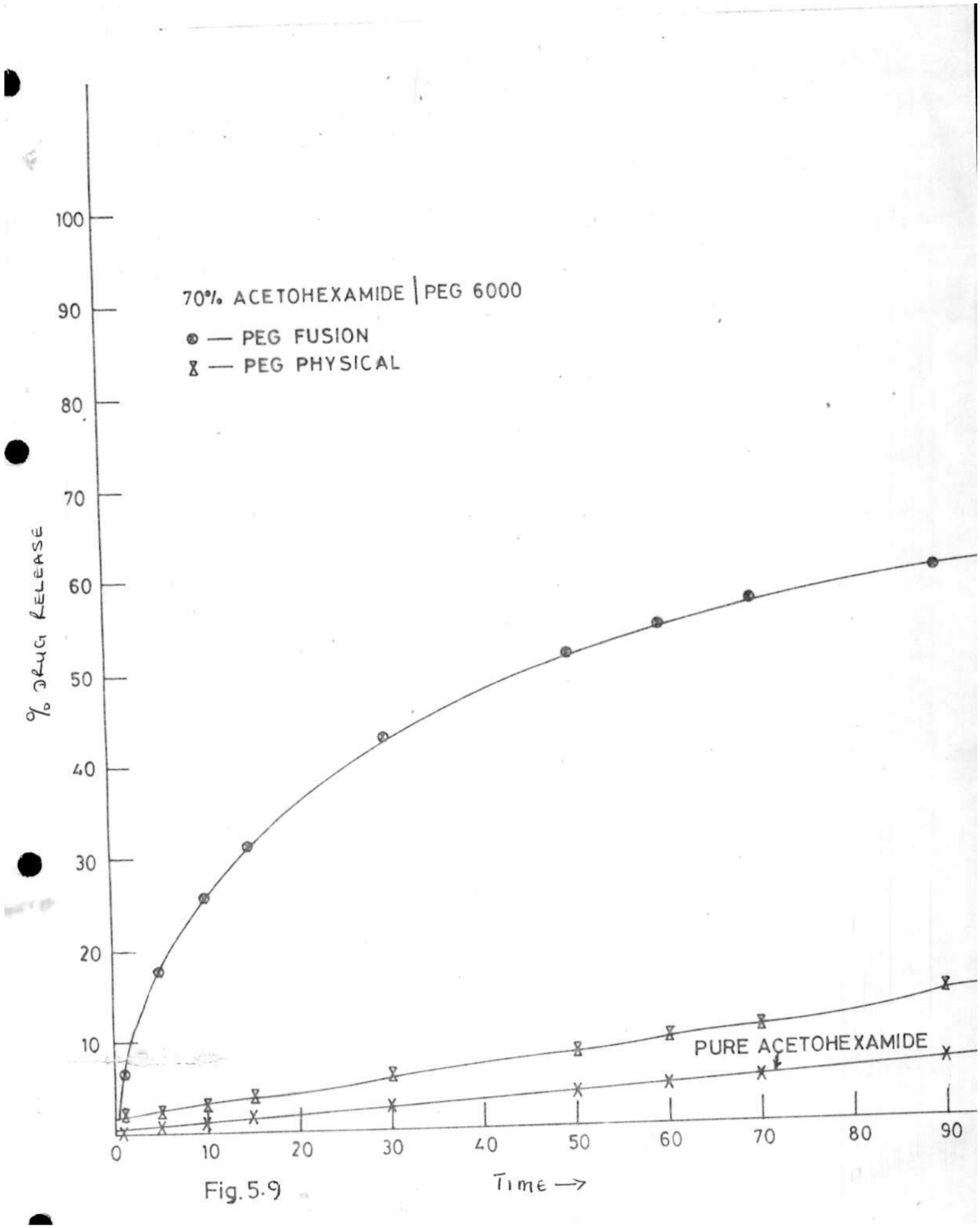

70% ACETOHEXAMIDE | PEG 6000
⊗ — PEG FUSION
⧖ — PEG PHYSICAL
% DRUG RELEASE
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
90
Time →
PURE ACETOHEXAMIDE

Fig. 5.9

(g) 80% DISPERSION

Fig. 5.10 shows the dissolution rate of 80% dispersion of acetohexamide in polyethylene glycol 6000.

Table 5.32 is the dissolution result of the fusion melt while Table 5.33 is that of the physical dispersion.

The release rate of acetohexamide from 80% dispersion is more than four times greater in the fusion melt than in the physical dispersion.

While about 7% of the total acetohexamide content in the test sample of the fusion melt is released in five minutes, nearly 32% in thirty minutes and 52.9% in ninety minutes; only 1.4% of the same equivalent is released in five minutes, 4.6% in thirty minutes and only 12.6% in ninety minutes.

TABLE 5.32

80% ACETOHEXAMIDE/POLYETHYLENE GLYCOL 6000

AMOUNT OF DISPERSION = 10.0mg.

QUANTITY OF ACETOHEXAMIDE IN THE DISPERSION = 8.00mg.

VOLUME OF DISSOLUTION MEDIUM = 400ml.

FUSION MELT

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.020	9.45	178.97	2.24
5	0.063	1.41	563.76	7.05
10	0.122	2.73	1091.72	13.65
15	0.176	3.94	1574.94	19.69
30	0.286	6.40	2559.28	31.99
50	0.378	8.46	3382.55	42.28
60	0.404	9.04	3615.21	45.19
70	0.432	9.66	3865.77	48.32
90	0.473	10.58	4232.66	52.91

PHYSICAL MIXTURE TABLE 5.33

TIME (MINUTES)	AVERAGE ABSORBANCE AT 251nm	CONCENTRATION OF ACETOHEXAMIDE (µg/ml)	QUANTITY OF ACETOHEXAMIDE RELEASED (µg)	% ACETOHEXAMIDE IN SOLUTION
1	0.010	0.22	89.48	1.12
5	0.012	0.29	116.33	1.45
10	0.019	0.42	170.02	2.12
15	0.025	0.56	223.71	2.80
30	0.041	0.92	366.89	4.59
50	0.068	1.52	608.50	7.61
60	0.074	1.65	662.19	8.28
70	0.092	2.06	823.27	10.29
90	0.113	2.53	1011.19	12.64

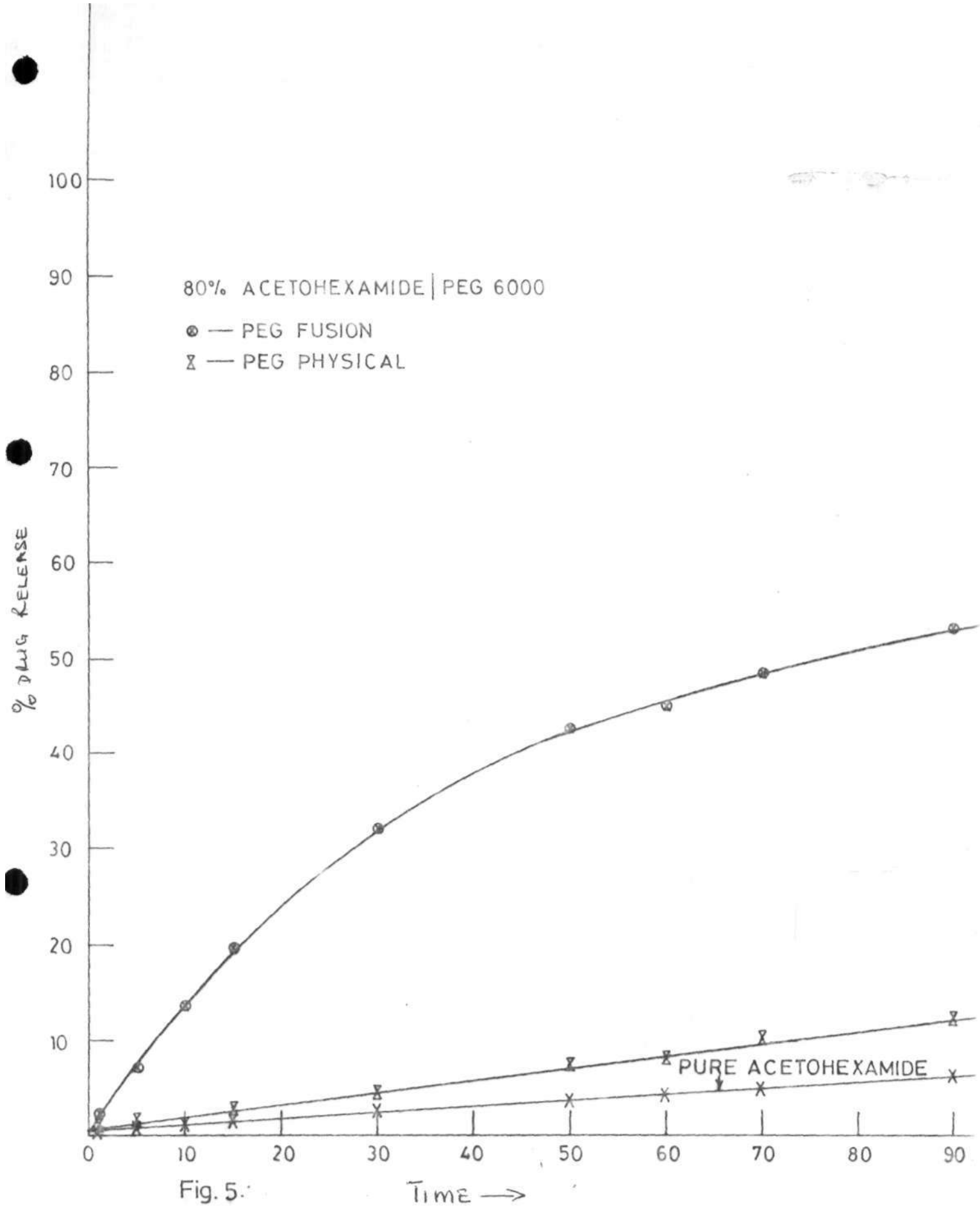

80% ACETOHEXAMIDE | PEG 6000
⊗ — PEG FUSION
⧖ — PEG PHYSICAL
PURE ACETOHEXAMIDE
% DRUG RELEASE
TIME →
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
90

Fig. 5.

TABLE 5.34

DRUG RELEASE RATES

Time for drug release T_{25}, T_{40}, T_{50}, T_{75}

a) With polyethylene glycol as carrier

Drug dispersion		T_{25} (minutes)	T_{40} (minutes)	T_{50} (minutes)	T_{75} (minutes)
5%	Melt	4	8		88
	physical	2	15	-	-
10%	melt	9	35	55	-
	physical	5	71	-	-
20%	melt	16	-	-	-
	physical	29	-	-	-
40%	melt	7	16		-
	physical	-	-	-	-
50%	melt	3	18		-
	physical	-	-	-	-
60%	melt	4	21		-
	physical	-	-	-	-
70%	melt	9	26	47	-
	physical	-	-	-	-
80%	melt	21	45	77	-
	physical	-	-	-	-

TABLE 5.35

b) With polyvinylpyrrolidone as carrier

% Drug dispersion		T_{25} (minutes)	T_{40} (minutes)	T_{50} (minutes)	T_{75} (minutes)
5%	Coprecipitate	less than 1	1	2	3
	physical	2	4	17	-
10%	Coprecipitate	1	2	3	-
	physical	8	38	83	-
20%	Coprecipitate	1.5	2	3	-
	physical	9	60	-	-
40%	Coprecipitate	3.5	10	33	-
	physical	58	-	-	-
60%	Coprecipitate	8	-	-	-
	physical	-	-	-	-

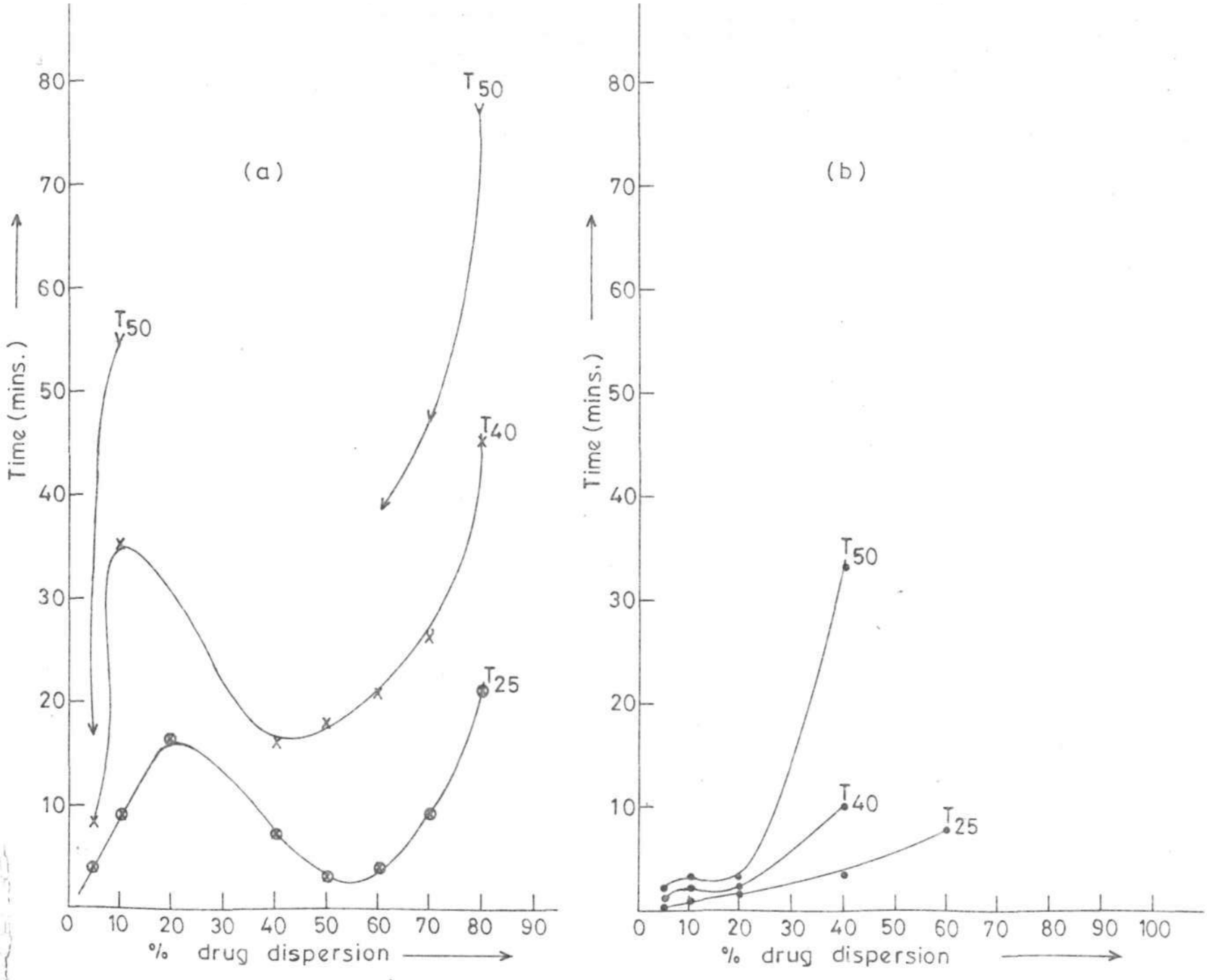


Fig. 5.11 Drug release time T_{25} T_{40} T_{50}

(a) With polyethylene glycol as carrier (melt)

5.3.3 DISCUSSION OF RESULTS

(a) POLYETHYLENE GLYCOL 6000 AS CARRIER

Generally, for any particular concentration dispersion the release of acetohexamide from its polyethylene glycol 6000 dispersion is greater in the fusion melt than in the equivalent concentration the physical mixture.

Goldberg et al [28] have stated that if two solids are melted together, the resulting liquids are either completely miscible, partially miscible, or immiscible. If the two liquids are totally miscible, the solids formed upon cooling may form

a) a new compound with a congruent melting point
b) a new compound with an incongruent melting point
c) a eutectic mixture, or
d) a solid solution

In the case of acetohexamide/polyethylene glycol 6000 melt dispersion, the resulting liquids after the melt of the two solids were totally miscible.

Stability studies by spectrophotometry and thin-layer chromatography shows that acetohexamide is stable in the dispersion and does not show any evidence of formation of a new compound. The fnfra-red

glycol 6000, the nature of which is yet to be determined. It then means that either a eutectic mixture or solid solution or both eutectic mixture and solid solution might have been formed in the solid dispersion upon cooling the melt of the two solids. Also the dispersion shows incongruent melting point as can be noted in table 4.6.

The solid solution formation involves molecular rearrangement between the molecules of the two solids which could be either substitutional solid solution or interestitial solid solution(9, 28) as mentioned earlier.

One of the essential criteria for the formation of an interstitial solid solution is that the host molecule (the solvent) must be larger than the guest (solute) molecule(8). In this case since the solvent molecule (polyethylene glycol 6000) is a polymer of molecular weight 6000 it must be larger than the organic drug (acetohexamide) of molecular weight 324.4 which is the guest molecule. It then means that formation of an interstitial solid solution may be favoured.

By comelting acetohexamide and polyethylene glycol 6000 the individual molecules become relatively free in the liquid state and can easily move over one another. This results in an intimately blended homogeneous mixture of the molecules of both the drug and the carrier. Polyethylene glycol 6000 is a high

molecular weight compound which is very viscous in its melted state even at a temperature of about 200°C(8). The viscosity increases greatly as the temperature decreases. Polyethylene glycol can generally be supercooled to about 40° (8). As the polyethylene glycol acetohexamide melt is allowed to cool, the crystallization of acetohexamide will be retarded due to the slow migration and the difficulty in nucleation of acetohexamide in the viscous medium(8). By rapidly quenching the melt from the high temperature with a resultant rapid increase in viscosity of the melt and probable supercooling effect, the solute (acetohexamide) can be arrested in the solvent (polyethylene glycol 6000) matrix by the instantaneous solidification process. The resultant solid mass is an intimately blended homogeneous single phase crystals of acetohexamide/polyethylene glycol 6000 solid dispersion.

If a solid solution is formed the particle size reduction of acetohexamide in the dispersion is reduced to minimum (9, 12, 30), i.e. to its molecular size. This means acetohexamide is already dissolved in polyethylene glycol 6000. If a simple eutectic mixture is formed both the acetohexamide and the polyethylene glycol 6000 simultaneously crystallize in very small particle sizes. The acetohexamide is not yet dissolved in the polyethylene glycol 6000 but

it exists in ultrafine crystals. Though the particle size reduction in the eutectic mixture may be great enough to enhance absorption and bioavailability, the particlse size reduction in the solid solution is still greater than the reduction in the simple eutexia since the particle size is of molecular dimensions in the quenching of the carrier drug melt from a high temperature and the instantaneous soldification process favour the formation of both simple eutectic mixture and solid solution.

When this solid dispersion composed of acetohexamide as drug and polyethylene glycol 6000 as a water soluble inert carrier is exposed to water the polyethylene glycol 6000 dissolves quickly in water, leaving the acetohexamide in molecular state of subdivision (in solid solution) or ultra fine-grained crystals (in simple eutectic mixture).

The above mentioned processes do not take place in either the acetohexamide/polyethylene glycol 6000 physical mixture or pure acetohexamide. It is, therefore, not surprising that the dissolution rate of the fusion melt dispersion of acetohexamide in polyethylene glycol is greater than its physical dispersion or the pure acetohexamide. In the physical mixture, however, there is increased percentage drug release in the dissolution studies over that of pure

acetohexamide. This behaviour may be purely that of "Solubilization", characteristic of surface active agents, which is a surface phenomenum.

As the concentration of the acetohexamide in the dispersion changes, there is a change in the rate of drug release from the dispersion. As the concentration of acetohexamide increases from 5% to 80% in the dispersion, then increases at 60% and 70% dispersion but decreases again when the dispersion increases to 80%. If no interaction exists between acetohexamide and polyethylene glycol at solid state and the only effect of the carrier on acetohexamide dissolution is only solubilisation in the microenvironment, it is then expected that the dissolution rate decrease with increase in acetohexamide concentration because the number of molecules of the carrier available per molecule of acetohexamide reduces. This has been observed in the physical dispersion. Aqueous solubility studies (Fig. 4.6) shows a slight increase in solubility of acetohexamide in PEG solution. This effect is not significant enough to justify the increased dissolution rate observed in the dispersion. The interaction in aqueous solution may only explain the increased dissolution rate in the physical dispersion as compared to the dissolution rate of pure acetohexamide.

The gradual decrease in dissolution rate of acetohexamide up to about 50% dispersion cannot be attributed to acetohexamide decomposition as no such decomposition has been observed in the stability studies. The infra red spectrum (Fig. 4.3) shows solid state interaction. The interaction in aqueous solution shown by acetohexamide/PEG (Fig. 4.6) is not significant enough to predict solid state interaction(31).

The explanation to the observed decrease in dissolution rate of acetohexamide as its concentration increases up to about 40% in the dispersion and starts increasing again in 60% and 70% may be that while complete miscibility is observed between the drug and the carrier at liquid state partial solubility may exist between them at solid state resulting in alpha and beta solid solutions and a eutectic formation. If a reasonable proportion of the drug/carrier forms a simple eutectic mixture the proportion that forms the solid solution is reduced. Goldberg et al (28, 30, 31, 32) have shown that simple eutectic formation may not produce enough particle size reduction to cause increase in dissolution rates. Though not clearly enough, the phase diagram (Fig. 4.4) tries to give an impression of eutectic formation with composition 45% acetohexamide, 55% polyethylene glycol 6000 at a temperature of about 51°C. Formation of

simple eutectic mixture of such a composition may, to some extent, affect the dissolution rate and may contribute to the observed decrease in dissolution rate with acetohexamide increase initially. If solid solutions are formed, the alpha solid solution is the solution of acetohexamide in polyethylene glycol and the beta solid solution is the solution of polyethylene glycol in acetohexamide. It has earlier been stated that the composition of the solid solution readjusts as the mixture is gradually cooled from the molten state to the solid state and that the rate of cooling affects the composition adjustment[12]. Gradual rate of cooling favours composition adjustment[12]. Since the rate of cooling in this dispersion has been rapid it appears that this could contribute to the observed decrease in dissolution rate of acetohexamide as the concentration increases up to about 50% in the dispersion coupled with the formation of simple eutectic mixture at about 45%. Another likely explanation to the observed increase in dissolution rate in the high percentage drug content of the dispersion could be the formation of a different polymorphic form of acetohexamide in the dispersion. Different polymorphic forms of substances are known to exhibit different dissolution rates [2, 3, 34].

b) Polyvinylpyrrolidone (PVP) 44000 as Carrier

Generally, as the concentration of acetohexamide dispersion in polyvinylpyrrolidone 44000 increases the rate of drug released from the dispersion decreases both in the coprecipitate and in the physical mixture. This is, however, expected. If the drug and the polymer coexist in the dispersion as a complex, the dissolution of drug can occur by either of two methods; (54) the bound drug can be removed from the polymer at the surface by solvent interaction and thereby precede the polymer into solution, or the drug/polymer complex can dissolve intact followed by dissociation of the drug-polymer complex in solution. Whatever the method of drug release from the dispersion the polyvinylpyrrolidone used as a carrier is a fast dissolving compound and can quickly release the drug in solution.

By dissolving the drug and the carrier together in a common solvent, both of them coexisted as individual molecules in solution. On drying the solvent to form a coprecipitate, the drug in the dispersion probably existed complexed (Fig. 4.2) with the carrier molecules either "encapsulated" or on the surface of the carrier. Hence as the concentration of the drug is increased in the dispersion less of the carrier molecules become available for use of the drug molecules. Aggregate molecules of the drug may then occur in the dispersion

so that when the dispersion is brought into the dissolution medium these aggregate drug molecules are large enough not to go into solution. Hence the rate of drug release from the dispersion decreases as the concentration of the drug is increased in the dispersion. (Fig. 5.14) and (table 5.35).

These processes do not occur in the physical mixture (Fig. 4.2) and therefore for a particular concentration the rate of drug release on dissolution is greater in the coprecipitate than in the physical dispersion of that same concentration. "Solubilization" by polyvinylpyrrolidone 44000 a surface phenomenon, may be responsible for the increased dissolution rate in the physical dispersion over the pure acetohexamide.

(c) Both Polyethylene glycol 6000 and Polyvinylpyrrolidone 44000 as carriers.

When comparing polyethylene glycol 6000 to polyvinylpyrrolidone 44000 it may be noted that for any particular concentration in the physical mixture, the rate of drug release in the physical dispersion of acetohexamide in polyvinylpyrrolidone 44000 is more than that in polyethylene glycol 6000. This is probably due to an inherent character, a fact that polyvinylpyrrolidone 44000 is more soluble and a better solubilizer than polyethylene glycol 6000. Also, the rate of drug release from the coprecipitate dispersion in polyvinylpyrrolidone is greater than the release from the fusion melt dispersion in polyethylene glycol. (Tables 5.35 and 5.35 and Fig. 5.14).

5.3.4. Conclusion

From the above discussions it can be infered that in the solid dispersion of acetohexamide in these carriers, the acetohexamide molecules or ultrafine particles probably exists partially or completely "encapsulated" in the carrier molecules. Because the carriers are fast soluble in water, they quickly dissolve away leaving the acetohexamide particles which may be of molecular or colloidal dimensions which then go into solution. This may be one of the factors

responsible for the increased dissolution rate observed in the coprecipitate dispersion of acetohexamide in polyvinylpyrrolidone 44000 and the melt dispersion of acetohexamide in polyethylene glycol 6000, over their physical dispersions in these carriers and over pure acetohexamide itself.

One of the determining factors of solubility and hence dissolution rate is wetability[9]. If the dispersed drug particles remain encapsulated in the carriers, this will enhance the wetability of the otherwise hydrophobic drug particles because the carriers are fast soluble in water and are in contact with the hydrophobic drug particles. The increased wetability will add to increased solubility and dissolution rate.

Another important point is the fact that the fine particles of drug produced from solid dispersion do not possess the charges that accompany particle size reduction by micronization. This is again probably due to the encapsulation of the drug particles by the carriers.

CHAPTER 6

TABLET FORMULATION

6.1 INTRODUCTION

The United States Pharmacopeia (U.S.P.) XIX defines tablets as "Solid dosage forms containing medicinal substances with or without suitable dilutents". Solid dosage forms started as early as about the 10th Century when tablets were made by placing portions of soft kneaded material into tablet moulds painied with an oily material and the weight adjusted to the required amount. The oily material probably served as a lubricant to prevent the tablets from stickening into the moulds. Since then there have been increasing interests in tableting by medical and Pharmaceutical Scientists. Modern machines have been developed for the purposes of tablet production. A lot of research has been concluded into what happens in the tableting machine during tableting. Devices are now available to measure the forces operating in a tablet press during tablet compression[33]. Shotton and Obiorah [52] have used the Piezoelectric sensor to measure the forces operating in a tablet machine and have characterised the compressional cycles of some granules. The compressional characteristics of powders and the forces involved in powder compression have been investigated by Ibrahim [36]. I do not intend to dwell much on this topic since the intention of this chapter is not to study such forces and powder behaviour in a tablet machine but to study and compare drug release from finished tablets.

From the dissolution rate studies described earlier ., it can be noted that solid dispersions of poorly water-soluble drugs and water-soluble carriers enhance in vitro drug dissolution rates. However, Chiou and Riegehman (8, 11)(1969) have noted that the use of the melt method for preparation may lead to the formation of solids which are unpulverizable because they are soft and sticky or even lead to formation of metastable or glassy forms(57).

The purpose of this study is to prepare tablets from the acetohexamide melt and physical dispersions in polyethylene glycol 6000 and study the dissolution rates of the tablets prepared.

In order for medicinal substances, with or without diluent to be made into dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form possesses a number of physical characteristics. These characteristics include the ability to flow freely, cohesiveness and lubrication(52). Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impact these desirable characteristics to the material which is to be compressed into tablets. New methods of granulation (41) and devices for measuring effects of certain additives on the granules have now been developed.

The techniques for preparing tablets may follow one or a combination of several established methods (20) which include ---

1) Dry methods.

   (a) Direct compression

   (b) Granulation by compression

2) Wet methods

   (a) Wet granulation

   (b) Special procedures

Most manufacturers agree that, when possible, the dry methods are superior to those employing liquids since these dry processes do not require the equipment and handling expenses required in wetting and drying procedures [33]. In addition, dry methods may obviate loss of activity with those drugs that are moisture and heat-sensitive.

For the purpose of this research work and in order not to complicate issues, the dry granulation using the direct compression vehicle is used.

6.2 THE DIRECT COMPRESSION VEHICLE

As the name implies, a direct compression pharmaceutical powder (active substances or diluents) are substances which may be easily compacted directly from powder material without modifying the physical nature of the material itself.

The target of a pharmaceutical direct compression is the formulation of tablets using all alone an active constituent; but the vast majority of the direct compressible powders lack sufficient bulk for satisfactory compression characteristics. Because of this set back there has been a search for direct compression vehicles which are inert substances that may be compacted with ease and which may do so even when quantities of drugs are mixed with it.

Since the pharmaceutical Industry is constantly making efforts to increase the efficiency of tableting operations and to reduce cost by utilising the smallest amount of floor space for a given operation increasing attention is being given to this method of tablet preparation. Compressible diluents currently available include

1) Microcrystalline Cellulose (Avicel)
2) Spray dried lactose
3) Microcrystalline dextrose with higher-molecular-weight Saccharides (Celutab).
4) Anhydrous lactose.
5) Calcium phosphate

6) Mannitol

7) Sorbitol

8) Dri-Tab - a mixture of Sucrose powder and inert sugar.

For the purpose of this work microcrystalline cellulose has been chosen as the direct compression vehicle to be used. It may be noted that the sugars cannot be used in this research work since the study is being carried out with an antidibetic agent - acetohexamide.

6.2.1 Microcrystalline Cellulose PH 101 (AVICEL)

This is an extremely compressible material which has a very poor flow ability probably due to the presence of fines. It is derived from a special grade of purified alpha wood cellulose by severe acid hydrolysis to remove the amorphous Cellulose portions, yielding needle-like microcrystalline particles. It is hygroscopic and expensive. It is capable of producing very hard tablets and yet disintegrated very rapidly in water due to swelling of the microcrystalline cellulose particles and destruction of the bonding forces holding them together (49). This substance has been shown to perform as an excellent disintegrant in almost all formulations, but only when it is present in concentration of 26% or greater (33).

6.2.2 CALCULATIONS

The 60% dispersion of acetohexamide in polyethylene glycol 6000 by the fusion melt method is chosen to be used for tablet formulation. When finally formulated each tablet would contain 150 mg of acetohexamide.

60% dispersion contains 60 mg acetohexamide per 100 mg dispersion and 40 mg polyethylene glycol 6000 per 100 mg dispersion.

If 60 mg acetohexamide is contained in 100 mg. dispersion and if each tablet is to contain 150 mg pure acetohexamide:

150 mg acetohexamide will be contained in $\frac{100 \times 150}{60} = \frac{1500}{6}$

But there is an additive, microcrystalline cellulose, which will act as a diluent as well as a disintegrant. To act as a disintegrant, its concentration should be up to 25% or greater. To increase the concentration of microcrystalline cellulose is to increase the tablet weight.

Therefore, the final tablet weight was decided to be 360 mg. The weight of microcrystalline cellulose in this tablet would be

(360 - 250) mg

= 110 mg.

The percentage of microcrystalline cellulose in the tablet would be

$$\frac{110}{360} \times \frac{100}{1} = \frac{1100}{36} = 30.55\%$$

This is enough quantity to impact disintegration.

FORMULA

	One Tablet 360.9 mg	500 TABLE 180.0G
60% dispersion -	250.0 mg	125.0 g
Microcrystalline Cellulose pH 101	110.0 mg	55.0 g
	360.0 mg	180.0G

6.2.3 Method

60% melt Dispersion

This microcrystalline Cellulose PH 101, is a very fine powder when compared to the granules of the melt dispersion used for dissolution rate studies. In order to avoid straftification and segregation of the powder

mass so as to ensure content uniformity of active material, constant, tablet weight and constant dosage of the tablets within close limit, the 60% dispersion was powdered and sieved $^{250}/_{180}$ ug sieve size. The required quantities of the dispersion and the microcrystalline cellulose were each weighed into a mixer and mixed thoroughly. The mixed powder was then tableted on an Erweka tablet machine (type Eko Nr. 10008) manually operated and using 10.0 mm diameter punch size. Four different forces were used, out of which the correct force would be chosen. The forces were:

1) 6.0 kg. force
2) 6.5 kg. force
3) 7.0 kg. force
4) 7.5 kg. force

b) Pure acetohexamide tablets

The same tablet formula used for preparing tablets from the melt dispersion was also used for preparing tablets from the pure acetohexamide powder. The polyethylene glycol 6000 served as a filler. The acetohexamide/polyethylene glycol 6000 mixture was wet granulated by adding little quantities of water to it until the whole mass became just moist. The wet mass was passed through sieve No. 16 mesh in a granulator. The granules were air dried at room temperature and sieved through $^{250}/_{180}$ ug sieve size before adding the microcrystalline cellulose. It was observed on tableting that more force was required for producing tablets from the physical mixture than from the melt

dispersion. Therefore, 8.5 kg and 9.0 kg forces were tried for producing tablets.

6.3 EVALUATION OF TABLETS

The tablets produced were subject to the following tests:-

6.3.1 Tablet Hardness

The stokes-monsants tablet tester [33] was used. Tablets produced from both melt dispersion and pure acetohexamide were tested. Five tablets were used in each sample test.

6.3.2 Results and discussion

The results are shown in table 6.1 for tablets produced using 60% Acetohexamide melt dispersion in polyethylene glycol 6000 and table 6.2 for tablets produced from pure acetohexamide. It can be observed that from the melt dispersion tablets produced using 6.0 kg force and 6.5 kg. force are soft tablets that may not be able to withstand the hazards of transport and handling.

Tables produce using 7.5kg. force are apparently too strong and may not disintegrate.

In the pure acetohexamide only two forces are used and the forces are reasonably high because the lower forces could not compress the powder into tablets. Hardness tests show that tablets produce using 8.5kg. force seem very soft while those produced using 9.0kg. force appear reasonable hard tablets.

TABLET CHARACTERISTICS

60% ACETOHEXAMIDE/PEG. 6000 MELT DISPERSION

TABLET HARDNESS

6.0kg force	6.5kg force	7.0kg force	7.5kg force
0.5	2.0	7.0	8.5
0.5	1.5	6.5	6.00
1.0	2.0	6.5	8.55
1.0	2.0	7.0	8. 0
0.5	1.5	6.5	8. 5
3.50	9.0	33.50	41.50
AVERAGE- 0.70 kgf	1.80kgf	6.70kgf	8.30kgf

Table 6.1(b)

PURE ACETOHEXAMIDE TABLETS

HARDNESS TEST

Force Used to Produce Tablet	I	II	III	Average
3.50kg force	0.5	0.5	1.0	1.667 kgf
9.0kg force	3.5	4.0	4.0	3.83 kgf

6.3.3. FRIABILITY TESTS

Table 6.2a is the result of the friability test of tablets produced from the melt dispersion while table 6.2b shows the results of friability tests of tablets produced from the pure acetohexamide. The Roche Friabilator was used. Ten tablets were weighed and taken in the friabilator in each operation and allowed to rotate at 20 rpm. for five minutes. After five minutes the tablets were weighed again to see the loss. Friability values are usually considered satisfactory if the weight loss is less than 0.8% (29).

6.3.4. Results and discussion

From table 6.2a it can be noted that tablets produced from the melt dispersions using 6.0kg. force are really too soft and cannot withstand handling harzards. Such tablets cannot be marketed commercially. Tablets produced using this force will no more be subjected to any tests since they are not of much value in the studies.

However tablets produced using 6.5kg. force, 7.0kgf. or and 7.5kg. force have passed the friability tests and can be regarded as reasonably hard tablets that can be used for further studies.

TABLE 6.2a

FRIABILITY

A weight loss of less than 0.8% is usually considered satisfactory.

MELT DISPERSION TABLETS

	6.0kg force	6.5kg force	7.0kg force	7.5kg force
Weight before Rotation(g)	3.6336g	3.6050	3.6120	3.6150
Weight after Rotation(g)	3.5200g	3.5990	3.6120	3.6150
Difference(g)	0.1136	0.0060	-	-
Percentage loss	3.13	0.17	-	-

TABLE 6.2b

FRIABILITY

PURE ACETOHEXAMIDE TABLETS

	8.5kg force		9.0kg force	
	I	II	I	II
Weight before Rotation(g)	3.6321	3.6221	3.6103	3.6133
Weight after Rotation(g)	3.5109	3.5018	3.6098	3.6130
Difference(g)	0.1212	0.1213	0.0005	0.0003
Percentage loss	3.34	3.35	-	-

6.3.5 TABLET DISINTEGRATION TIMES

The basket-rock method as described in USP XIX 1975 was used for the disintegration rate studies. The disintegration medium was water maintained at 37°C. The disintegration times of tablets prepared from both the pure acetohexamide the melt dispersions of acetohexamide in polyethylene glycol 6000 were determined.

Results and discussion

Table 6.3a is the result of the disintegration studies of tablets produced from the melt dispersion of acetohexamide in polyethylene glycol 6000 while table 6.3b shows the disintegration time of tablets produced from pure acetohexamide. It can be noted that tablets produced from the melt dispersion using 6.5kg. force have disintegrated within one minute while those produced using 7.0kg. force have disintegrated within four minutes. These disintegration times are reasonably short. This may be due to the effect of microcrystalline cellulose as a good disintegrator and a dry binder. Tablets produced using 7.5kg. force are too strong to disintegrate. These tablets will no more be used in further studies.

TABLET DISINTEGRATION TIMES

MELT DISPERSION TABLETS

Table 6.3a

TABLET SAMPLES	DISNTEGRATION TIME I	II	III	Average
6.5kg force	55 sec	1 minute	56 sec	57 sec.
7.0kg force	3min.45sec	4 minutes	3 min.51 sec.	3 min 52 sec
7.5kg force	No DISIN.	No	No	-

PURE ACETOHEXAMIDE TABLETS

Table 6.3b

Tablet Sample = 9.0kg force tablets

DISINTEGRATION TIMES I	II	III	Average
2 minutes 30 sec.	2min.45 sec.	2min.40 sec	2min. 30 sec

Though tablets produced from pure acetohexamide have used high compression pressure they still disintegration in good times (about 2½ minutes). Again the microcrystalline cellulose may be responsible for this effect.

6.3.6. Tablet Dissolution Rate Studies

The U.S.P. XIX method of dissolution rate was used to determine the dissolution rate of the tablet produced from both the melt dispersion and the physical dispersion. The dissolution medium was 900.0ml. distilled water maintained at 37°C. The basket was rotated at 50 r.p.m. 5ml. aliquots were withdrawn from the dissolution medium at the intervals shown in the tables but replaced each time with the same quantity of distilled water to keep a constant volume of the dissolution medium. Each individual tablet was weighed before being used.

6.3.7. Results and Discussion

Tables 6.4 - 6.6 show results of all the dissolution rate studies of the tablets. The average of the results is shown in tablet6.6.

From table 6.6 and Fig. 6.1 it can be observed that there is an increased dissolution rate in the tablets produced from the melt dispersion over the

pure acetohexamide tablets. Also a superior dissolution rate is observed in tablets produced from the melt dispersion using 6.5kg. force when compared to tablets produced using 7.0kg. force. No reason other than the force can be advance for this behaviour.

Tablet dissolution rate studies

Pure acetohexamide — Table 6.5a I

Tablet Weight - 0.3602g.

Acetohexamide Content - 0.150mg.

Volume of dissolution medium - 900ml.

TIME (MINUTES)	ABSORBANCE (AT 251nm)	ACETOHEXAMIDE (RELEASED (mg)	% ACETOHEXAMIDE RELEASED
1	0.048	4.785	3.19
5	0.073	7.275	4.85
10	0.082	8.160	5.44
15	0.093	9.315	6.21
30	0.134	13.35	8.90
50	0.174	17.43	11.62
60	0.193	19.305	12.87
70	0.209	20.895	13.93
90	0.228	22.785	15.19

II

Tablet Weight - 0.3615g

Acetohexamide Content - 0.1506g

TIME (MINUTES)	ABSORBANCE (AT 251nm)	ACETOHEXAMIDE (RELEASED (mg)	% ACETOHEXAMIDE RELEASED.
1	0.044	4.43	2.94
5	0.072	7.18	4.77
10	0.084	8.42	5.59
15	0.093	9.31	6.18
30	0.133	13.25	8.80
50	0.173	17.33	11.51
60	0.195	19.50	12.95
70	0.210	21.02	13.96
90	0.230	23.04	15.30

Tablet Dissolution times

6.5kg force Tablet (CONT.) Table 6.4a

I

Tablet Weight 0.362g

Volume of Dissolution Medium - 900.0ml

TIME (MINUTES)	ABSORBANCE AT 251nm	ACETOHEXAMIDE RELEASED	%ACETOHEXAMIDE RELEASED
1	0.115	11.5	7.62
5	0.312	31.2	20.66
10	0.525	52.5	34.77
15	0.660	66.0	43.71
30	0.850	85.0	56.29
50	0.920	92.0	60.93
60	0.944	94.4	62.25
70	0.949	94.9	62.85
90	0.961	96.1	63.64

II

Tablet Weight - 0.362g

Volume of Dissolution Medium - 900.0ml

TIME (MINUTES)	ABSORBANCE AT 251nm)	ACETOHEXAMIDE RELEASED	%ACETOHEXAMIDE RELEASED
1	0.109	10.9	7.22
5	0.318	31.8	21.06
10	0.530	53.0	35.10
15	0.669	66.9	44.30
30	0.859	85.9	56.89
50	0.926	92.6	61.32
60	0.948	94.8	62.78
70	0.953	95.3	63.11
90	0.965	96.5	63.90

7.0kg Force - Table 6.4b (1)
Acetohexamide Content - 0.152g.
Tablet Weight - 0.3645
Volume of Dissolution Medium - 900.0ml

TIME (MINUTES)	ABSORBANCE (AT 251nm)	ACETOHEXAMIDE RELEASED	% ACETOHEXAMIDE RELEASED
1	0.024	2.4	1.58
5	0.119	11.9	7.83
10	0.305	30.5	20.08
15	0.395	39.5	26.00
30	0.732	73.2	48.19
50	0.889	88.9	58.52
60	0.923	92.3	60.76
70	0.925	92.5	60.89
90	0.953	95.3	62.74

II

Acetohexamide Content - 0.152g.
Tablet Weight - 0.3640
Volume of Dissolution Medium - 900.0ml

TIME (MINUTES)	ABSORBANCE (AT 251nm)	ACETOHEXAMIDE RELEASED	% ACETOHEXAMIDE RELEASED
1	0.026	2.6	1.7
5	0.122	12.2	8.04
10	0.310	31.0	20.43
15	0.403	40.3	26.57
30	0.740	74.0	48.78
50	0.893	89.3	58.87
60	0.929	92.9	61.24
70	0.934	93.4	61.57
90	0.960	96.0	63.28

AVERAGE VALUE OF PERCENTAGE ACETOHEXAMIDE RELEASED FROM THE TABLETS.

Table 6.6

TIME (MINUTES)	MELT DISPERSION 6.5kg. FORCE	MELT DISPERSION 7.0kg FORCE	PURE ACETOHEXAMIDE TABLETS 9.0kg. FORCE
1	7.42	1.64	3.065
5	20.83	7.935	4.81
10	34.935	20.225	5.515
15	44.005	26.285	6.195
30	56.59	48.485	8.85
50	61.125	58.695	11.565
60	62.515	61.00	12.91
70	62.98	61.23	13.945
90	63.77	63.06	15.245

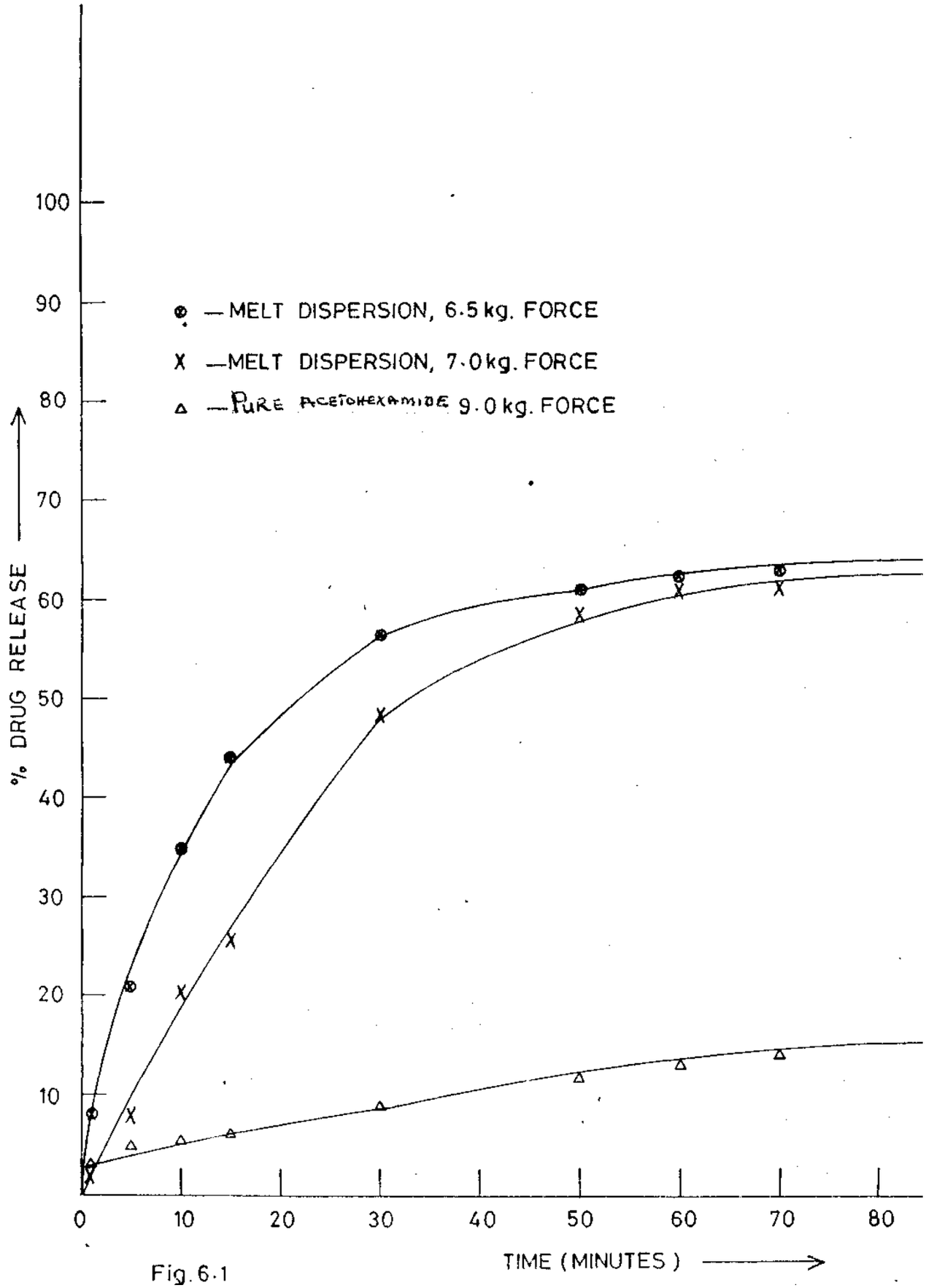

⊗ — MELT DISPERSION, 6.5 kg. FORCE
X — MELT DISPERSION, 7.0 kg. FORCE
△ — PURE ACETOHEXAMIDE 9.0 kg. FORCE
% DRUG RELEASE
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
TIME (MINUTES)

Fig. 6.1

6.4 GENERAL SUMMARY AND CONCLUSION

Acetohexamide, a poorly water soluble, sulphonylurea, hypoglycaemic agent, solid dispersed in readily water soluble inert carriers, polyethylene glycol 6000 and polyvinylpyrrolidone 44000, by the melt method and the coprecipiate method respectively, has been found to be stable in all the dispersions.

Aqueous solubility studies of acetohexamide in different concentrations of polyethylene glycol 6000 did not show enough evidence of interaction in aqueous medium between acetohexamide and polyethylene glycol 6000 to predict solid state interaction, but the infrared spectrum shows some solid state interaction, the nature of which was not determined. The phase diagram of acetohexamide/polyethylene glycol 6000 dispersion did not show any clear picture of solid solution but shows a eutectic of composition 45% acetohexamide, 55% polyethylene glycol 6000.

Two methods of dissolution rate studies, the bag method and the tape method, were compared and the tape method was prefared. Increased dissolution rate was observed in all the solid dispersions. The increased dissolution rate observed in the melt dispersion of acetohexamide in polyethylene glycol 6000 could not be explained on the basis of solid solution formation but rather on simple particle size reduction with increased surface area, reduced electrostatic charges and wetability in the presence of the water soluble polyethylene glycol 6000.

GENERAL SUMMARY AND CONCLUSION (Contd')

Tablet formulation using the melt dispersion of acetohexamide in polyethylene glycol 6000 and pure acetohexamide containing an equivalent amount of polyethylene glycol 6000 as filler showed increased dissolution rate of tablets from the melt dispersion over tablets using pure acetohexamide. In conclusion, it can be stated that solid dispersiion of a poorly water soluble drug in a readily water soluble, inert carrier generally provides particle size reduction resulting in increased dissolution rate, a means that can be used for the formulation of aceeptible oral dosage forms of poorly water soluble drugs.

REFERENCES

1. Allen, V. L, Jr., Yanchick, A. V. and Maness, D. D. (1977), "Dissolution rates of corticosteriods utilising sugar glass dispersions", Journal of Pharmaceutical Sciences, Vol. 66, No. 4 PP. 494 - 496.

2. Al-Saieq, S. S. and Riley, G.S. (1982 (a)), "Polymorphism in sulphenylurea hypoglycaemic agents: II. "Chlorpropamide", Pharmaceutica Acta Helvetiae, Vol. 57, No. 1, PP. 8 - 11.

3. Al-Saieq, S. S. and Riley, G. S. (1982 (b)) "Polymorphism in sulphenylurea hypoglycaemic agents: III. "Acetohexamide" Pharmaceutica Acta Helvetiae, Vol. 57, No. 2 PP. 43 - 46.

4. Balant, L. (1981) "Clinical pharmacokinetics of sulfonylurea hypoglycaemic drugs" Clinical Pharmacokinetics, Vol. 6 PP. 215 - 224.

5. Bloch, D. W., Elegakey, M. A. and Speiser, P.P., (1982) "Solid dispersion of chlorthalidone in urea, phase diagram and dissolution characteristics". Pharmaceutica Acta Helvetiae, Vol. 57, No. 8, P.P. 231 - 235.

6. Braun, R. J. and Parrott, E. (1972) "Influence of viscosity and solubilization on dissolution rate". Journal of Pharmaceutical Sciences, Vol. 61, No. 2, PP. 174 - 179.

7. Browing, R. (1974), Education Chromatography, Griffin and George Limited, England.

8. Chiou W. L. and Riegelman, S. (1969) "Preparation and dissolution characteristics of several fast - release solid dispersions of griseofulvin". Journal of Pharmaceutical Sciences, Vol. 58; No. 12 PP. 1505 - 1509.

9. Chiou, W. L. and Riegelman, S. (1971 (a)) "Pharmaceutical application of solid dispersion systems". Journal of Pharmaceutical Sciences, Vol. 60, No. 9, PP. 1281 - 1302.

10. Chiou, W.L. and Riegelman, S. 1971 .b) "Increasing dissolution rates of water insoluble cardiac glycosides and steriods via solid dispersions in polyethylene glycol 6000".
Journal of Pharmaceutical Sciences, Vol.60, No.10 PP.1569 - 1571

11. Chiou, W.L. and Njazi, S. (1971) "Phase diagram and dissolution studies on sulfathiazole - urea solid dispersions"
Journal of Pharmaceutical Sciences,Vol.60, No.9 PP. 1333 - 1337.

12. Clark, D.S. and Varney, W.R. (1962) Physical metallurgy for engineers, 2 edition, D. Van Nonstrand company inc. New Jessey.

13. Deshpande A.V. and Agrawal D.K. (1982) "Increasing the dissolution rate of some benzothiadiazine derivatives by solid and liquid dispersion techniques"
Drug Development and Industrial Pharmacy, Vol.8, No.6 PP.883 - 896

14. Deshpande,A.V. and Agrawal,D.K. (1982 b) "The influence of various dispersing agents on the dissolution rate of hydrochlorothiazide".
Drug Development and Industrial Pharmacy, Vol.8, No.6, PP.965-978.

15. Deshpande, A.V. and Agrawal,D.K. "Increasing the dissolution rate of chlorpropamide by dispersion technique using various dispersing agents". In press.

16. Deshpande, A.V. and Agrawal, D.K. "Effect of different grades of polyvinylpyrrolidone on dissolution rate of chlorpropamide and its absorption through rat stomach".
In Press.

17. Elworthy, P.H., Florence, A.T. and Macfarlane, C.B., Solubilization by Surface Active Agents. Chapman and Hall Ltd, London.

18. Felmeister; A. (1975)
"Powders"
Remington's Pharmaceutical Sciences, 15 edition PP. 1554
Mack publishing Company, Easton pp.1554;

19. Fincher, J.H., (1968),
"Particle size of drugs and its relationship to absorption and activity"
Journal of Pharmaceutical Sciences, Vol.57 No.11, PP.1825 - 1835.

20. Fonner, D.E. (Jr.), Banker G.S. and Swarbick, (1966)
Micromeritics of granular pharmaceutical solids I. Physical properties of particles prepared by five different granulation methods".
Journal of Pharmaceutical Sciences, Vol.55, No.2, PP. 181 - 186

21. Ford, J.L. and Rubinstein, M.H., (1977) "The effect of composition and ageing on the dissolution rates of chlorpropamide - urea solid dispersions".
Journal of Pharmacy and Pharmacology, Vol.29, PP. 688 - 694

22. Ford, J.L., Stewart, A.F., and Rubinstein, M.H., (1979)
"The assay and stability of chlorpropamide in solid dispersion with urea"
Journal of Pharmacy and Pharmacology, Vol.31, PP. 726 - 729.

23. Ford, J.L. and Rubinstein M.H.(1980) "Formulation and aging of tablets prepared from indomethacin - polyethylene glycol 6000 solid dispersion".
Pharmaceutical Acta Helvetiae, Vol.55, No.1, PP.1-7.

24. Ford, J.L. and Rubinstein, M.H. (1981) "Preparation, properties and ageing of tablets prepared from the chlorpropamide - urea solid dispersion".
International Journal of Pharmaceutical Sciences, Vol.8, PP.311 - 322.

25. Geneidi, A.S., Adel, M.S. and Shehata, (1980)
"Preparation and in vitro dissolution characteristics of various fast - release solid dispersions of glibenclamide"
Canadian Journal of Pharmaceutical Sciences, Vol.15, No.4,
PP. 78 - 80

26. Geneidi, A.S., Adel M.S., Shehata E. (1980/a)
"Enhanced dissolution of glibenclamide from glibenclamide-Poloxamer and glibenclamide - PVP, coprecipitates".
Canadian Journal of Pharmaceutical Sciences. Vol.15, No.4, PP.81-84.

27. Gibaldi, M. (1976)
'Biopharmaceutics' in Lachman, L., Lieberman, H.A. and Kanig J.L. (1976),
Theory and Practice of Industrial Phermacy. 2 edition
Lea and Febiger, Philadelphia PP.78

28. Goldberg, A.H. Gibaldi, M. and Kanig J.L. (1965), "Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and Eutectic Mixtures I. Theoretical Considerations and discussion of the literature",
Journal of Pharmaceutical Sciences, Vol.54, No.8, PP.1145-1148.

29. Goldberg, A.H., Gibaldi, M., Kanig, J.L. and Shanker, J. (1965),
"Method of determining dissolution rates of multiparticulate systems",
Journal of Pharmaceutical Sciences, Vol.54, No.12 PP.1722 - 1725.

30. Goldberg, A.H., Gibaldi, M. and Kanig J.L. 1966 (a),
"Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II. Experimental evaluation of a eutectic mixture: Urea-Acetaminophen System".
Journal of Pharmaceutical Sciences, Vol.55, No.5 PP.482 - 487.

31. Goldberg, A.H., Gibaldi, M. and Kanig, J.L. 1966 (b),
"Increasing dissolution rates and gastrointestinal absorption drugs via Solid Solutions and Eutectic Mixtures. III.
Experimental Evaluation of Griseofulvin-succinic acid solid solution".
Journal of Pharmaceutical Sciences, Vol.55, No.5, PP.487 - 492.

32. Goldberg, A.H., Gibaldi, M., Kanig J.L. and Mayersohn M., (1966),
"Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures IV.

chloramphenical - urea systems".

Journal of Pharmaceutical Sciences, Vol.55, No.6, PP.581 - 583.

33. Gunsel, W.C. and Kanig J.L., (1976) "Tablets". Theory and Practice of Industrial Pharmacy, 2 Edition, Lea and Febiger, Philaldephia PP.321 - 358

34. Haleblian, J. and McCrone W. (1969), "Pharmaceutical applications of Polymorphism",

Journal of Pharmaceutical Sciences, Vol.58, No. PP.911-

35. Hiestand E.N., (1966) "Powders: Particle - Particle interactions",

Journal of Pharmaceutical Sciences, Vol.55, No.12, PP.1325 - 1344.

36. Ibrahim, A. (1979), "The Uniaxial compression of powders".

Ph.D. Thesis of the University of Bradford.

37. Kaur, R. Grant, D.J. W. and Eaves, T. (1980) (a)

Comparison of polyethylene glycol and polyoxyethylene Stearate as excipients for solid dispersion systems of griseofulvin and tolbutamide I. Phase equilibria.

Journal of Pharmaceutical Sciences, Vol.69, No.11, PP.1317-1321

38. Kaur, R., Grant, D.J.W. and Eaves, T. (1980) (b)

"Comparison of Polyethylene glycol and polyoxyethylene Stearate as excipients for solid dispersion systems of griseofulvin and tolbutamide II: Dissolution and solubility studies.

Journal of Pharmaceutical Sciences, Vol.69, No.11, PP.1321-1326

39. King, R.E. (1975)

"Tablets Capsules and Pills"

Remington's Pharmaceutical Sciences, 15 edition Mack Publishing Company, Easton.

40. Lachman, L. and Lin S. (1968), "Electrostatic characteristics of Pharmaceutical solids and packaging materials I. Design of testing equipment and preliminary findings.

Journal of Pharmaceutial Sciences, Vol.57, No.3, PP. 504 -

41. Levenberger,,H., (1982), "Gramulation, new techniques". Pharmaceutical Acta Helvetiane, Vol.57, No.3, Pp.72-82.

42. Lien, E.J. and Kennon, L. (1975), "Atcomic and molecular structures and States of matter".

Remington's Pharmaceutical Sciences 15 Edition Mack Publishing Company Easton, Pp. 171.

43. Lin, S., Meng, J., and Lachman, L. (1968), "Interdepence of Physiological surfactant and drug particle size on the dissolution behaviour of water-insoluble drugs, Journal of Pharmaceutical Sciences, Vol. 57, No. Pp.2143-

44. Marks, A.M., and Sciarra, (1968), "Effect of size on other physical properties of granules and their corresponding tablets", Journal of Pharmaceutical Sciences, Vol.57, No.3, Pp.497-504.

45. Martin, A.N. Swarbick, J. and Camarata A., (1973), Physical Pharmacy, 2 Edition, Lea and Febiger, Philadelphia, Pp. 65

46. Martindale, (1978) The Extra Pharmacopoeia The Pharmaceutical Press, London.

47. McBain M.E.L. and Huchinson E. 1955 Solubilization and Related Phenomena Academic Press, Inc. New York.

48. Merkle, H.P. (1982), "Ageing of coprecipitates: self-association as observed by Phnamic dialysis of supersaturated aqueous solutions of hydrocortisone". Pharmaceutical Acta Helvetiae, Vol. 57, No.5-6, Pp. 160-163.

49. Reier, G.E. and Shangraw, R.F., (1966), "Microcrystalline cellulose in tableting", Journal of Pharmaceutical Sciences, Vol.55, No.5,Pp. 510-514.

50. Said, S.A., EL-Fatatry, H.M. and Geneidi A.S., (1974) "Co-precipitates of tolbutmide with polyvinylpyrrolidone and fusion mixtures with macrogol". Australian Journal of Pharmaceutical Sciences, Vol. NS3, No.2

51. Said, S.A. and Saad, S.F. (1975) "Bioavailability of tolbutamide from its polyvinylpyrrolidone co-precipitates and macrogol fusion mixtures".
Australian Journal of pharmaceutical Sciences, Vol NS, 4, No.4, PP.121 - 122

52. Shotton, E. and Obiorah, G.A., 1975), "Effects of physical Properties on compression characteristics".
Journal of Pharmaceutical Sciences, Vol.64, PP.1213 -

53. Sienko, M.J., and Plane, P.A.
Chemistry: Principles and Properties, 1 Edition,

54. Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., (1969) "Dissolution rates of high energy polyvinylpyrrolidonie (PVP)-sulfathiazole coprecipitates",
Journal of Pharmaceutical Sciences, Vol.58, No.5, PP.538 - 549.

55. Strickland, R.D. (1966) "Seperation and detiction of Oral hypoglycaemic agents by thin-layer chromatography".
Journal of Chromatograph, Vol.24, PP.455-458.

56. Stupak, E.I. and Bates, T.R., (1972), "Enhanced absorption and dissolution of reserpine from reserpine-polyvinypyrrolidone coprecipitate",
Journal of Pharmaceutical Science, Vol.61, No.3, PP.400 - 403.

57. Summers, M.P. and Enever, R.P., (1977), "Effect of Primidone concentration on class transition temperature and dissolution of solid dispersion systems containing primidone and citric acid",
Journal of Pharmaceutical Sciences, Vol.66, No.6 PP.825 - 828.

58. Swinyard E.A. (1975 a) "Diuretic drugs"
Remingtons Pharmaceutical Sciences, 15 Edition, Mack Publishing Company, Easton. PP.861

59. Swinyard E.A. (1975 b), "Pharmaceutical necessities". Remingtons Pharmaceutical Sciences, 15 edition, Mack Publishing Company, Easton. PP. 1221

60. Thakkar A.L., Hirsh, C.A. and Page, J.C. (1977) "Solid dispersion approach for overcoming bioavailability problems due to polymorphism of nabilone, a cannabinoid derivative". Journal of Pharmacy and Pharmacology, Vol.29, PP.783-784

61. The United States Pharmacopeia XIX (1975) Mack publishing company, Easton, Pa.

62. Wurster, D.E. and Taylor P.W. (1965) "Dissolution Rates" Journal of Pharmaceutical Sciences, Vol.54, No.2 PP.169 - 175

63. York, P. (1975) "Application of powder failure testing equipment in assessing effect of glidants on flowability of cohesive pharmaceutical powders". Journal of Pharmaceutical Sciences, Vol.64 PP.1216.