ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

ISSN 2277-7695

Vol. 1 No. 12 2013
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Solid Dispersion – A Approach To Enhance The Dissolution Rate of Poorly Water Soluble Drugs

Debjit Bhowmik[1*], G.Harish1, S.Duraivel[1], B. Pragathi Kumar[1], Vinod Raghuvanshi[2], K. P. Sampath Kumar[3]

1. Nimra College of Pharmacy, Vijayawada, Andhra Pradesh, India.
   [E-mail: debjit_cr@yahoo.com]
2. Micro Advance Research Centre, Bangalore, Karnataka, India.
3. Department of Pharmaceutical Sciences, Coimbatore medical college, Coimbatore, India.

In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality. This frequently results in potentially important products not reaching the market or not achieving their full potential. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy. The enhancement of dissolution rate and oral bioavailability is one of the greatest challenges in the development of poorly water soluble drugs. Dissolution is the rate limiting step in case of poorly soluble drugs in process of drug absorption. Poorly soluble drugs are presented with problems of variable bioavailability. Many techniques have been exercised to improve oral bioavailability of drugs. Among several methods, solid dispersion has attracted attention of the researchers for previous 50 years. Solid dispersions improve solubility of drug particles thus enhancing dissolution characteristics of drugs they increase the oral bioavailability. This review will focus on different aspects of solid dispersion preparation; their advantages, major challenges and preparation methods. Various solubility enhancers like water soluble carriers, cosolvents, surfactants and super disintegrates have been examined to aid in solubility enhancement. These significantly help to improve the bioavailability.

Keyword: Solid-dispersion, Bioavailability, Dissolution Rate, Reliable Therapy

1. INTRODUCTION: The bioavailability of a poorly water soluble drug is often limited by its dissolution rate, which in turn is controlled by the surface area available for dissolution. The effect of the particle size of a drug on its dissolution rate and its biological activity is well known. For example, Atkinson et al reported that micronization of griseofulvin resulted in reduction of the therapeutic dose by half. The conventional method for reducing particle size and increasing surface area include trituration, grinding, ball milling, fluid energy micronization

and controlled precipitation. Coprecipitates and melts are solid dispersions that provide a means of reducing particle size to the molecular level. Sekiguchi and Obi first introduced the concept of using solid dispersions to improve bioavailability of poorly water-soluble drugs in 1961.

They demonstrated that the eu tectic of sulfathiazole and the physiologically inert water-soluble carrier urea exhibited higher adsorption and excretion after oral administration than sulfathiazole alone. Chiou and Reigelman defined the term solid dispersion as "a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (Fusion), solvent, or melting-solvent method". Dispersions obtained through the fusi on process are often called melts, and those obtained by the solvent melts are frequently referred to as coprecipitates or coevaporates. Example include sulfathiazole-providone (PVP-4) and reserpine PVP(5). Solid dispersions is an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly soluble drugs.

This article reviews the various types of solid dispersion, preparation techniques for solid dispersion and compiles some of the recent technologies. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterization, along with nature of drugs in solid dispersionsThe solubility of the drug is the factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. There are various available techniques, alone or in combination can be used to enhance the solubility of the drug. Although in all techniques mentioned solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling. Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs. Currently only 8% of new drug candidates have both high solubility and permeability.

More than 60% of potential drug products suffer from poor water solubility. This frequently results in potentially important products not reaching the market or not achieving their full potential. Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. Most of the newly invented chemical entities are poorly water soluble. Experience with solid dispersions over the last 20-30 years indicates that this is a very fruitful approach to improving the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. Solid dispersion is used to produce a homogeneous distribution of a small amount of drug in solid state. This article summarize some of the practical aspects for the preparation of solid dispersion like selection of carrier ,method of physicochemical characterization, their advantages, limitations and applications along with an insight into the molecular arrangement of drug in solid dispersion.

Solid dispersion technique is a very useful method for pharmaceutical point of view because of its capability to solve the solubility problems by using solid dispersion method.

2. SOLUBILITY AND VARIOUS SOLUBILIZATION TECHNIQUES:

a. Solubility:

When an excess of a solid is brought into contact with a liquid, molecules of the former are

removed from its surface until equilibrium is established between the molecules leaving the solid and those returning to it. The resulting solution is said to be saturated at the temperature of the experiment, and the extent to which the solute dissolved is referred to as its solubility[2]. Poorly water-soluble drugs are increasingly becoming a problem in terms of obtaining the satisfactory dissolution within the gastrointestinal tract that is necessary for good bioavailability. It is not only existing drugs that cause problems but it is the challenge of medicinal chemist to ensure that new drugs are not only active pharmacologically but have enough solubility to ensure fast enough dissolution at the site of administration, often gastrointestinal tract[3]. Always check the physical properties of the ingredients being used. This provides some very useful information. Always check the solubility of any solid materials. If they are soluble in any of the other ingredients of the product then this will be of considerable benefits in achieving uniform dose distribution. Solution is achieved more quickly if the particle size is small and so size reduction should be considered for any soluble ingredients which are presented in a lumpy or granular form. If the substance is not soluble, or if not granular form. If the substance is not soluble or if not already in a finely divided form it should always be size reduced[4]. Solubility of an agent in a part icular solvent indicates the maximum concentration to which a solution may be prepared with that agent in that solvent. When a solvent, at a given temperature, has dissolved all the solute it can, it is said to be saturated. Solubilities for medicinal agents in a given solvent are stated in the British Pharmacopoeia (BP) and Martindale (Reynolds 1996) as well as in other reference sources. Solubilities are usually stated as the number of parts (by weight or volume of a liquid) of the substance. Most solutions for pharmaceutical use are not saturated with solute[5]. As a drug particle undergoes dissol ution, the drug molecules on the surface are the first to enter into solution creating a saturated layer of drug solution, which envelops the surface of the solid drug particles. This layer of solution is referred to as the diffusion layer. From this diffusion layer, the drug molecules pass throughout the dissolving fluid and make contact with the biologic membranes and absorption ensures. As the molecules of drug continue to leave the diffusion layer, the layer is replenished with dissolved drug from the surface of the drug particle and the process of absorption continues. If the rate of dissolution for a given dr ug particle is slow, as may be due to the physiochemical characteristics of the drug substance or the dosage form, the dissolution process itself would be a rate limiting step in the absorption process. Slowly soluble drugs such as digoxin may not only be absorbed at a slow rate, they may be incompletely absorbed, or in some cases largely unabsorbed following oral administration, due to the natural limitation of time that they may remain within the stomach or the intestinal tract. This poorly soluble drugs or poorly formulated drug product may result in a drug incomplete absorption and its passage, unchanged, out of the system via feces[5].

b. Solubilization Techniques:

Solubilization is the process by which the apparent solubility of a poorly water soluble substance is increased. Solubilization techniques include addition of a cosolvent, salt formation, prodrug design, complexation, particle size reduction and the use of surface active agent (micellization)[7]. Use of solvates and hydrates, pol ymorphs, hydrotrophy, pH adjustment, solubilizing vehicles etc. are the some other physico-chemical approaches to enhancing oral absorption of poorly water soluble drugs.

c. Use of Cosolvents:

Co-solvents are defined as water miscible organic solvents that are used in liquid drug formulation to increase the solubility of poorly water soluble drugs or to enhance the chemical stability of the drug[8]. A common example of a class of form ulations containing cosolvent is the elixir, which by definition is sweetened hydroalcoholic solution intended for internal use. Tinctures, which are generally contain even higher amount of alcohol, are another classic example of a

liquid dosage form containing a cosolvent. Weak electrolytes and non-polar molecules frequently have a poor water solubility. Their solubility usually can be increased by the addition of a water miscible solvent in which the drug has good solubility. This process is known as co-solvency and the solvents used in combination to increase the solubility of solute are known as cosolvents[9]. Cosolvents such as ethanol, propylene glycol and polyethylene glycol are used as an aid to solubilization of nimesulide in aqueous vehicles. Solubility of nimesulide was found to increase appreciably when semi-polar solvents such as ethanol or propylene glycol were used as solvents. Small non-polar hydrocarbon region does not interact strongly with water and hence reduce the ability of the aqueous system to squeeze out non-polar solutes. Enhancement of solubility of a number of drugs in the presence of ethanol, propylene glycol, etc. has been reported in the literature[10].

d. pH Adjustment:

If a compound is ionizable, it may be possible to increase solubilities by adjusting pH. Compounds with pKa/b values between 3-11, namely weak acids andbases, may have solubility enhanced in this way, if a drug is poorly soluble at low pH, it is conceivable that co-administration or co-formulation with an acid neutralizing material provides a gastric environment more conducive to better solubility and dissolution rate. Elevation of gastric pH could also reduce presystemic degradation of acid labile compounds, leaving more available for absorption. Magnesium and calcium carbonate can be used as compression aids in tablet formulations. It is feasible that their acid-neutralizing effects could be capitalized onto enhance absorption of acid labile compounds or those with poor solubility at normal gastric pH. Some antacids have also shown to increase the rate of passage from the stomach to small intestine, consequent to elevating gastric pH. This can have theoretical benefit, not only for acid-unstable drugs or acid-insoluble drugs, but also where increased rate of absorption can have therapeutic benefit.

e. Solubilizing Vehicles:

The least complex way to present a mate rial to the GIT for absorption is to administer in solution, thereby removing any dissolution stage. Occasionally, non-aqueous (organic) solvents are used to solubilize drugs for parenteral use. Use in oral products is constrained and complicated by many factors. They may not exert sufficient solubilizing action to be of practical values unless the dose of drug is low. Otherwise the volume of vehicle required cannot be readily contained in a convenient dose unit. Liquid filled gelatin capsules offer possibilities for compounds when the drug dose is approximately 40-60 mg but only a limited number of non-aqueous solvents can be employed for such presentations. Some synthetic aluminosilicates or silicates can absorb significant amounts (up to and exceeding and equal mass) of certain organic solvents while retaining the properties of a solid. Drug dissolved in the organic solvents and then absorbed on the silica provides a form that can be filled into capsules and even compressed to tablets. The drugs “in solution”, but can be formulated as solid dosage form. This approach requires that the drug has higher solubility (and good stability) in the chosen organic solvent. These requirement restrict the applicability to potent medicine agents (does not greater than 10-20 mg) that have high solubility suitable of organic solvents[11].

f. Salt Formation:

Many poorly soluble drugs can be solubilized in salt form. The compound (2-piperidyl)-3,6-bis(trifluoromethyl)-9-phenanthenemethanol, an antimalarial agent, and its hydrochloride salt are both only slightly soluble in water. However, its lactate salt is approximately 200 times more soluble than the hydrochloride. This enhanced aqueous solubility is attributed in part to the decrease in crystal lattice energy, as indicated by a reduction in the melting point. If a particular salt form cannot be isolated because of its very highly solubility, the same end result (i.e., desired aqueous solubility) can be achieved by in-situ salt formation. This is accomplished by using an

appropriate acid or base to adjust the pH level while formulating the drug product solution.

g. Prodrug Method:

The solubility characteristics of a drug can be altered by chemical modification, this is referred to as the "prodrug" approach. The term was first used by Albert for a compound that undergoes biotransformation before eliciting a pharmacological response. This method has been successful in the case of corticosteroids. The solubility of betamethasone in water for example, is 5.8 mg/ 100 ml at 25 C. The solubility of its disodium phosphate ester is more than 10g/ 100 ml, an increase in solubility greater than 1500-fold. Although methods such as salt and prodrug formation can result in high increases in solubility, they require synthesis of essentially new drug entities as well as additional animal studies to confirm their efficacy and safety. Thus an undertaking of this magnitude can be justified only if no other reasonable approaches is available[12]. Stella has reviewed some of the reasons for formation of prodrugs. The prodrug approach is widely used as a method of improving oral absorption of poorly absorbed drugs. The ideal prodrug is one which is non-toxic, does not produce toxic fragments upon liberation of the active drug, releases the active drug at the desired rate, and is at least as stable as the parent compound towards degradative pathways which limit availability[13].

h. Complexation:

Complexation is another means of improving the aqueous solubility of insoluble compounds; Complexation is another means ofimproving the aqueous solubility of insoluble compounds; it is described by equation-1. A complex is an entity formed when two molecules such as a drug and a solubilizing agent (ligand), are bound by weak forces (e.g., dipole-dipole interaction or hydrogen bonding). For complex formation to occur, drug and ligand molecules must be able to donate or accept a pair of electrons. Complexation has several advantages, such as the reversibility of the interactions. Dissociation of the complex to the individual reactants occurs rapidly and spontaneously on dilution. Consequently, the biological effects of complexes can be predicted on the basis of knowledge of the pharmacological properties of each of the reactants. Another advantage is the predictability and physical stability of the systems. Decrease complex formation involves equilibrium attainment, once the necessary data defining the system parameters such as stability constants and solubility properties of the complexes have been gathered, the behaviour of the system is totally reproducible and predictable. This is in contrast to the polymorphs and other crystal modifications, which can be thermodynamically unstable; they may undergo time-dependent changes, that may lead to changes in solubility behaviour.

i. Micellization:

Micellization has b een defined by McBain as the spontaneous passage of poorly water soluble solute molecules into an aqueous solution of a soap or detergent in which a thermodynamically stable solution is formed. The mechanism for this phenomenon has been studied extensively and involves the properties of surface-active agents forming colloidal aggregates known as micelles. When surfactants are added to a liquid at low concentrations, they tend to orient at the air-liquid interface. As addition surfactants are added, the interface becomes fully occupied, and the excess molecules are forced into the bulk of the liquid.

At still higher concentrations, the molecules of surfactants in the bulk of the liquid begin to form oriented aggregates or micelles; this change in orientation occurs rather abruptly, and the concentration of surfactant in which it occurs is known as the critical micelle concentration (CMC). Solubilization is though to take place by virtue of the solute entrapped in a or absorbed onto the micelle. Thus, the ability of surfactant solutions to dissolve or solubilize water-insoluble material starts at the critical micelle concentration and increases with the concentration of the micelles[14].

j. Hydrotropy:
Hydrotropy is a solubilization process whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. The commonly used hydrotropic agents for solubilization of drugs include nicotinamide, urea, etc[15]. Nicotinamide (vitamin B_3) is well known as a hydrotropic agent and has demonstrated the ability to solubilize a wide variety of therapeutic entities including riboflavin. Urea, widely known as a protein denaturant, is also known to have some hydrotropic properties[16].

k. Polymorphs:
Medicinal compounds may exists in a variety of crystal forms that can have differing aqueous solubilities. Riboflavine has three polymorphs with solubilities varying from 0.06-1.2 mg/ml. Bioavailability of various morphic forms of cimetidine was shown to correlate with dissolution rates suggesting that solubility might be important for oral absorption. Kimura et al obtained differing plasma levels in dogs when dosed with different polymorphs of the poorly soluble hypoglycemic agent tolbutamide. *In vivo* performance reflected in vitro differences in dissolution rates and solubilities between the forms. Polymorphs with the lowest free energy (lowest solubility) are usually most stable in thermodynamic terms; more soluble forms tend to transform to the low energy state. Such transformation can occur during storage, processing or even during dissolution. This makes polymorph selection for solubility enhancement an uncertain process. It is important therefore, that any promising crystal form is thoroughly assessed to confirm that: It can be prepared consistently by a realistic and reliable process. The preferred form can be readily identified by a technique suitable for routine quality control. It does not transform to a less useful form on storage, during process or after incorporation in the dosage form. It does not transform to the less soluble state after ingestion but prior to absorption;that is, in the GIT environment. Amorphous materials can be more soluble and have faster dissolution rates than crystalline forms because of lower salvation energy. Amorphous novobiocin dissolves rapidly and is well absorbed in humans. The crystalline form, by contrast, is less soluble, has slower dissolution rates, and exhibits poor and erratic bioavailability[17].

l. Hydrates/ Solvates (Pseudopolymorphism):
The crystalline form of a drug can either be a polymorph or a molecular adduct or both. The stoichiometric type of adducts where the solvent molecules are incorporated in the crystal lattice of the solid are called as the solvates, and the trapped solvent as solvent of crystallization. The solvates can exist in different crystalline forms called as solvent of crystallization. The solvates can exist in different crystalline forms called as pseudopolymorphs. This phenomenon is called as pseudopolymorphism. When the solvent in association with the drug is water, the solvate is known as hydrate. Hydrates are most common solvate forms of drugs. Generally, the anhydrous form of a drug has greater aqueous solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal break-up in comparison to the anhydrates (thermodynamically higher energy state). For further interaction with water. The anhydrous form of theophylline and ampicillin have higher aqueous solubilities, dissolve at a faster rate and show better bioavailability in comparison to their monohydrate and trihydrate forms respectively. On other hand, the organic (non-aqueous) solvates have greater aqueous solubility than the non-solvates – For example, the n-pentanol solvate of fludrocortisone and succinyl sulfathiazole and the chloroform solvate of griseofulvin are more water-soluble than their non-solvated forms. Like polymorphs, the solvates too differ from each other in terms of their physical properties. In case of organic solvates, if the solvent is toxic, they are not of the therapeutic use[18].

m. Use of Surfactants:
The surface active agents enhance di ssolution rate primarily by promoting wetting and

penetration of dissolution fluid into the solid drug particles. They are generally used in concentration below their critical micelle concentration (CMC) values since above CMC, the drug entrapped in the micelle structure fails to partition in the dissolution fluid. Non-ionic surfactants like polysorbates are widely used. Examples of drugs whose bioavailability has been increased by use of surfactants in the formulation includes steroids like spironolactone[19].

n. Surfactants as Solubilizing Agents:

Solubilization can be defined as "the preparation of a thermodynamically stable isotropic solution of a substance normally insoluble or very slightly soluble in a given solvent by the introduction of an additional amphiphilic component or components. The amphiphilic components (surfactants) must be introduced at a concentration at or above their critical micelle concentrations. Simple micellar systems (and reverse micellar) as well as liquid crystalline phases and vesicles referred to above are all capable of solubilization.

o. Solubilization by Micelles:

The location of a solubilized mol cecule in a micelle is determined primarily by the chemical structure of the solubilizate, solubilization can occur at a number of different sites in a micelle: On the surface, at the micelle-solvent interface. Between the hydrophilic head groups. In the palisades layer, i.e., between the hydrophilic groups and the first few carbon atoms of the hydrophobic groups that comprise the outer regions of the micelle core, More deeply in the palisades layer, and In the micelle inner core. In aqueous system, non-polar additives such as hydrocarbons tends to be intimately associated with the hydrocarbon core of the micelle. Polar and semi-polar materials, such as fatty acids and alcohols are usually located in the palisades layer, the depth of penetration depending on the ratio of polar to non-polar structures in the solubilizate molecules. A preferred location of the solubilizate molecule within the micelle is largely dictated by chemical structure. However, solubilized systems are dynamic and the location of molecules within the micelle changes rapidly with time, solubilization in the surfactant aqueous systems above the CMC offers one pathway for the formulation of poorly soluble drugs (7). From a quantitative point of view, the solubilization process above the CMC may be considered to involve a simple partition phenomenon between aqueous and a micellar phase.

p. Surfactant Classification:

Surfactant molecules may be classi fied based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows:

1. Anionic surfactants, where the hydrophilic group carries a negative charge,

such as carboxyl ($RCOO^{-}$), sulphonate (RS) or sulphate (ROS). Examples of pharmaceutical importance include potassium

laurate.

2. Cationic surfactants, where the hydrophilic group carries a positive charge

(e.g., quaternary ammonium halides, $R_4N^{+}{}^{-}Cl$).

3.Ampholytic surfactants (also called Zwitter ionic surfactants), where the

moleculecontains, or can potentially contain, both a negative and a positive charge (e.g., the sulfobetaines, Examples of pharmaceutical importance include N-dodecyl-N, Ndimethyl betaine.

4. Non-ionic surfactants, where the hydrophile carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene ($OCH\ CH_{22}O$-) groups. Examples of pharmaceutical importance include polyoxy ethylated glycol mono-ethers (e.g., etomacrogol), sorbitan esters (spans) and polysorbates (Tweens)[20].

q. Use of Surfactants in Solid Dispersion Systems:

Chowdary KPR et al studied the effect of two surfactants, sodium lauryl sulphate (SLS) and tween 80, on the aqueous solubility and dissolution rate of nimesulide from tablets formulated employing starch paste and PVP as binders. A marked increase in the solubility as

well as dissolution rate of nimesulide was observed with both the surfactants. Sreenivasa Rao et al studied the release of rifampicin from a matrix compressed from a physical mixture of rifampicin, gaur gum and SLS. When SLSwas incorporated in the matrix, the release of rifampicin was found to be linearly related to the square root of time, however, the release depended on the concentration of SLS. As the concentration of SLS increased up to 15% the release progressively slowed to a minimum, which could be due to the formation of a poorly soluble complex. As the concentration increased further, the release increased as the complex was micellarly solubilized. Dhanaraju MD et al studied the effect of surfactant on release of griseofulvin solid dispersion and dissolution release studies indicated that drug release from PEG (60%); Tween 80 (40%) was significantly increased in 1:1 drug carrier ratio. Dispersions of PEG with Tween 80 provided dissolution rates faster than dispersion prepared with PEG alone. Murlimohan Babu GV et al studied development of dissolution medium for a poorly water soluble drug, celecoxib and a new dissolution medium was developed as there is no official dissolution medium. The composition of the medium was selected on the basis of solubility data of celecoxib at 37 . Solubility data revealed that water consisting of 2% w/v sodium lauryl sulphate could be a suitable dissolution medium.

3. SOLID DISPERSION TECHNOLOGY:

Historical Background:

The effect of particle size of drugs on their dissolution rates and biological availability was reviewed comprehensively by Fincher. For drugs whose GI absorption is rate limited by dissolution, reduction of the particle size generally increases the rate of absorption and/or total bioavailability. This commonly occurs for drugs with poor water solubility. For example, the therapeutic dose of griseofulvin was reduced to 50%.by micronization, and it also produced a more constant and reliable blood level. Particle size reduction is usually ac hieved by (a) conventional trituration and grinding (b) ball milling; (c) fluid energy micronization; (d) controlled precipitation by change of solvents or temperature, application of ultrasonic waves, and spray drying; (e) administration of liquid solutions from which, upon dilution with gastric fluids, the dissolved drug may precipitate in very fine particles; and (f) administration of water-soluble salts of poorly soluble compounds from which the parent, neutral forms may precipitate in ultrafine form in GI fluids. In 1961, a unique approach of solid dispersion to reduce the particle size and increase rates of dissolution and absorption was first demonstrated by Sekiguchi and Obi. They proposed the formation of a eutectic mixture of a poorly soluble drug such as sulfathiazole with a physiologically inert, easily soluble carrier such as urea. The eutectic mixture was prepared by melting the physical mixture of the drug and the carrier, followed by a rapid solidification process. Upon exposure to aqueous fluids, the active drug was expected to be released into the fluids as fine, dispersed particles, because of the fine dispersion of the drug in the solid eutectic mixture and the rapid dissolution of the soluble matrix. Levy and Kanig subsequently noted the possibility of using a solid solution approach in which a drug is dispersed molecularly in a soluble carrier. In a series of report in 1965-1966, Goldberg et al presented a detailed experimental and theoretical discussion of advantages of the solid solution over the eutectic mixture[25].

4. Definition and Classification of Solid Dispersions:

Definition:

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, enhanced release of drugs from ointment and suppository bases, and improved solubility and stability.

5. ADVANTAGES OF SOLID DISPRESION

Generally, solid dispersion is mainly used

- ✓ To reduced particle size
- ✓ To improve weetability

- ✓ To improve porosity of drug
- ✓ To decrease the crystalline structure of drug in to amorphous form
  To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical
- ✓ To mask the taste of the drug substance
- ✓ To prepare rapid disintegration oral tablets.

Table 1: Types of Solid Dispersion

Solid dispersion type		**Matrix***	**Drug****	**Remarks No.**	**phases**	**Reference**
1	Eutectics	**C**	**C**	The first type of solid dispersion prepared	**2**	(Chiou and Riegelman, 1971)
2	Amorphous precipitations in crystallinematrix	**C**	**A**	Rarely encountered	**2**	(Breitenbach AH, 2002); (Mullins and Macek, 1960)
3	Solid solutions					
A	Continuous solid solutions	**C**	**M**	Miscible at all composition, never prepared	**1**	(Goldberg *et al.*, 1965]
B	Discontinuous solid solutions	**C**	**M**	Partially miscible, 2 phases even though drug is molecularly dispersed.	**2**	Sekiguchi K and Obi N (1961)
C	Substitutional solid solutions	**C**	**M**	Molecular diameter of drug (solute) differs less than 5% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed.	**1 or 2**	(Rastogi and Verma,1956); (Wilcox *et al.*, 1964)
d	Interstitial solid solutions	**C**	**M**	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility,	**2**	(Chiou and Riegelman, 1971); (Chiou and Riegelman, 1969)

				discontinuous.		
4	Glass suspension	**A**	**C**	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	**2**	(Chiou and Riegelman, 1971); (Sarkari M et al., 2002)
5	Glass suspension	**A**	**A**	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	**2**	(Chiou and Riegelman, 1971); (Sarkari M *et al*., 2002)
6	Glass solution	**A**	**M**	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP	**1**	Simonelli AP*et al*., 1969

6. CHARACTERISTICS

6.1. Solid solutions:

Solid solutions consist of a solid solute dissolved in a solid solvent. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems[26]. They are generally prepared by fu sion method whereby a physical mixture of solute and solvent are melted together followed by rapid solidification. Such systems, prepared by fusion, are often called as melt. E.g., griseofulvin-succinic acid. The griseofulvin from such solid solution dissolves 6 to 7 times faster than pure griseofulvin. If the diameter of solute molecules is less than 60% of diameter of solvent molecules or its volume less than 20% of volume of solvent molecule, the solute molecule can be accommodated within the intermolecular spaces of solvent molecules e.g., digitoxin-PEG 6000 solid solutions. Such systems show faster dissolution. When the resultant solid solution is a homogeneous transparent and brittle system, it is called as glass solution. Carriers that form glassy structure are citric acid, urea, PVP and PEG and sugars such as dextrose, sucrose and galactose[27].

6.2. Simple eutectic mixture:
An eutectic mixture of a sparingly water soluble drug and a highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component. The increase in surface area is mainly responsible for increased rate of dissolution. This led to a conclusion that the increase in dissolution was mainly due to decreased particle size.

6.3. Compound or complex formation:
This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of the drug from the complex is dependent on the solubility dissociation constant and the intrinsic absorption rate of the complex.

6.4. Amorphous precipitation:
Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug[28].

7. REDUCED PARTICLE SIZE
Solid dispersions represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers (Leuner and Dressman, 2000). A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability (Leuner and Dressman, 2000 and Kang et al. 2004).

8. IMPROVED WETTABILITY
The enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions . It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects .

9. INCREASE POROSITY
Particles in solid dispersions have been found to have a higher degree of porosity . The increase in porosity also depends on the carrier properties, for example, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate .The increased porosity of solid dispersion particles also hastens the drug release profile.

10. DRUGS IN AMORPHOUS STATE
Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility (Pokharkar et al., 2006). The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process .In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, if drugs precipitate it is as a metastable polymorphic form with higher solubility than the most stable crystal form .For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions.

11. METHODS OF PREPARATION:

a. Melting Method:
The melting or fusion method was first prepared by Sekiguchi and Obi to prepare fast-release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved.

Such a technique was subsequently employed with some modification by Goldberg et al and Chiou and Riegelman. To facilitate faster solidification, the homogeneous melt was poured in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. The solidified masses of drug-polyethylene glycol polymer systems were often found to require storage of 1 or more days in a dessicator at ambient temperatures for hardening and ease of powdering. The main advantages of this dire ct melting method are its simplicity and economy. In addition, a supersaturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. Similarly, a much fine dispersion of crystallites was obtained for systems of simple eutectic mixtures if such quenching techniques were used.

b. Solvent Method:

This method has been used for a long time in the preparation of solid solutions or mixed crystals of organic or inorganic compounds. They are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents.

c. Melting-Solvent Method:

It was shown recently that 5-10% (w/w) of liquid compounds could be incorporated into polyethylene glycol 6000 without significant loss of its solid property. Hence, it is possible to prepare solid dispersions by the first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, obtained below 70 , without removing the liquid solvent. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol. The polymorphic form of the drug preci pitated in the solid dispersion may be affected by the liquid solvent used. Such a unique method possess the advantages of both the melting and solvent methods[29].

12. POLYMERS USED IN SOLID DISPERSIONS ARE AS FOLLOWS:

a. Polyethylene Glycol (PEG):

The term polyethylene glycol refers to compounds that are obtained by reacting ethylene glycol with ethylene oxide. PEGs whose molecular weight is above 300000 are commonly termed as polyethylene oxides[30].

b. Phospholipids:

The complexity of glycerides adva nces by modification of the terminal hydroxyl with phosphate linked head groups to form phospholipids, common phospholipid head groups include choline, ethanolamine, serine, inositol and inositol phosphate, and glycerol esters. As with the triglycerides, numerous species are possible by various combinations of different head groups and fatty acyl substitution at the first and second positions of the glycerol backbone, fluidity differences are evident as a function of the gel to liquid crystalline transition temperatures. Solubility of phospholipids is intimately linked to the confirmation of the aggregate material rather than strictly a chemical function of the molecule. Monoacyl phospholipids, which tend to form micelles, are usually more readily soluble in aqueous solutions[31].

c. Polyvinyl Pyrrolidone (PVP):

PVP has a molecular weight ranging from 10000 to 700000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not suitablefor preparation of solid dispersions prepared by melt method because of its melt at a very high temperature above 275 , where it becomes decomposed.

d. Effect of PVP Molecular Weight:

The effect of molecular weight of PV P on the rate of dissolution of a drug is more consistent

than for PEG. An increase in molecular weight of PVP will decrease the dissolution rate of most drugs. An increase in viscosity of PVP solution due to an increase in molecular weight decreases diffusion of drug molecules from the surface of viscous material into the dissolution medium, lower molecular weight PVP has a short swelling time prior to dissolution resulting in an increase in dissolution rate of the polymer and drug.

Table 2: List of Carriers Used In Solid Dispersion

S.No.	NATURE	CARRIER
1	Acids	Citric acid, tartaric acid, succinic acid, phosphoric acid
2	Sugars	Dextrose, Mannitol, Sorbitol, Sucrose, Maltose, Galactose, Xylitol , Lactose, Soluble starch, D- glucose (Chitosan), Galactose, Xylitol, Galactomannan, British gum, Amylodextrin
3	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000,PVP, CMC, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, HPMC, Dextrin, ß-CD, HPß-CD, Eudragit® L100 sodium salts
4	Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Docusate sodium, Myrj-52, Pluronic-F68,SLS, Gelucire 44/14, Vitamine E TPGS NF
5	Hydrotropes	Sodium acetate, Sodium- o- hydroxy benzoate, Sodium-p- hydroxy benzoate, Sodium citrate,Resorcinol,Ascarbic acid
6	Dendrimers	polyamidoamine (PAMAM), Starburst
7	Others	Pentaerythritol,Urea, Urethane, Hydroxyalkyl xanthenes, Microcrystalline cellulose, Dicalcium phosphate, Silica gel, Sodium chloride, Skimmed milk

e. Cyclodextrins:

Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment.

Advantages of Cyclodextrins:

1. Increasing the stability of the drug
2. Release profile during gastrointestinal transit through modification of drug
3. Release site and time profile.
4. Decreasing local tissue irritation.
5. Masking unpleasant taste.

Polymers and Surface Active Agent Combinations:

The addition of surfactants to dissolution medium lowers the interfacial tension between the drug

and dissolution medium and promote the wetting of the drug thereby they enhance the solubility and dissolution of drugs. Ternary dispersion systems have higher dissolution rates than binary dispersion systems[32].

Table 3: List of Solvents Used In Solid Dispersion

S.No.	SOLVENT	MELTING POINT (°C)	BOILING POINT (°C)
1	Water	0	100
2	Methanol	-93.9	65
3	Ethanol	-117	78.5
4	Acetic acid	17	118
5	1-propanol	-85	97.4
6	2-propanol	-127	82.4
7	Chloroform	-63	62
8	DMSO	19	189

Table 4: List of Poorly Soluble Drugs with Carriers

S. No.	DRUG	CARRIER
1	Griseofulvin	Polyethylene glycol (PEG)
2	Acyclovir	PEG, Urea, Mannitol, PVPK-30
3	Flufenamic acid	PVP
4	Aceclofenac	PEG, Urea, Mannitol, Lactose
5	Diazepam	Sodium salicylates
6	Glipizide	Urea, Polaxamer-188, PVP

12. CONCLUSION

Although there was a great interest in solid dispersion systems during the past four decades to increase dissolution rate and bioavailability of poorly water-soluble drugs, their commercial use has been very limited, primarily because of manufacturing difficulties and stability problems. Solid dispersions of drugs were generally

produced by melt or solvent evaporation methods. The materials, which were usually semisolid and waxy in nature, were hardened by cooling to very low temperatures. They were then pulverized, sieved, mixed with relatively large amounts of excipients, and encapsulated into hard gelatin capsules or compressed into tablets. These operations were difficult to scale up for the manufacture of dosage forms. The situation has, however, been changing in recent years because of the availability of surface-active and self-emulsifying carriers and the development of technologies to encapsulate solid dispersions directly into hard gelatin capsules as melts. Solid plugs are formed inside the capsules when the melts are cooled to room temperature. Because of surface activity of carriers used, complete dissolution of drug from such solid dispersions can be obtained without the need for pulverization, sieving, mixing with excipients, etc. Equipment is available for large-scale manufacturing of such capsules. Some practical limitations of dosage form development might be the inadequate solubility of drugs in carriers and the instability of drugs and carriers at elevated temperatures necessary to manufacture capsules.

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