CHAPTER 1

I N T R O D U C T I O N

INTRODUCTION

A solid dispersion may be defined as a dispersion of one or more active ingredients in an inert carrier or matrix at a molecular level in a solid state. Dispersion of a drug or drugs in a solid diluent or diluents by mechanical mixing is often reported in the literature. However, these are not dispersions at molecular levels and hence are not true solid dispersions. The solid dispersions are also sometimes called solid state dispersions (Mayersohn & Gibaldi, 1966). Co-precipitates are those dispersions prepared by solvent methods, for example coprecipitates of sulphathiazole - polyvinylpyrrolidone (Simonelli et al, 1969), reserpine - polyvinylpyrrolidone (Bates, 1969), reserpine - cholanic acid (Stoll et al, 1969) and nitrofurantoin - deoxycholic acid (Stoll et al, 1973).

Dissolution studies have been receiving greater attention in the last decade or two. Dissolution rates are shown to be a rate limiting step in the absorption of drugs from the gastro-intestinal (GI) system by numerous workers. Several review articles have appeared in the literature covering dissolution aspects in varying depths for drugs whose GI absorption is limited by dissolution, especially drugs with poor water solubility, reduction of particle size generally increases the rate of absorption and/or total bioavailability.

Particle size reduction is usually achieved by

(a) conventional trituration or other mechanical methods, for example ball mill, hammer mill, fluid energy mill, spray drying, etc.

(b) Controlled precipitation by change of solvents or temperature, on application of ultrasonic waves.

(c) Liquid solutions of drugs which upon dilution with gastric fluids in vivo may precipitate the dissolved drug in fine particles.

Of the three methods outlined above, method (a) is not applicable to all drugs due to their physicochemical properties. Although the particle size is reduced easily and directly, the resultant fine particles may not produce the expected dissolution or absorption due to aggregation and agglomeration or due to their poor wettability in water. Method (b) poses problems such as selection of non-toxic solvent, limitations to drugs with low dose and high cost of production, and finally method (c) creates problems of obtaining the drug in a liquid dosage form.

Sekiguchi & Obi (1961) were the first to demonstrate the unique approach of solid dispersions to reduce the particle size and increase rates of dissolution. They prepared the eutectic mixture of sulphathiazole with urea, made by rapid cooling of the molten eutectic mixture, showed increased dissolution of sulphathiazole. Goldberg et al (1965, 1966 a, b, c) reported a detailed experimental and theoretical

discussion of the advantages of a solid solution over those of eutectic mixture. Tachibana and Nakamura (1965), reported a new method for preparing solid dispersions (solvent method) of β- carotene in polyvinylpyrrolidone. The method is now widely accepted and utilized by workers in the field.

Solid dispersion of drugs, one of the pharmaceutical techniques play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs. Todate two solid dispersions, Grispeg (Sandoz - Wander) a griseofulvin - polyethylene glycol solid dispersion and cesamet (Lilly) a nabilone PVP solid dispersion are known to have reached the market place.

The enhancement in drug release reported as a result of solid dispersion formation relative to pure drug vary from as high as four hundred fold (Said et al, 1974) to less than two fold. An understanding of the mechanisms of release from solid dispersions would allow the formulator to predict the potential gain in dissolution resulting from a given solid dispersion. The mechanism of release of drugs from these solid dispersions is relatively simple to understand. For a single drug, the mechanism of dissolution is generally explained by any one of the three mathematical models namely the diffusion layer model, the interfacial barrier model or Danckwert's model (Higuchi, 1967). However, these models fail to explain mechanisms of dissolution from solid dispersions. This can be best understood in terms of mathematical models proposed by Higuchi et al, (1965). Fig. 1 shows the dissolution behaviour of a two phase mixture of drug, A, in an inert carrier, B.

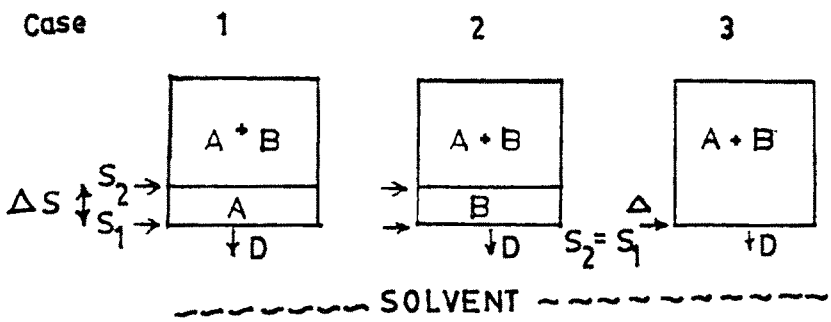


Fig. 1 RELEASE OF DRUG A, FROM SOLID DISPERSION SYSTEM (A+B). B = INERT CARRIER; S_1 = PURE DRUG SOLVENT BOUNDRY : S_2 = SOLID DISPERSION PURE DRUG BOUNDRY : ΔS = THICKNESS OF PURE LAYER D = DIFFUSION COEFFICENT

If A and B do not interact with each other, then upon contact with solvent, both the components of a mixture tend to dissolve at rates proportional to their individual solubilities, C_s and their diffusional coefficients, D (assumption : rates are diffusion controlled). After sometime, t , any one of the three possibilities shown in Fig. 1 is likely to occur. In Fig. 1, Case 1, the carrier has a solubility greater than the drug thus leaving behind pure drug. S_1 is pure drug solvent boundary and S_2 is solid dispersion - pure drug boundary. At $t = 0$, $S_1 = S_2$, at $t > 0$, $S = S_2 - S_1$ which gives the thickness of pure drug layer. Since pure drug is always on the surface (assumption : steady state diffusion), the dissolution rate, Ga, of pure drug can be obtained by using one of the three models for dissolution of single drug (diffusion layer model, interfacial barrier model or Danckwert's model). Using the diffusion layer model, Higuchi, et al (1965) obtained expressions for dissolution rates for A & B, as shown in Table : 1.

The equations generally hold true provided that CsA & CsB do not differ greatly and other assumptions are met. The equations shown in Table : 1 show that in case 1, the dissolution of drug is not dependent upon the dissolution rate of the carrier but that of the carrier is dependent upon that of the drug. In case 2, the dissolution rate of the drug is dependent upon the dissolution rate of the carrier and in case 3, the dissolution rates of both the carrier and the drug are independent of each other.

TABLE : 1

Mathematical solutions to Fig. 1 (Dissolution rates from solid dispersions of Drug A and Carrier B).

Ratio of amounts A & B	Case 1	Case 2	Case 3
$\frac{N_A}{N_B}$	$> \frac{D_A\ CsA}{D_B\ CsB}$	$< \frac{D_A\ CsA}{D_B\ CsB}$	$= \frac{D_A\ CsA}{D_B\ CsB}$
Dissolution rate of A			
GA	$= \frac{D_A\ CsA}{h}$	$= \frac{N_A}{N_B}\ GB$	$= \frac{D_A\ CsA}{h}$
Dissolution rate of B			
GB	$= \frac{N_B}{N_A}\ GA$	$= \frac{D_B\ CsB}{h}$	$= \frac{D_B\ CsB}{h}$

D = diffusion coefficient, C = solubility,
h = diffusion layer thickness.

Similar to the above two components system, three component systems may also be possible which are more complicated, there being thirteen different possibilities at solid - liquid interface (Simpson & Parott, 1983).

Many carrier materials readily form soluble complexes with drugs thereby enhancing the drug's apparent solubility (Chiou & Riegelman, 1971). When two such components are present in a solid dispersion, dissolution of each component is enhanced by the contribution from the diffusing complex. The maximum rates occur at the critical mixture ratio given by

$$\frac{Nd}{Nc} = \frac{Dd.\ Csd + Dcd\ K\ Csd.\ Csc}{Dc\ Sc + Dcd\ K.\ Csd.\ Csc}$$

where k is the binding constant & Dcd, the diffusion coefficient of the complex (Corrigan & Stanley, 1982). The magnitude of the dissolution rates of each component (G^{max}) at the critical

mixture ratio are

$$Gd^{max} = (Dd.\ Csd + Dcd.\ K.\ Csd.\ Csc)/h$$

$$Gc^{max} = (Dc.\ Csc + Dcd.\ K.\ Csd.\ Csc)/h$$

It is to note that the absolute magnitude of the increase in the rate at critical mixture ratio is the same for each component (Dcd. K. Csd. Csc). (Higuchi, et al, 1965). Therefore the relative maximum increase in rate is greatest for the less soluble component.

The relative increase in drug dissolution rate is given by

$$\frac{Gd^{max}}{Go} = 1 + \frac{Dcd.\ Csc.\ K}{Dd}$$

where Go is the intrensic dissolution rate of the drug (Corrigan & Stanley, 1982).

Solid State Changes - During the process of forming a solid dispersion the individual components may precipitate in different solid phases from those present in a similar physical mixture i.e. as polymorphic, solvated or amorphous phases (Simonelli, et al, 1969; Corrigan & Timoney, 1974 & Corrigan & Timoney, 1975) and these result in increased dissolution rate.

Coacervate formation - An alternative dissolution model has been proposed by Sekikawa et al for drug - PVP coprecipitates, which envisages formation of a coacervate at the coprecipitate - solvent interface (Sekikawa, et al, 1979), resulting in faster drug release observed from lower molecular weight PVP coprecipitates. Coacervate formation has also been implicated in the release from PVP - sulphathiazole systems (Badawi & El-Sayed, 1980).

Types of Dispersion Systems

Basically solid dispersion systems can be divided into four major groups. Here the discussion is restricted on system containing two components only, since they are the most encountered in pharmaceutical practice. They are eutectic

Eutectic mixtures - These are solidified fused simple systems of two components. They show complete liquid miscibility and negligible solid - solid solubility. Thermo-dynamically, these systems are regarded as intimately blended physical mixtures of two crystalline components (Goldberg et al, 1965; Findlay, 1951; Moore, 1963). Generally when the eutectic of a poorly soluble drug is exposed to water or GI fluids, the rate of dissolution is increased relative to pure drug. There could be any one of the following factors responsible for such an increase :-

(a) Reduction in the crystallite size of each component.

(b) An increase in the drug solubility, if majority of its solid crystalites are extremely small.

(c) If the carrier completely dissolves in a short time, then a possible solubiliation effect by the carrier takes place in the diffusion layer immediately surrounding the drug particle, especially so in the early stages of dissolution.

(d) In case of hydrophobic drugs, the absence of aggregation and agglomeration between the crystallites causes an increase in the rate of dissolution.

(e) Excellent wettability and dispersibility of a drug in a eutectic system made with water soluble matrix results in an increased dissolution rate of the drug.

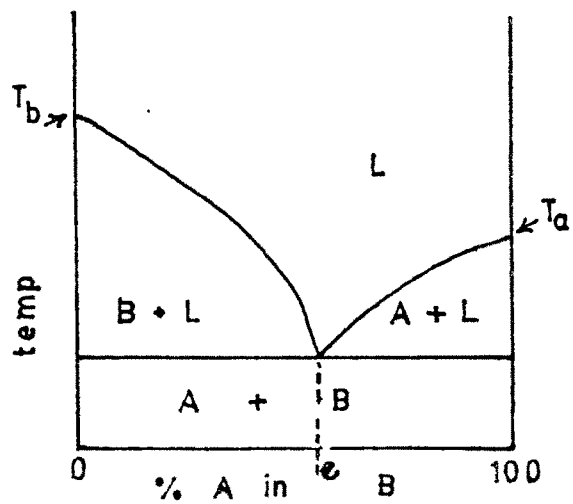


Fig. 2 PHASE DIAGRAM OF A SIMPLE EUTECTIC MIXTURE.
A = DRUG ; B = INERT CARRIER

(f) A drug may crystallise in a metastable form after solidification from the fused solution. A metastable, crystalline form has a higher solubility, which in turn is responsible for a faster dissolution rate.

Two further points are noteworthy

(i) Rapidly crystallised (quenched) eutectics are characterised by increased hardness. It is believed that the hardening effect of the eutectic may retard dissolution (Savchenko, 1959).

(ii) A frozen melt having high weight fraction of a drug may not result in ultrafine crystallisation of the drug.

Solid solutions - A solid solution is made up of a solid solute dissolved in a solid solvent. Solid solutions of a poorly soluble drug in a rapidly soluble carrier generally have a faster dissolution rate than a eutectic mixture (Goldberg et al, 1965). This is because the particle size of a drug in a solid solution is reduced to its molecular size. In addition factor (b), (c), (d) & (e) discussed under simple eutectic mixture may also contribute to the increased rates of dissolution.

Solid solutions are generally classified as follows :-

A. Based on the extent of miscibility between two components

(i) continuous solid solutions (isomorphous, unlimited, or complete)

(ii) discontinuous solid solutions (restricted, limited, incomplete or partial).

B. Based on the crystalline structure of the solid solutions -

(i) substitutional solid solutions

(ii) interstitial solid solutions

A(i) Continuous Solid Solution - The two components are miscible or soluble in the solid state in all proportions as shown in Fig. 3.

It is possible, atleast theoretically, that if a drug is present as a minor component, a faster dissolution rate would be obtained. However, no established solid solution of this kind has been shown to exhibit fast release dissolution properties.

A(ii) Discontinuous Solid Solutions - Here there is only a limited solubility of solute in a solid solvent as shown in Fig. 4. α & β are the regions of solid solutions. Each component is capable of dissolving the other to a certain degree above the eutectic point. As the temperature is lowered, the solid solutions regions become narrower. Sekiguchi & Obi (1961) showed that sulfathiazole - urea system forms a discontinuous solid solution.

B(i) Substitutional Solid Solutions - In this type of solid solution, the solute molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent. It can form a continuous or discontinuous solid solution. Examples of continuous solid solution system include mixtures of p-dibromobenzene & p-chlorobromobenzene

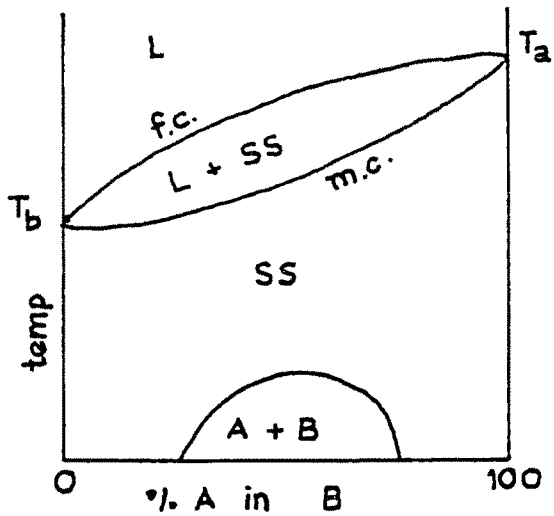


Fig. 3 A TYPICAL PHASE DIAGRAM OF A CONTINUOUS SOLID SOLUTION. A = DRUG : B = INERT CARRIER : L = LIQUID SOLUTION : SS = SOLID SOLUTION : f.c = FREEZING CURVE m.c. = MELTING CURVE

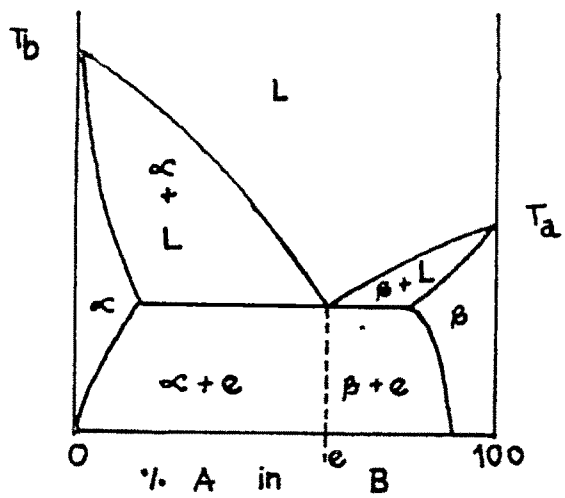


Fig 4 TYPICAL PHASE DIAGRAM OF A DISCONTINUOUS SOLID SOLUTION A = DRUG : B = CARRIER : L = LIQUID SOLUTION : α & β = SOLID SOLUTIONS

(Welcox et al, 1964), anthracene and acenaphthalene (Rastogi & Varma, 1956). The size and steric factors of the solute molecule were shown to play a decisive role in the formation of solid solutions (Findlay, 1951; Moore 1963; Vasil'ev, 1964; Reed-Hill, 1964). The size of solute and solvent molecule should be as close as possible. According to Hume -Ruthery rule (Red-Hill, 1964; Evans, 1964), an extensive solid solution can only be formed when the effective diameter of the solute differs by less than 15 percent from that of the solvent(Fig 5).

The distortion of the crystal lattice of the solvent by steric effect or chemical interaction is also important. The solubility of the solute increases until the distortion of the lattice field of the solvent by the solute molecule can be no longer tolerated. Naphthalene, for example, forms solid solutions with its β-substituted halogen, hydroxyl or amino group derivatives but not with α-substituted derivatives, where it forms eutectic mixtures.

The degree of molecular isomorphism, e, is often used in the literature. It expresses the degree of similarity of the shape of two components. Fig. -5A shows two superimposed molecules. If r is the overlapping volume then e is equal to $1 - \Delta/r$. For wide or complete solubility, a value for e of about 0.9 is necessary.

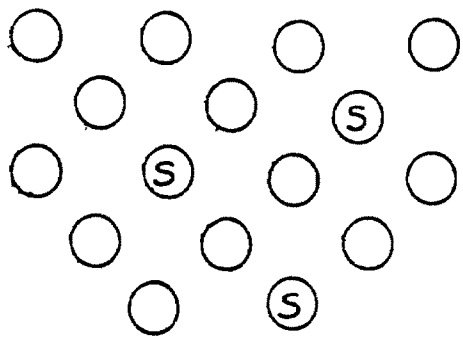


Fig. 5 SCHEMATIC DIAGRAM OF SUBSTITUTIONAL SOLUTION
S = SOLUTE MOLECULES
OTHERS = "SOLVENT" MOLECULES

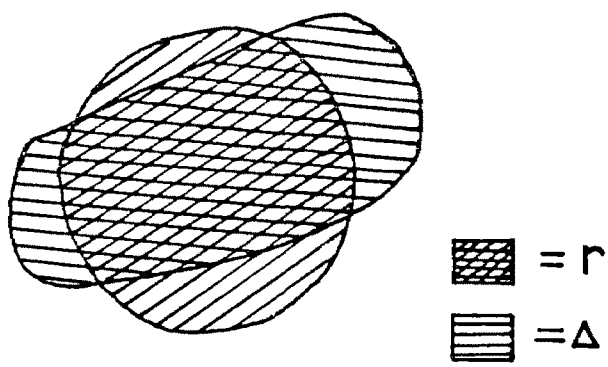


Fig. 5A TWO SUPERIMPOSED MOLECULES SHOWING DEGREE OF MOLECULAR ISOMORPHISM

B(ii) Interstitial solid solutions - The solute molecule occupies the interstitial space of the solvent lattice as is shown in Fig. 6.

Based on earlier work on metals, the volume of the solute molecule required should be less than 20 percent of that of the solvent. Using the same principle, polyethylene glycols which are polymers with two parallel helices in a unit cell, is expected to trap a low molecular weight drug in the halical interstitial spaces when melts are solidified. Chiou & Riegelman (1969, 1971) dispersed griseofulvin, digitoxin, methyltestosterone, prednisolone acetate and hydrocortisone-acetate in polyethylene glycol 4000, 6000 & 20,000. In all cases a marked increased in dissolution rate was shown.

If the drug-polyethylene glycol melt is solidified rapidly (quenched), a metastable solid solution is formed due to factors such as high viscosity, supercooling and physical-chemical interaction between the drug and polymer. Using x-ray diffraction methods, this hypothesis was supported in the case of griseofulvin-polyethylene glycol (Chiou & Riegelman, 1971 a) and indomethacin - polyethylene glycol (Allen & Kwan, 1969). The freshly quenched samples show no noticeable x-ray diffraction peaks of active drug (in low concentrations) while powdered samples exhibit such

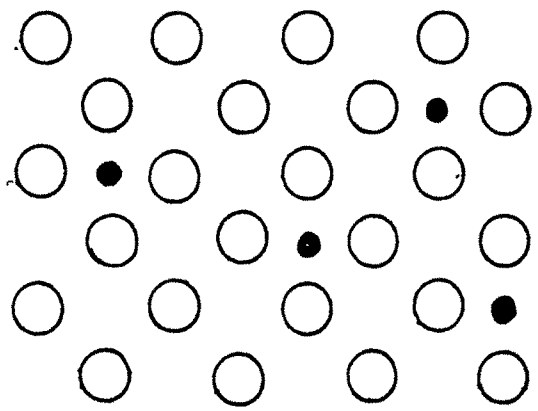


Fig. 6 INTERSTITIAL SOLID SOLUTION

● - SOLUTE MOLECULES

O - SOLVENT MOLECULES

peaks. This is because the powdering process causes some of the supersaturated active drug in the metastable solid solution to precipitate out.

If the concentration of the pure drug is much greater than its solid solubility and the drug-polyethylene glycol melt is solidified rapidly, it produces an ultrafine or colloidal crystallisation of the pure drug. This was shown by the solid dispersion of 40 percent griseofulvin - 60 percent polyethylene glycol 6000, which showed a faster dissolution rate than wetted micronised griseofulvin (Chiou & Riegelman, 1969).

Glass solutions and glass suspensions - A glass solution is a homogeneous glassy system in which a solute dissolves in a glassy solvent. The glassy or vitreous state can usually be obtained by an abrupt quenching of a melt. Generally any liquid or supercooled liquid whose viscosity is greater than 10^{13} poises is called a glass (Clark & Hawley, 1966). Glass solutions are metastable. A glass suspension is a mixture in which precipitated particles are suspended in a glassy solvent.

If a water insoluble drug forms a glass solution with a water soluble glass forming carriers like sugars, sucrose, glucose, ethanol and 3-methylhexane etc., than the in-situ dissolved drug is released into the aqueous medium rapidly because the carrier quickly dissolves upon exposure to the aqueous medium. This concept was used in incorporating greseofulvin, phenobarbitone and hexobarbitone in glassy citric acid solutions (Chiou & Riegelman, 1969 ; 1971 a).

A marked increase in the dissolution rate of griseofulvin in the citric acid glass solution was found. Polyvinyl-pyrrolidone is also soluble in a variety of organic solvents and is useful in accomodating various drugs with limited solubility properties. Mayersohn & Gibaldi (1966) showed marked enhancement of griseofulvin - PVP co-precipitate. A 1 : 6 reserpine - PVP co-precipitate gave a 200-fold increase in dissolution in comparison with pure drug of equal particle size (Bates, 1969).

Miscellaneous - Although frequently reported in the literature during the preparation of solid dispersion systems, complex formation (Dn Cm) between a drug (D) and soluble carrier (C) is not a solid dispersion of a drug.

A solid dispersion does not always fall neatly into any of the three categories mentioned above. Quite often it falls into more than one classification. Griseofulvin dispersed at high concentrations in polyethylene glycol exists as individual molecules and/or as microcrystalline particles.

Methods of preparations

There are basically three methods of preparing solid dispersions

Melting method (fusion method) - The physical mixture of a drug and carrier is heated directly until it melts,

molten mixture then cooled and solidified in an icebath under vigorous stirring. The final solid mass is crushed, pulverised and sieved. This method was first reported by Sekiguchi & Obi (1961) and later subsequently modified and used by Goldberg et al (1966 a,b, c) and Chiou and Rigelman (1969).

The main advantages are simplicity and economy. The main disadvantage is that many substances, drugs and/or carriers, decompose, evaporate or are oxidised during the melting method at high temperatures. These problems can be overcome by heating in a sealed container or under vacuum or under an inert gas or using much lower temperatures.

Solvent method - The two solid components are dissolved in a common solvent. The solvent is then evaporated to yield a solid dispersion.

The main advantage is that the thermal decomposition of the drug and/or carrier can be prevented. The main disadvantages are high cost, difficulty in completely removing solvent and in reproducing crystal forms, the effect of solvent on chemical stability of a drug, and supersaturation of the solute in the solid system can't be achieved except in a system showing highly viscous properties.

Melting/Solvent method - The drug is first dissolved in a suitable liquid solvent. The solution is then incorporated

directly into the melt of a carrier, without removing the liquid solvent. The liquid solvent is then removed to obtain a solid dispersion. It has been applied only to few drug_carrier systems (Chiou & Smith, 1971).

Solid dispersions studied so far (Table : 2) shows pharmaceutical solid dispersions that have been studied. The commonly used inert carriers are polyethlene glycols, PVP, urea etc. Selection of the carrier has an ultimate influence on the dissolution characteristics of dispersed drug, as the dissolution rate of one component (drug) from a surface is affected by the second component (carrier) in a multicomponent system. A comprehensive list is as

Table : 2

Drug	Carrier	Method of preparation	Type of solid dispersion	Effect on Dissoln. rate.	Reference
Sulphathiazole.	Urea	a	Simple eutectic	not studied.	Sekiguchi & Obi (1961)
Chloramphenicol.	Urea	a	"	"	Sekiguchi et al, (1964)
Griseofulvin	PVP	b	not studied	increase.	Mayersohn & Gibaldi (1966)
Paracetamol	Urea	a	solid solution	"	Goldberg et al (1966 a)
Griseofulvin	Succinic acid.	a	"	"	" (1966 b)
Chloramphenicol.	Urea	a	"	"	" (1966 c)
Reserpine	Deoxycholic acid	b	not studied	"	Gibaldi et al (1968)

Drug	Carrier	Method of prepa-ration.	Type of solid disper-sion.	Effect on Dissoln. rate	Reference
Griseofulvin	PEG 4000	a,b	not studied	increase	Chiou & Riegelman (1969)
	PEG 6000	a,b	"	"	"
	PEG 20000	a,b	"	"	"
	Succinic acid.	a	"	"	"
	Anhydrous citric acid.	a	Glass suspens-ion.	"	"
Griseofulvin	Pentaer-ythritol	a	not studied	"	Chiou & Riegelman (1969)
	Pentaer-ythritol tetraace-tate.	a	"	"	"
Indomethacin	PEG 6000	a	"	"	Allen & Kwan (1969)
Sulphathiazole	Urea	a	"	"	"
Reserpine	PVP	b	"	"	Bates (1969)
Sulphathiazole	PVP	b	"	"	Simonelli et al (1969)
Reserpine	Cholanic acid	b	"	"	Stoll et al (1969)
	Litho-cholanic acid.	b	"	"	"
	5β - cholanic acid.	b	"	"	"
	3-12-24-trihydroxy choline.	b	"	decrease	"
	Deoxycho-lic acid.	b	"	increase	"

Drug	Carrier	Method of prepa-ration	Type of solid disper-sion.	Effect on Dissoln. rate.	Reference
Chloramphenicol.	Urea	a	Simple eutectic	not studied	Chiou (1971)
Benzonatate	PEG 6000	c	not studied	increase	Chiou & Smith (1971)
Clofibrate	"	c	"	"	"
Methyl Salicylate.	"	c	"	"	"
Benzylbenzoate	"	c	"	"	"
dl-α-tocopheryl acetate.	"	c	"	"	"
Sulphathiazole	Urea	a	Solid solution	"	Chiou & Riegelman (1971 b)
Indomethacin	PEG 6000	a	not studied	"	Chiou & Riegelman (1971 c)
17-methyl testosterone	PEG 6000	a	"	"	"
Hydrocortisone acetate	PEG 6000	a	"	"	"
Nitrofurantoin.	Deoxycholic acid	b	"	"	Stoll et al (1973)
Griseofulvin	Succinic acid	a	Simple eutectic	not studied	Chiou & Niazi (1973)
Allopurinol	PVP	b	not studied	increase	Collett & Kesteven (1974)
Griseofulvin	Succinic acid	a	Eutectic mixture	increase	Chiou & Niazi (1976)
Hydroflumethiazide	PVP	b	not studied	"	Corrigan & Timoney (1975)

Drug	Carrier	Method of preparation	Type of solid dispersion	Effect on Dissoln. rate	Reference
Sulphathiazole	PEG4000	-	not studied	increase	Niazi (1976)
Primidone	Citric acid	a	Simple eutectic	"	Summers & Enever (1976)
Tolbutamide	PEG4000		not studied	"	Salibetal(1976)
	PEG6000		"	"	" (1976)
	PEG 4000 + PEG 6000	a,b	"	"	"
Corticosteroids	Sugars	a	"	"	Allen et al (1977)
Griseofulvin	PVP 30	Spray embedding.	Solid solution	"	Juninger (1977)
Primidone	citric acid	a	Glass	"	Summers & Enever (1977)
Frusemide	PEG 6000	a	-	"	
Rutin					
Phenindione	PVP40,000	b			
Prednisolone	Microcrystalline cellulose Aerosil 200 Dibasic calcium-phosphate	adsorbate.			Said et al (1975)
Griseofulvin	PVP-30	spray drying	not studied	"	Juninger (1977)
Paracetamol	Mannitol	a	eutectic	"	El-Banna et al (1977)
Caffeine	nicotinamide.	a	Peritectic	"	"

Drug	Carrier	Method of preparation	Type of solid dispersion.	Effect on Dissoln. rate	Reference
Indomethacin	PEG6000	a	eutectic with solid solution	increase	Ford & Rubinstein (1978)
Griseofulvin	Cholic acid - PVP complex	a	not studied	"	Badawi et al(1978)
Amminopyrine -cyclobarbital molecular compound.	PVP	b	"	"	Kiryu et al (1979)
Spironelactone Diazepam	Mannitol Sorbitol 50% mannitol 50% Sorbitol, 50% Mannitol 50% sucrose, PEG 4000 PEG 6000 PEG10000	a	"	"	Geneidi & Hamadhen (1980)
Phenacetin	PEG 6000	a	eutectic	"	Daabis & Mortada (1980).
,	Urea	a,b	not studied.	"	
Indomethacin	PEG 6000	a	"	"	Ford & Rubinstein (1980)
Prednisolone Nitrofurantoin Nitrofural	PVP K-90 & PVP K-25	b	"	"	Voigt & Terborg (1980)
Griseofulvin Tolbutamide	PEG 2000 & Polyoxyl-40-stearate	a,b	monotectic & eutectic	not studied	Kaur et al (1980)
Griseofulvin Tolbutamide	PEG 2000 & Polyoxyl-40-stearate	a,b	not studied	increase	Kaur et al (1980)

Drug	Carrier	Method of preparation	Type of solid dispersion.	Effect on Dissoln. rate	Reference
Phenylbutazone.	PVP & Urea	b	not studied	increase	Mortada (1980)
Phenylbutazone.	Poloxamer 188 & pEG 6000	-	Eutectic with partial solid solution.	"	Banna & Abdallah (1980)
Trimethoprim	PVP K-25 PVP K-90	b	not studied	"	Grahnem et al (1980)
Lonetil	PVP PEG 4000	b	"	"	Bogdanova et al (1980)
Phenobarbital	Sucrose	a	Interstitial solid solution	"	Leucuta & Neamtu (1980)
Phenobarbital	Sorbitol	a	Glassy dispersions	"	"
Phenobarbital	PVP	b	Glassy dispersions	"	"
Phenobarbitone	PEG 4000	b	not studied	"	Kassem et al (1978) Pub. 1980
Phenobarbitone	PVP 40000	b	"	"	"
Phenobarbitone	Carboxy methyl cellulose	b	"	"	"
Diazepam	PEG 4000	a	Eutectic with solid solution	not studied	Duchene et al (1981)
Hydrocortisone.	PVP	b	not studied	increase	Hajratwala & Ho (1981)
Cinnarizine	PVP	b	"	"	Bogdanova et al (1981)
Cinnarizine	Dextrose	b	"	"	"

Drug	Carrier	Method of prepa-ration	Type of solid disper-sion.	Effect on Dissoln. rate.	Reference
Acetohexa-mide	PVP 25000	b	-	increase	Graf et al (1982)
Flufenamic acid	PVP	(Computer application in optimization of formulation).			Takayama et al (1983)
Flufenamic acid	MC				
Sulfonolac-tone	HPMC	b	not studied	increase	Kuchiki et al (1984)
Phenytoin	PVP				
Griseofulvin					
Griseofulvin	HPC	b	(Computer optimization of various formulation variables to get for the best formulation.		Takai et al (1984)
Sulphametho-xazole.	PVP	b	not studied	increase	Sekikawa et al (1982)
Chloramphe-nicol	PEG 4000	b	"	"	Kassem et al (1979)
	PEG 6000				
	PEG 12000				
	PEG 20000				
	PVP 11000				
	PVP 40000				
Sulfadimid-ine	PEG 4000	b	"	"	Kassem et al (1980)
	PEG 6000				
	PEG 12000				
	PEG 20000				
	PVP 11000				
	PVP 40000				
Griseofulvin	Poloxamer 188	a	eutectic	"	Froemming & Heyer (1981)
Hydrocorti-sone.	PEG 4000	a	not studied	"	Ho & Hajrat-wala (1981)
17β -estrad-iol.	PVP	b	"	"	Resetarits et al (1979)

Drug	Carrier	Method of preparation	Type of solid dispersion	Effect on Dissolution rate	Reference
Phenprocoumon Griseofulvin Phenytoin Ethyl biscoumacetate Tolbutamide Hexobarbital	PVP	b	not studied	increase	Loppold (1978)
Glibenclamide	PVP	b	"	"	Geneidi et al (1980)
Glibenclamide	Poloxamer.	b	"	"	"
Ketoprofen	Seventeen water soluble polymers including dextrans & povidone.	b	"	"	Takayama et al (1982)
Indomethacin	PVP Gums Cellulose derivatives, etc.	b	"	"	Takayama et al (1982)
Dicumerol	PVP B-cyclodextrin.	b	"	"	Sekikawa et al (1983)
Ketoprofen	Urea	a	Simple eutectic	"	Rogers & Anderson (1982)
Chlorothiazide Hydrochlorothiazide Flurmethiazide Cyclopenthiazide. Bendroflumethiazide Methylclothiazide	PEG 6000	a,b	not studied	"	Deshpande & Agrawal (1982)

Drug	Carrier	Method of preparation	Type of solid dispersion	Effect on Dissolution rate	Reference
Hydrochlorothiazide	PEG	-	not studied	increase	Kassem et al(1982)
Hydrochlorothiazide	PVP				
"	citric acid				
Diazepam	PEG 4000	a	eutectic	"	Henry et al (1983)
Nifedipine (on lactose particles)	PVP	b	not studied	"	Sugimoto et al (1982)
"	HPC				
Phenytoin	PVP	spray embedding	"	"	Kala & Trave (1983)
Medazepam	PEG				
Indomethacin	PVP	b	"	"	Imaizumi et al (1983)
Chlorpropamide	PVP44000	a,b	"		Deshpande & Agrawal (1983)
	PEG 6000				
	citric acid *				
	sorbitol				
	succinic acid				
	urea.				
Spironolactone	Poloxamer 188	spray embedding	solid solution	"	Gyorgy et al (1984)
Spironolactone	Poloxamer 407.	"	"	"	"
Phenytoin	PEG 200	a	not studied	"	Shigeru et al (1986)
	PEG 300				
	PEG 400				
	PEG 600				
	PEG 1000				
	PEG 4000				

* drug decomposed

Drug	Carrier	Method of prepa-ration	Type of solid disper-sion	Effect on Dissolu-tion rate	Reference
Phenytoin	Cholate Sod. Sod.litho-cholate Sod.deoxy-cholate	b	not studied	increase	Shigeru et al (1986)
Oxyphenyl-butazone	PEG 6000	a	"	"	Ghaly & Abdallah (1986)
Paracetamol	Different molecular weight PEG	-	"	"	Vila et al (1986)
Mefanamic acid Apazone Glafenine Flotafenine	PVP PEG 6000	b	"	"	Ramadan et al (1987)

(a) Melting method (b) Solvent method (c) Melting/Solvent method.

One of the ultimate objectives of solid dispersion system is to increase the bioavailability of drugs. Whether enhanced dissolution rate achieved by using this technique can be translated to increased bioavailability is a question to be answered by conducting bioavailability trials. However, most in-vivo studies done often show marked and dramatic increase in the absorption of drugs. Some noteworthy studies are by Sekiguchi & Obi (1961) on sulphathiazole - urea systems; by Sekiguchi et al (1964) on Chloramphenicol - urea systems ; by Chiou & Riegelman (1970) on griseofulvin - polyethylene glycol systems; by Decato et al (1969) on reserpine - cholanic acid; by Stoll et al (1973) on nitrofurantoin-deoxycholic acid; by Krowczynsk, et al, (1979) on Phenylbutazone - urea system; by Kuchiki et al (1984) on Griseofulvin - water soluble polymers; by Sekikawa et al (1982) on Sulphamethoxazole - PVP system; by Sekikawa et al (1983) on Dicumerol - PVP & Dicumerol - B - cyclodextrin ; by Sugimoto et al (1982) on Nifedipine - PVP & Nifedipine - HPMC systems; by Shigeru et al (1986) on Phenytoin - PEG system.

It may be observed that not many in-vivo studies are reported in comparision to in-vitro studies.

The effect of aging and storage on solid dispersions is not extensively reported. For a potential dosage form which modifies dissolution and absorption rates of poorly soluble drugs, this information is vital before any wide and long range practical approach is feasible.

Here are some reports :

The dispersed phase particles tend to become coarser on aging because the interfacial energy of the system is reduced by concomitant reduction in interfacial area. This phenomenon occurs in eutectic systems with or without solid solution formation and the extent of coarsening increases with time and temperature. In case of naphthalene - phenanthrene system, this was attributed to recrystallization of fine grains (Rastogi & Bassi, 1964).

Precipitation from solid solution occurs on aging with subsequent changes in physical-chemical properties. Glass solution (metastable form) may be converted to more stable form on aging and conversion of metastable polymorphic form to stable polymorph may also occur. All these factors may lead to the change in dissolution behaviour of solid dispersion system on aging.

Some examples are :

Chlorpropamide - urea solid dispersion (Ford et al, 1977); Indomethacin - PEG 6000 system (Ford & Rubinstein, 1979); Indomethacin - PEG 6000 system (F_ord & Rubinstein; 1980); Chlorpropamide - urea system (Ford & Rubinstein, 1981); Griseofulvin - poloxamer 188 system (Froemming & Heyer; 1981); Diazepam - PEG 4000 system (Henry et al, 1983); Nifedipine - PVP & Nifedipine - HPMC systems (Sugimoto et al, 1981); Hydrocortisone - PEG 4000 and Hydrocortisone - PVP solid

dispersion systems (Hajratwala & Ho, 1984); Nifedipine - PVP K-25, PVP K-30, PVP K-90, PEG 4000, PEG 6000 and PEG 10000 dispersion systems (Sumnu, 1986); Glibornuride - PEG 6000 system (Vila et al, 1986).

The above discussion on literature reveals that there remains sufficient scope to carry out further work in this direction, particularly working out with relatively less used, water soluble polymers like poloxamers, polyoxythylene - 40 - stearate etc., using simple method of preparation.

Present Investigation - Phenytoin, Nifedipine and Ketoprofen were selected as model drugs based on the following considerations :

Phenytoin, a widely used antiepileptic drug, is a slightly water soluble weak acid, having potential bioinequivalence problem, accompanied with lower attainable plasma level with narrow therapeutic range. Nifedipine, a poorly water soluble compound having low bioavailability, with considerable pharmaceutical inequivalence and bioinequivalence problems. At the same time, its photosensitivity in liquid dosage forms prompted us to consider this drug as a potentital candidate for the present study. Ketoprofen, an antiinflammatory agent belonging to propionic acid group has gained great importance as a substitute for steroids. It being a weak acid, the solubility and, hence, its dissolution properties are expected

to vary with the pH of the environment. However, at gastric pHs, its solubilities are very low (less than 0.02 %). Thus, it becomes a prime candidate for the formulation studies designed to improve its dissolution characteristics from solid dosage forms.

Apart from some common excepients like urea, citric acid, mannitol, polyethylene glycol 6000, polyoxyl-40 - stearate, two of the higher molecular weight linear polymers Poloxamers 188 & 407 (Polyoxyethylene polyoxypropylene copolymers) were also tested as carriers for their efficacy to increase the dissolution rates of poorly water soluble drugs. Favourable reports on toxicological and dermatological properties of the Poloxamers (data from Wyandotte Chemical Corp., U.S) encouraged the study of their use as potential stabilizers and adjuncts in pharmaceutical technology. Poloxamers series of compounds are now included in N.F.

Thus, the objectives of the proposed study are :

i) To improve the aqueous solubilities of selected drugs having poor solubilities and minimise bioinequivalence problems.

ii) To optimise the pharmaceutical availability (In-vitro availability)

iii) To aim at formulations designed to improve the overall bioavailability.

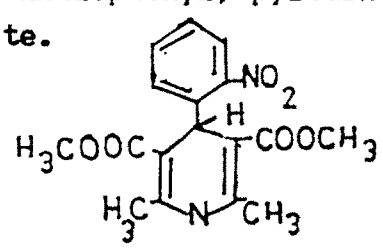
iv) To study the physicochemical properties (like DTA, x-ray diffraction etc) of few selected systems to arrive at some conclusion regarding the observed increase in pharmaceutical availability.

Drugs

Nifedipine - It is an antagonist of calcium influx through slow channel of cell membrane and has been shown to be effective and relatively well tolerated in the treatment for stable, variant and unstable angina, mild to severe hypertension and Raynaud's phenomenon. It thus acts by reducing cardiac work and myocardial oxygen demand and by reducing peripheral resistance (via vasodilation) and heart load.

Physicochemical and pharmacokinetic data of Nifedipine -

Chemical name - Dimethyl, 1, 4-dihyro - 2,6-dimethyl - 4-(2-nitrophenyl) pyridine - 3,5 -dicarboxylate.



Chemical formula - C_{17} H_{18} N_2 O_6 Mol. wt. 346.3

Description - A yellow, odourless, tasteless, crystalline powder.

Solubility - Practically insoluble in water, slightly soluble in alcohol, soluble in acetone and chloroform.

Melting point - 172 - 174°C

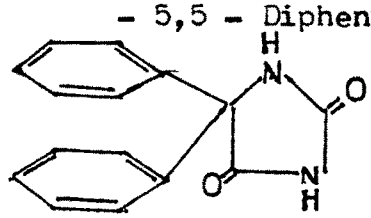
Stability	-	Nifedipine, a dihydropyridine derivative, is very light sensitive and breaks down rapidly on exposure to daylight, tungsten bulb light, standard flourescent light or ultraviolet radiation to its more stable nitroso or nitropyridine derivatives. Hence, it should be protected from light. It is however stable when 'gold' fluorescent light is used.
Dose	-	Usual, oral, 10 mg. three times daily during or after meals.
Absorption, fate & excretion.	-	Nifedipine is rapidly and completely absorbed from gastrointestinal tract but only 45 to 68% reaches systemic circulation. Nifedipine undergoes almost complete (95 %) hepatic oxidation to three inactive metabolites. Nifedipine is largely distributed in liver, kidney serum and lungs and to a smaller extent in brain, skeletal muscle and testes. About 70 - 80% drug is eliminated via urine as metabolites, the remaining being excreted in faeces.

Volume of distribution	-	Vd oral : 1.32 L/kg ; Vd IV : 0.62 to 1.12 L/kg.
Protein bending	-	92 to 98 %, concentration dependent.
Elimination half life	-	Oral tablet : 6-11 hrs. Oral capsule : 2-3.4 hrs. Intravenous : 1.3 to 1.8 hrs.
Minimum effective concentration	-	15 ug/L
Maximum plasma concentration (Cmax) oral.	-	25.9 to 62.6 ug/L
Time to maximum plasma concentration	-	Oral tablet : 1.6 - 4.2 hrs. Oral capsule : 0.57 - 2.17 hrs. Sublingual : 0.5 - 1.0 hr. capsule.

Phenytoin - It is one of the more widely used antiepileptic agents, and it is effective in most forms of epilepsy except absence seizures. It has been used with variable results for the treatment of disturbed nonepileptic psychotic patients. Some cases of trigeminal and related neuralgias respond well to phenytoin and also it is of some use in the treatment of cardiac arrythmias.

Physicochemical and pharmacokinetic properties -

Chemical name - 5,5 - Diphenylhydantoin



Chemical formula - C_{15} H_{12} N_2 O_2 , mol. wt. 252.3

Description - A white or almost white, odourless or almost odourless, tasteless, crystalline powder.

Melting point - About 295°C

Solubility - Practically insoluble in water, slightly soluble in alcohol, soluble in hot alcohol, soluble 1 in 500 of Chloroform and 1 in 600 of ether; soluble in solutions of alkali hydroxides.

Dose - Initial daily dose for adults is 100 mg. twice daily. Dosage is subsequently increased, preferably

- with monitoring of plasma concentration, as needed for control of seizures or as limited by toxicity. Increments in dosage may be made at 1 week intervals at low dosage but at 2-week intervals when dosage exceeds 300 mg. daily. Because of its relatively long half life and slow absorption, a single daily dose is often satisfactory for adults, but gastric intolerance may dictate divided dosage. If loading dosage is deemed necessary, 600 to 1000 mg, in divided portions over 8 to 12 hrs, will provide effective plasma concentrations within 24 hrs. in most patients.

Absorption and fate - The pharmacokinetic characteristics of phenytoin are markedly influenced by its limited aqueous solubility and its dose dependent elimination. Absorption of phenytoin after oral ingestion is slow, sometimes variable and occasionally incomplete. Peak plasma concentration after a single dose may occur as early as 2 hrs. or as late as 6 hrs. It is extensively

bound (about 90%) to plasma proteins, mainly albumin. The drug is widely distributed in all tissues. About 2% of phenytoin is excreted unchanged in the urine. The remainder is metabolized primarily by the hepatic microsomal enzymes. The major metabolite, the parahydroxyphenyl derivative, is inactive. Other apparently inactive metabolites include the dihydroxy - catechol and its 3-methoxy derivative and the dihydrodiol.

Volume of distribution- 0.64 litres/kg.

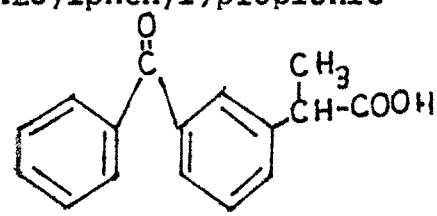
Plasma half life - Dose dependent, 17-22 hrs.

Effective concentration - 10 to 20 ug/ml.

Toxic concentration - Concentration above 20 ug/ml.

Ketoprofen - It is one of the non steroidal analgesic and anti inflammatory agent, used in Rheumatoid arthritis oesteoarthritis , ankylosing spondylitis and related conditions. The intensity of untoward effects is less than that associated with the ingestion of indomethacin or high doses of aspirin.

Physicochemical and pharmacokinetic data of Ketoprofen

Chemical name	- 2-(3-Benzoylphenyl)propionic acid. 
Chemical formula	- C_{16} H_{14} O_3, Mol. wt. 254.3
Description	- A white or almost white, odourless or almost odourless, crystalline powder.
Melting point	- 93 to 96°C
Solubility	- Practically insoluble in water, freely soluble in alcohol, chloroform and ether; soluble in methyl alcohol.
Dose	- Usual dose 50-100 mg. twice daily with food.
Absorption and fate	- It is readily absorbed from gastrointestinal tract, extensively bound to plasma

		proteins, metabolised mainly by conjugation with glucuronic acid and is excreted in urine and to a lesser extent in the faeces.
Time to peak plasma concentration.	-	½ to 2 hrs.
Plasma half life	-	1 to 4 hrs.

Solid dispersions are not only used to enhance the action of poorly soluble drugs, but its application has been extended to produce prolonged release or delayed release of drugs too. Solid dispersions of Nifedipine, Spironolactone and Griseofulvin using some of the enteric coating materials were evaluated in order to control the release of these poorly water soluble drugs (Hasegawa et al, 1985).