

A REVIEW ON FORMULATION ASPECTS OF SOLID DISPERSIONS

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ABSTRACT

Drugs emerging in drug discovery process often are poorly water soluble. Therefore, techniques which overcome this problem needs to be explored. Improved solubility will lead better absorption and thereby increased bioavailability. Solid dispersions form an excellent formulation alternative for such drugs. Solid dispersion molecularly disperses the drug in carrier and thus improve solubility and dissolution rate of the drug and carrier respectively. This review gives an insight on the formulation aspects of solid dispersions. The article is based on formulation requirements and the mechanism of drug release from solid dispersions. A comprehensive knowledge on the carriers used in solid dispersions and the interactions taking place in solid dispersion in the drug-carrier system is discussed. Basic features of solid dispersion have also been stated but the main focus is to understand solid dispersions from interaction point view of carriers used. This review will thus help in understanding to develop an optimized solid dispersion.

KEYWORDS: Solid dispersions, Types of solid dispersions, Drug release, Carriers, Polymers, Drug-polymer interactions.

1. INTRODUCTION^[1]

Oral route of drug administration is the most preferred route in terms of stability, accurate dosing, smaller bulk and easy production. The major problem associated with oral formulations is solubility and dissolution problems. About 40% new chemical entities (NCE) are waiting in industrial pipeline, one of the major roadblock being the water solubility problems. Poor solubility poses a challenge in pre-formulation and formulation of the drug. It is also problematic for in vivo assessment of pharmacokinetic parameters. Due to poor solubility large dose needs to administered but it may lead to toxicity, so it would be better to overcome solubility by using various formulation approaches. The approaches applied for enhancement of solubility of poorly soluble drugs are salt formation, prodrug, micronisation and nanonisation, complexation, micelles, emulsions, solid lipid nanoparticles and also solid dispersions. Amongst these solid dispersions is gaining tremendous significance to enhance solubility and dissolution of poorly soluble drugs. Numerous studies on solid dispersions has been published and it has promising results in improving the solubility and dissolution rate of poorly water soluble drugs. The advantages of solid dispersions over other approaches include reducing particle size, possibly to molecular level, enhancing wettability and porosity, as well as changing drug crystalline state, preferably into amorphous state. In the Biopharmaceutical Classification System (BCS) (Figure 1) drugs with low aqueous solubility and high membrane permeability are

categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

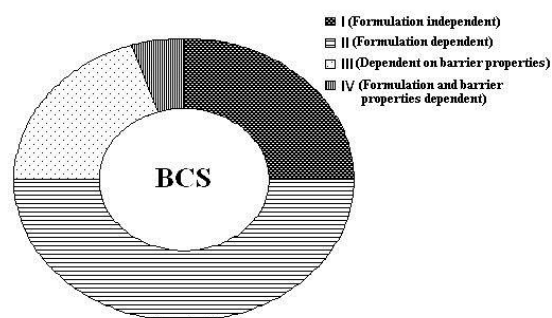


Fig 1: Biopharmaceutical Classification System break down of the pharma new chemical entity pipeline.^[2]

1.1. DEFINITION OF SOLID DISPERSION^{[3],[4]}

Solid dispersions can be defined in number of ways as given below,

- A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures (Win Loung Chiou, Sidney Riegelman)
- It is simply a drug dispersed in a solid matrix
- The dispersion of one or more active ingredients in an inert excipient or a matrix whereby active

ingredient could exist in fine crystalline, amorphous or solubilized state

- Molecular mixture of poorly water soluble drugs in hydrophilic carriers which present a drug release profile that is driven by polymer properties

1.2. NEED OF SOLID DISPERSIONS

- To improve solubility of poorly soluble drugs
- To enhance dissolution of drug and increase its bioavailability
- To process thermally unstable drugs using extrusion technique for manufacture of solid dispersions

1.3. SOLUBILITY AND DISSOLUTION^{[5],[6],[7]}

Solubility and dissolution of a drug candidate is decided based on BCS (Biopharmaceutical Classification System). BCS class II drugs are excellent candidates for solid dispersions. The solubility of a drug depends on the dissolution of the drug substance from dosage form. According to the Noye's and Whitney equation given below,

$$dC/dt = k(C_s - C_t) \quad (\text{equation 1})$$

Where,

dC/dt = dissolution rate of drug

K = proportionality constant

C_s = saturation concentration

C_t = concentration at time t

dissolution is determined by the rate of diffusion of a thin layer of saturated solution surrounded alongside the solid particle.

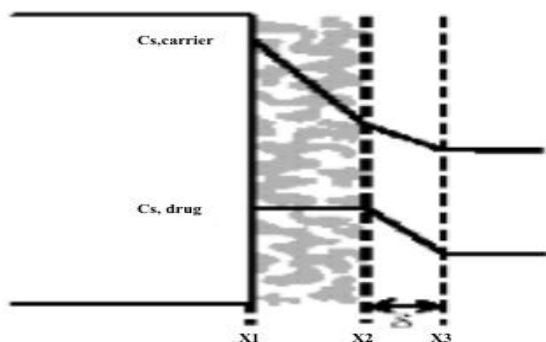


Fig 2: Concentration profiles of drug and carrier during dissolution of a binary mixture.^[5]

Hence, we come to know that dissolution is a necessary step which is directly proportional to solubility. Hence, increasing the dissolution will increase the solubility of the drug. To get a more insight into this phenomenon Nernst and Brunner introduced the diffusion layer model. This model assumed that dissolution at solid liquid interface is rapid and that the transport to the bulk is through diffusion from stagnant boundary layer. The equation is,

$$dm/dt = A \cdot D/h (C_s - C_b) \quad (\text{equation 2})$$

Where,

dm/dt = dissolution rate

A = area available for dissolution

D = diffusivity of dissolving compound in solvent

h = thickness of boundary layer

C_s = saturation solubility

C_b = concentration in bulk

From the discussions above and the definition of solid dispersions we come to know that solid dispersions are two component system and therefore dissolution profile is complex for such type of systems. Following points can be drawn for solid dispersions based on equation 2 and as shown in fig 2,

- The carrier (C) dissolves faster forming a porous layer
- In this porous layer the lipophilic drug (D) is present

The porous layer and the formulation composition of solid dispersions effects rate of dissolution. Following assumption have been made based on Eq.1 and Eq.2

- Steady state release is considered and dissolution of D is assumed to remain unchanged
- In porous layer the concentration of D is equal to its solubility which implies that supersaturation is absent in porous layer and also a constant flux of D to the bulk of solution since stagnant layer is constant

2. HISTORY

The first and foremost study on solid dispersions was carried out by Sekiguchi and Obi in 1961. Thereafter various studies have been carried out on solid dispersions to overcome solubility problems.

Table 1: Historical Developments in SD.

Year	Author	Contribution	Reference
1961	K. Sekiguchi and N. Obi	Innovator of SD by using sulphathiazole as drug and urea as carrier.	[6]
1963	G. Levy	Demonstrated a simple and precise method for the preparation of SD and solid solution. Finally the study ends with a conclusion that solid solution may enhance the drug dissolution.	[8]
1965	T. Tachibani and A. Nakamura	Described a solvent evaporation method for the preparation of an aqueous colloidal dispersion of carotene utilising polyvinyl pyrrolidone (PVP) as hydrophilic carrier. Analytical data showed that carotene is molecularly dispersed in SD with prominent solubility enhancement property.	[9]
1966	M. Mayersohn and M. Gibaldi	Studied and disclosed a method for the preparation of griseofulvin SD with marked increment in its solubility.	[10]

1979	S. Reigelman and W. L. Chiou	Reported that bioavailability of drug can be enhanced by preparing its glassy matrix.	[3]
1989	P. Baudier et al	Revealed the skilful method of preparation of a novel galenic form, i.e. micro-granules. Study suggested that SD may enhance the solubility of drugs as it is having porous membrane.	[11]
1994	Nakano et al.	Described a novel thermal-mechano-chemical process for preparation of SD. It was most suitable technique for thermal sensitive drugs.	[12]
1995	K. Nakamichi et al.	Reported the solvent free and temperature independent approach for the formulation of SD using the twin screw extruder. The resulting SD was found to be superior in terms of its performance and stability.	[13]
1997	Fort et al.	They introduced one of the pharmaceutical SD compositions comprising of an HIV protease inhibitor as drug and PEG as carrier system. The SD claimed to effectively cure HIV; it was able to enhance the solubility and thereby the bioavailability of drug.	[14]
2000	D. Terracol and R. Duclos	Described a simple solvent evaporation method for the production of SD, comprising of at least one therapeutic agent. Finally, it was found that the SD enhances the solubility of drug in aqueous media.	[15]
2007	C. L. Bedrosian	Reported a method for oral administration of mTOR inhibitors especially in case of oral cancer patient SD technique. Invented SD reduces the dose and minimises its side effects to a reasonable level.	[16]
2008	K.H. Patel and R.S. Pillai.	Expressed the composition and therapeutic use of water dispersible molecular SD constituting of sparingly water soluble drug or any salt in particulate lipidic matrix.	[17]
2011	Tiwari et al.	Reported a method of preparation of solid dosage form comprising of SD, containing an anti-HIV drug with hydrophilic polymer of low glass transition temperature approx. 50 C.	[18]
2013	Peng Hou et al.	Solid dispersion technique based on EPDC (Early stage Preparation Discovery Concept) was successfully employed for improvement of dissolution and absorption of a water insoluble compound.	[19]
2016	Tukaram Kalyankar et al.	Reported increased solubility and dissolution rate of telmisartan by formulating drug as solid dispersion using PEG8000 as hydrophilic carrier.	[20]

3. TYPES OF SOLID DISPERSIONS

Solid dispersions can be broadly classified as:

3.1. On the Basis of Carrier Employed^{[3],[4],[21]}

The carriers affect the properties of solid dispersion. Based on the hydrophilic carriers employed solid dispersions can be classified as shown in fig3 below.

3.1.a. First generation solid dispersions

Formulation of eutectic mixtures releases drug as micro crystals and improves drug release and consequently bioavailability of poorly water soluble drugs. These produce faster release and increased bioavailability than conventional formulations. These are designed using crystalline carriers which include urea and sugars such as mannitol.

3.1.b. Second generation solid dispersions

These type of solid dispersions are single phase homogenous systems and consist of amorphous carriers which are generally polymers (amorphous drug +

amorphous carrier). The drug is irregularly dispersed in very small size and exists in supersaturated state because of forced solubilization.

Dissolution is fast due to low thermodynamic stability and therefore enhanced drug release.

3.1.c. Third generation solid dispersions

Recent advancement in solid dispersions constitute the third generation solid dispersions. They are either self-emulsifying or surfactant assisted amorphous carrier.

They have an advantage over previous ones in avoiding the problem of recrystallization associated with this type of formulations. The components employed for formulation include Inulin, Compritol 888ATO, Poloxamer 407, which have shown to be effective in maintaining high polymeric purity and enhanced bioavailability.

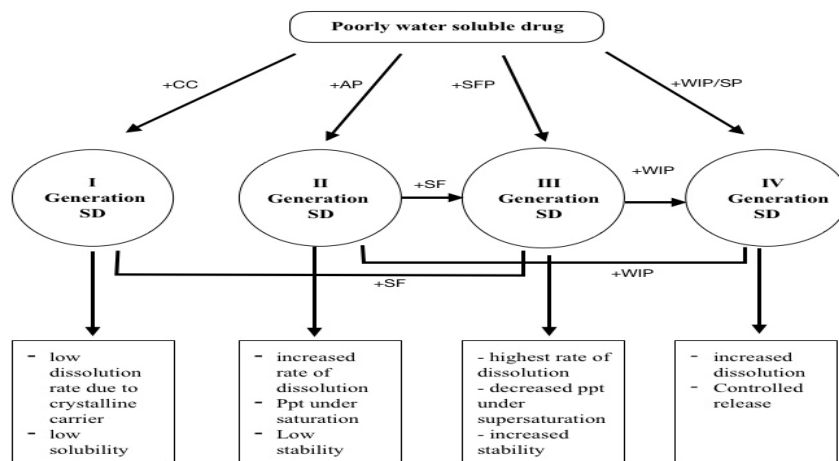


Fig 3: Classification of solid dispersions based on carriers.^[21]

CC: crystalline carrier; AP: amorphous polymers; SFP: surfactant polymer

WIP: water insoluble polymer; SP: swell able polymer; SF: surfactant

3.1.d. Fourth generation solid dispersions

These are the most recent type of solid dispersions are Controlled Release Solid Dispersions (CRSD). They contain poorly water soluble drug with a short half-life and therefore provide extended release in a controlled manner. Drug is dispersed in a carrier which improves solubility while an insoluble swellable polymer may provide extended release. They may be released by diffusion or erosion. Cui et al prepared sustained release nitrendipine microspheres having solid dispersion structure. HPMCP-55 and Aerosol were used as dispersing agent whereas Eudragit[®] RS PO and EC are

used to retard drug release.^[22] EC can retard drug release form SD.

3.2. ON THE BASIS OF NUMBER OF COMPONENTS EMPLOYED

Solid dispersions are sub classified into binary and ternary solid dispersions based on number of components employed. When only two components are involved i.e. drug and carrier they are known as binary dispersions ex sulphathiazole with urea and the ternary solid dispersion such as furosemide-PEG6000-MCC.^[23]

3.3. BASED ON STRUCTURE OF SOLID DISPERSIONS^{[1],[24]}

This classification is based on the structure of solid dispersions and based on the release mechanisms of the drug. They are classified as given by the fig4 and explained below:

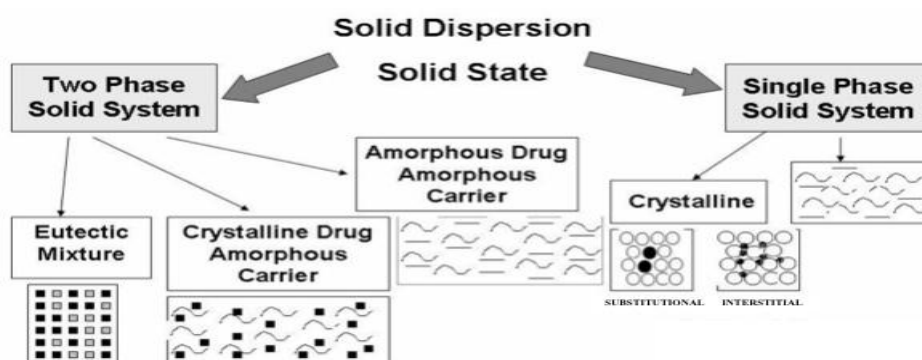


Fig 4: Classification of Solid Dispersions Based On Structure.^[2]

3.3.a. Simple eutectic mixtures

Simple eutectic mixtures consist of two components which are completely miscible in liquid state or melt but show limited miscibility in solid state. At specific composition indicated by point E in fig5, the two components simultaneously crystallize when the temperature is decreased. Point E indicates the eutectic composition of A and B. A true eutectic mixture exists

for a defined composition of the two components present in the mixture. Any deviation from this eutectic point leads to one component being crystallized before the other. When the eutectic is exposed to water or GIT, the carrier dissolves rapidly releasing fine crystals of the drug. Thus enhanced surface area causes increase in dissolution rate.^[25]

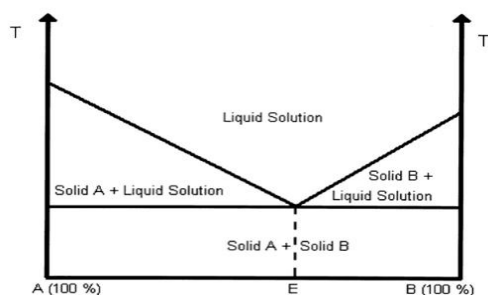


Fig 5: Phase diagram of a Eutectic mixture.

3.3.b. Solid solutions

Solid solutions are formed when a solute is nonstoichiometrically incorporated into the crystal lattice of the solvent. Solid solutions can be classified in two ways. First according to the solubility of the solute in the crystal lattice (continuous vs. discontinuous) and secondly according to the way in which the solute molecules are distributed. In general, “solid solution” refers to systems that contain a crystalline carrier, distributed.

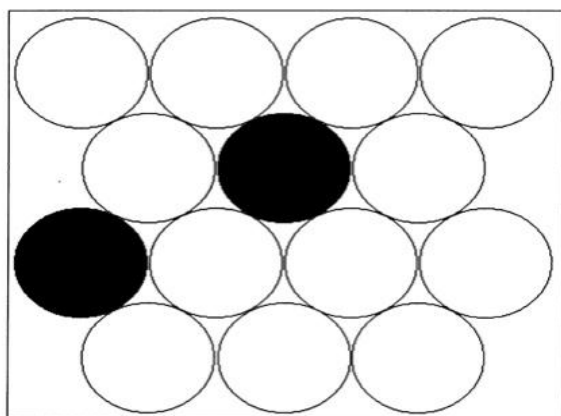


Fig 6: Structural Representation of Substitutional Solids.

3.3.b.i. Continuous solid solution

The components of solid solutions are miscible at all proportions. The bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Organic molecules do not show such type of bonding hence these are of little interest in pharmaceutical field.

3.3.b. ii. Discontinuous solid solution

Solid solubility for this type of system only exists at specific compositions of the mixture and not over entire compositional range. Each component of the solid dispersion is capable of dissolving the other component in a specific compositional region where the solubility is temperature dependent. The solubility is maximum at eutectic temperature and decreases when temperature is reduced. Goldberg et al. have proposed to use “solid solution” only if mutual solubility of the two components exceeds 5%.

3.3.b.iii. Substitutional solid solution

In solid solutions with crystalline carrier a solute molecule may take place of the carrier in the lattice arrangement. These solutions can be continuous or discontinuous solid solutions.

Substitutions only possible when the size of the solute is approximately similar to the carrier molecule or when difference in size is less than 15% of the carrier size.

3.3.b. iv. Interstitial solid solution

Solid solutions of this type result when the solute molecules are smaller than the solvent molecules (i.e. carrier molecule). The solute molecules occupy the interstitial spaces in the crystalline lattice. The diameter the solute must not exceed more than 0.59 times the diameter of the solvent or carrier molecule, also the diameter volume should be less than 20% of the solvent. Interstitial solid solutions form discontinuous type of solid solutions.

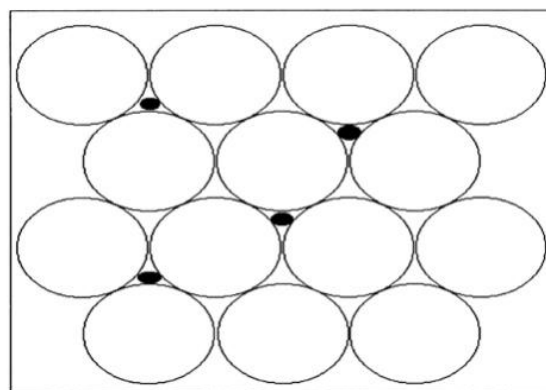


Fig 7: Structural Representation of Interstitial Solids.

3.3.c. Glass solutions and glass suspensions

Glass solutions are homogenous one phase systems which the carrier is amorphous and the solute is molecularly dispersed in the amorphous carrier. Homogenous distribution within the glass solutions is to be ensured by proper mixing. Mixing enables uniform distribution of the solute due to high viscosity of the glass solution. If the solubility of drug in carrier is not exceeded the solid dispersion can be thermodynamically stable. Organic polymers such as poly vinyl pyrrolidone (PVP) and cellulose derivatives are commonly used as they exhibit amorphous regions.

If the drug in glass suspension forms a separate amorphous phase (or a drug rich amorphous phase), it is known as glass suspension. In glass suspension the drug still shows increased dissolution compared to crystalline form but it has a high tendency for recrystallization of the amorphous drug.

3.3.d. Amorphous precipitates in crystalline carriers

These are formed when drug precipitates into an amorphous form in inert carrier. It has been observed that drugs exhibiting high super cooling property can

undergo such precipitation hence these systems are of little use. However, the high energy state of the drug in this system provides much higher rates of dissolution than the crystalline forms of the drug.

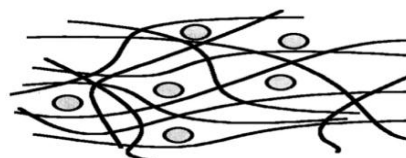


Fig 8: Amorphous Precipitates in Crystalline Carriers.

Table 2: Different types of solid dispersions ^[26]				
Type	Matrix	Drug	Remark	Phases
Eutectics	C	C	First type of dispersions prepared	2
Amorphous precipitates in crystalline carriers	C	A	Rarely encountered	2
Continuous solid solutions	C	M	Miscible at all concentrations, never prepared	1
Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed	2
Substitutional solid solutions	C	M	Molecular diameter of drug less than 15% from matrix diameter. Can be continuous or discontinuous. When discontinuous, 2 phases present.	1or2
Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: drug in helical interstitial spaces of PEG.	2
Glass solutions	A	M	Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP.	1or2
Glass suspensions	A	C	Particle size of dispersed phase depend on cooling/evaporation rate. Obtained after crystallisation of drug in amorphous matrix.	2
Glass suspensions	A	A	Particle size of dispersed phase depend on cooling/evaporation rate. Many solid dispersions of this type.	2

In the above table the matrix and drug column describe the form of the constituents in the solid dispersions.

A: Amorphous form C: crystalline form

M: molecular dispersion of the components of drug or matrix

4. CARRIERS USED IN SOLID DISPERSION FORMULATION^[2]

Carriers form the most important part of solid dispersion formulation. Therefore, their selection is critical for formulating a desired solid dispersion.

4.1. Criteria for Selection of Carriers

Following properties are desirable for a carrier material,

- High water solubility - improves wettability and enhances dissolution
- High glass transition temperature - it improves the stability
- Minimal water uptake and thereby reduction in T_g
- Soluble in common solvents with the drug - ease in formulation by using solvent evaporation method
- Relatively low melting point - suitable for melting process
- Should be capable of forming a solid solution with drug - will possess similar solubility parameter

- GRAS: Generally regarded as safe and should be inert (supersaturation potential screening studies from DMSO and DMF)

4.2. Solvent Selection for Solid Dispersions

- Should dissolve drug and carrier
- Toxic solvents should be avoided due to risk of residual levels after preparation e.g. chloroform, dichloromethane
- Ethanol is the best solvent due to less toxicity and is one of the best alternate compared to other solvents
- Preferable solvent system which can be used as solvent is water based systems

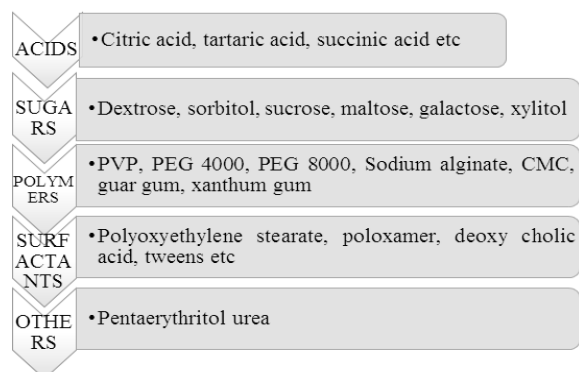
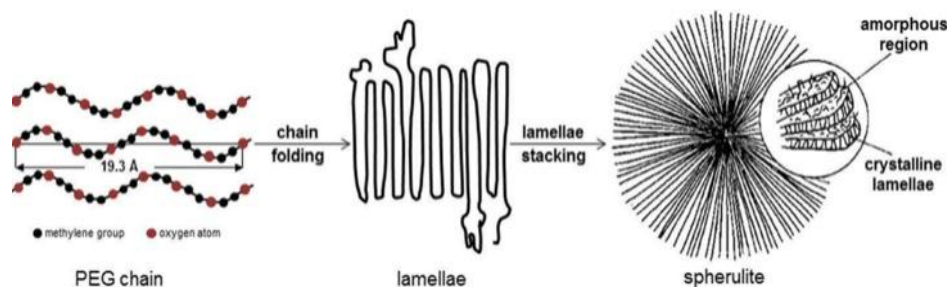
Solvents need to be compatible with surfactants to enable formation a carrier-drug solution.

4.3. Types of Carriers Used in Solid Dispersions

Types of carriers used in solid dispersion are listed in table 3 based according to the generation of carriers. Also, the carriers are classified based on the chemical nature as given in fig9.

Table 3: Types of carriers^[2]

1st generation	2 nd generation	3 rd generation
Crystalline carriers: urea, sugars, organic acids	Amorphous carriers: PEG, povidone, Poly vinyl acetate, Polymethacrylate, cellulose derivatives	Surface active self-emulsifying carriers: poloxamer408, Tween 80, Gelucire44/14

**Fig 9: Examples of carriers based on chemical nature.^[2]****Fig10: Chemical Structure of PEG.^[28]**

5.2. Poly Vinyl Pyrrolidone

It is commonly referred to as PVP and is hydrophilic polymer. It is available of average molecular weight 2.5 to 3000kDa and is classified on the basis of K value obtained using Fikenschin's equation. PVP has good film formation property. In general, T_g (glass transition temperature) is high. PVP is suitable for preparation of solid dispersion by solvent method. Solid dispersions containing PVP have improved wettability and dissolution rates.

Some studies have shown that PVP inhibits the crystallization in SD hydrogen bonding, hence inhibits nucleation and crystallization.

5.3. Cellulose Derivatives

5.3.a. Hydroxy propyl methyl cellulose

These are mixed ethers of cellulose in which (6.5-30%) of hydroxyl group are methylated and 4-32% derivatized with hydroxypropyl groups. They show good solubility in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane. Poorly soluble

5. POLYMERS AS CARRIERS IN SOLID DISPERSIONS^{[27],[28]}

Amorphous solid dispersions are preferred as they molecularly release the drug from dosage forms. Polymers have been the most successful carrier material for formulation of solid dispersions as they are readily able to form amorphous solid dispersions.

5.1. Polyethylene Glycol

For solid dispersion molecular weight of 1500-2000 are usually employed. Their solubility in water is generally good but reduces with molecular weight. Advantage of PEG is that they have good solubility numerous organic solvents. The melting point of PEG's of interest is 65 degrees Celsius in every case. Additional advantage includes their ability to solubilize some compounds and also prove compound wettability. Problems associated with PEG's is the toxicity of these type of polymer. In general low molecular weight PEGs tend to show slightly greater toxicity than high molecular weight.

weak acidic drugs show faster release from solid dispersion consisting of HPMC.

5.3.b. Hydroxy propyl cellulose

These type of polymers show good solubility in wide range of solvents. It also includes water upto 40-degree C. HPC enhances release rate with their increased composition in the formulation and also when low molecular weight HPC are used as carriers.

5.3.c. Carboxy methyl ethyl cellulose

It is resistant to dissolution under gastric (acidic) condition. It dissolves readily at pH values above 5-6, with lowest dissolution pH being dependent on grade of the CMEC.

5.3.d. Polyacrylates and polymethacrylates

Polymerization of acrylic and methacrylic acid and derivative of these polymers such as esters of amides produce the glassy substances called polyacrylates and polymethacrylates. These are mainly used as coatings to change release of drug from dosage form. They have

trade name of Eudragit. Among them Eudragit E is used to improve release rate in stomach as it is soluble in pH ranges upto 5 and swells at higher pH while Eudragit L is used when it is desirable to avoid release in stomach.

5.4. Block Copolymer^[1]

Block copolymers are used as dispersed agent, when other carriers and surfactants cannot be used. A block copolymer of polyoxyethylene and the polyoxypropylene are mostly used. These polymers form monomolecular micelles which aggregate and associate in such a way that hydrophobic chains are blocked by hydrophilic chains. These aggregates have the potential to solubilize the drug. Block copolymers also help to overcome stability problems of solid dispersion. Examples include Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), Poly (beta-Benzyl-L-aspartate), B-poly (ethylene oxide) etc In fig 11A-Aggregates of monomolecular micelles after association in such a way that Hydrophobic chains blocked by hydrophilic chains and in fig 11 B-Chain block co-polymer: a- Hydrophilic chain, b- Hydrophobic chain.

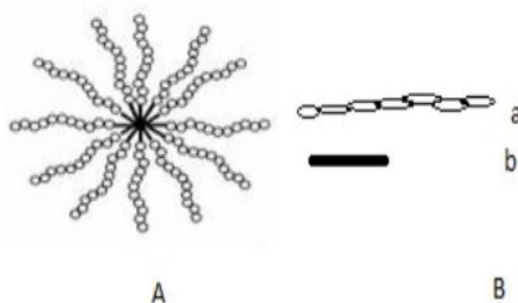


Fig 11: Representation of Block co-polymers.^[1]

5.5. Other Carriers Used

5.5. a. Urea

It shows good solubility in many of the common organic solvents. It also includes water in which the solubility is greater than 1. In one of the bioavailability studies it has been shown that sulfathiazole was better absorbed in rabbits when given as a eutectic with urea.

5.5.b. Sugar, polyols and their polymers

Although sugars and related compounds are highly water soluble and have few, if any, toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare co-evaporates. Even with these drawbacks, several attempts have been reported to prepare solid dispersions using sugars and their derivatives. Mannitol, which has a melting point of 165-168°C and decomposes only above 250°C, can be employed in some cases to prepare dispersions by the hot melt method.

5.5.c. Organic acids and their derivatives

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin method.

5.5.d. 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

- *Increasing the stability of the drug
- *Release profile during gastrointestinal transit through modification of drug Release site and time profile
- *Decreasing local tissue irritation
- *Masking unpleasant taste

5.6. Polymers And Surface Active Agents Combination^{[29],[30]}

The addition of surfactants to dissolution medium lowers the interfacial tension between the drug and dissolution medium and promote the wetting thereby they enhance the solubility and dissolution of drugs. Ternary dispersion systems have higher dissolution rates than binary dispersion systems.

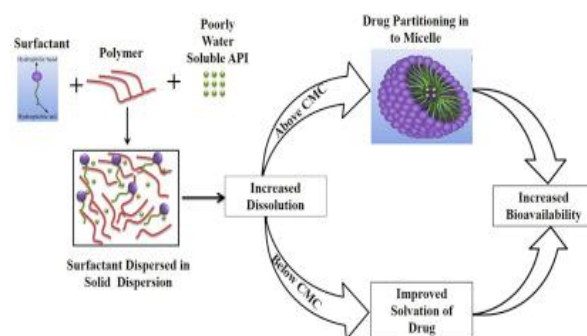


Fig 12: Mechanism of combined action of polymers and surfactants.

The effect of surfactant type on the properties of a sparingly soluble drug in solid dispersion was determined for anionic, cationic and non-ionic surfactants. The surfactants, sodium lauryl sulfate (sodium dodecyl sulfate; SDS), dodecyltrimethylammonium (DTAB) and polyethylene dodecyl ether are anionic, cationic and non-ionic, respectively. When these surfactants were used to prepare ternary dispersion systems with PEG and griseofulvin, a complete instant dissolution was seen for dispersion containing 2% of SDS, and SDS was found to be the most effective surfactant. It was observed that the amount of a crystalline drug decreased with increasing concentration of anionic or cationic surfactant except for the non-ionic.

6. DRUG RELEASE FROM SOLID DISPERSIONS

6.1. Mechanism of Drug Release From Solid Dispersions^[31]

Mechanism of drug release from solid dispersions can be explained on based on two properties such as particle size and solubility/dissolution rate. Enhanced dissolution forms the basis of drug release mechanism. Particle size reduction and increased dissolution rate will probably cause drug release. Particle size reduction and reduced agglomeration suggests a link between solid state structure and release for eidetic and solid formulation. Increased dissolution rate of drug works on the assumption that concentration of carrier after complete dissolution in water bath maybe used as a model for dissolution at dissolving surface. This explanation is based on seminal review by Chiou and Riegelman (1971).

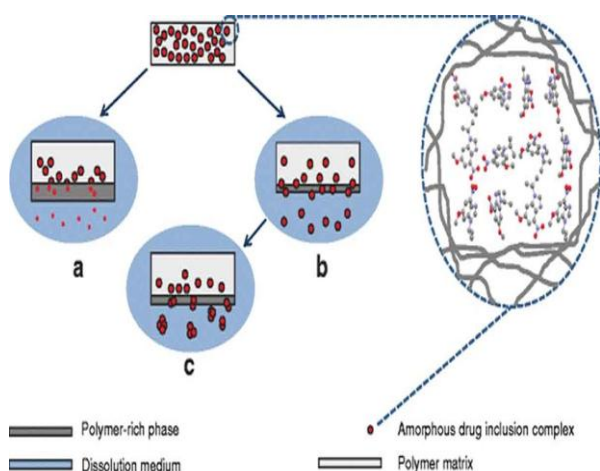


Fig13: Schematic diagram showing fate of drug particles during dissolution.

Schematic shows various release mechanisms during dissolution of a solid dispersion. The schematic can be explained as; (a) carrier mediated dissolution: the carrier forms a polymer rich phase aiding in initial drug complex dissolution; (b) drug mediated dissolution: high solubility of carrier in dissolution of drug occurs following diffusion of the amorphous complex from dispersion to dissolution medium; (c) complex aggregation following drug mediated dissolution: amorphous inclusion complexes agglomerate upon diffusion into the dissolution medium.

6.2. Factors Affecting Drug Release From Solid Dispersion^[32]

Nature of carrier

Drug release from solid dispersion is dependent upon the nature of carrier, whether hydrophilic or hydrophobic. Thus, incorporation of poorly water soluble drug into inert and slightly water soluble carrier leads to retardation of drug release from matrix. However, incorporation of poorly water-soluble drug into water-soluble carrier(s) leads to acceleration of drug release.

Drug carrier ratio

The dissolution of a drug increases with increase in proportion of drug carrier being used. However, this applies to a certain limit only beyond which the dissolution rate decreases. The decrease in release rate can be attributed to leaching of drug from carrier during dissolution which forms a concentrated layer of solution around the drug particle

Method of preparation

Solid dispersions prepared by melting generally showed faster dissolution rates than those prepared by solvent method. This rapid release is attributed to very fine state subdivision of the drug particles, and solubilizing plus wetting effect of the carrier. However, the corresponding solid dispersion prepared by coprecipitation possesses slower dissolution owing probably to greater size of drug particles.^[33]

Cooling conditions

In melt technique, drug is incorporated in a molten carrier and subsequently cooled, forming the dispersion. The method of cooling, whether slow or flash, affects the rate of dissolution. While preparing tolbutamide-PEG 6000 (1:2) dispersion^[33], the melt has cooled by two processes. More than 15% of drug release was observed in case of flash cooled dispersion as that of slow cooled dispersion due to the difference in particle size, as flash cooled dispersion gives smaller particle size and low crystallinity.

Synergistic effect of two carriers used

This has been exemplified in ibuprofen solid dispersions^[34] using PEG, talc and PEG-talc as dispersions carriers. It was reported that in 9.1% drug loading, ibuprofen dissolved at the end of 120min was about 66% 73% and 93% from Ibuprofen talc, ibuprofen-PEG and PEG-talc dispersions respectively. Workers attributed this synergism to the partial replacement of PEG with talc. This would cause improved wettability of ibuprofen and hence enhanced solubility of drug by overlapping the diffusion layers between PEG and ibuprofen.

7. INTERACTIONS IN SOLID DISPERSIONS^{[35],[36]}

Solid dispersion is a drug-polymer two component system. Therefore, the interaction between drug and polymer is the determining factor in design and performance of the formulation. It is obvious to study solid dispersions from the point view of dissolution and in solid state. As drug which require high drug loading and those having tendency to precipitate are formulated as solid dispersions, issues such as drug loading efficiency stability of the system and dissolution performance need to be understood.

7.1. Drug Polymer Interaction in Solid State

This can be studied under the headings drug crystallization, phase separation and storage stability.

7.1.a. Drug crystallization

Three conditions are possible in relevance to the drug polymer interaction.

When drug loading is lower than the equilibrium solubility of drug in polymer the drug is molecularly dispersed in the polymer matrix. This molecularly dispersed solid dispersion is the most preferred structure (fig.14A). This structure is possible only with low drug loading or high temperature or both. Second condition is such that when temperature is decreased precipitation occurs due to supersaturation resulting in crystalline dispersion of drug in polymer (fig.14B). Concentration of drug corresponds to equilibrium solubility at that temperature. It may also happen that a meta stable structure may be formed in which amorphous drug aggregates are dispersed in polymer matrix containing drug at its amorphous solubility at that temperature (fig.14C). This is due to slow crystallization of drug posing high energy barrier that amorphous separation.

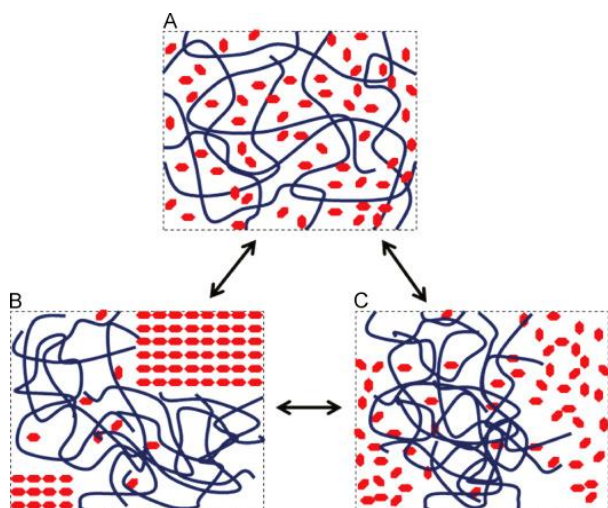


Fig 14: The three possible structures of a drug/polymer solid dispersion.^[36]

In the figure hexagonal symbols represent drug molecules and curvy lines represent polymer chains (A) The ideal structure of a solid dispersion where the drug is molecularly dispersed in the polymer matrix; (B) a drug-polymer system in which crystalline drug formation has occurred and (C) a drug-polymer system containing amorphous drug-rich domains dispersed in the polymer matrix.

7.1.b. Phase separation

Phase separation is the result of crystallization. A phase diagram is useful to understand the changes in development of solid dispersion under different conditions. The curve of drug solubility in polymer (solid curve) is important to determine lower limit of processing temperature and also to understand the supersaturation level of SD at storage temperature by melt method. Tg is essential in predicting storage stability. Also Tg can freeze a system in particular

structure hence important to understand the effect of Tag. Usually Tg decreases continuously from polymer to pure drug.

Two phase separation curves are possible as in fig15. In fig 15A, phase separation occurs below the whole Tag curve. Fig15B the shows two curves intersect at a particular point known as Birghman's point. Also in fig15B phase line (dashed curve) is formed corresponding to drug rich and polymer rich phases. This phase line is the result of fall in temperature and amorphous phase separation. This phase separation occurs until the Tag of polymer rich phase is reached, further reduction in temperature does not cause phase separation.

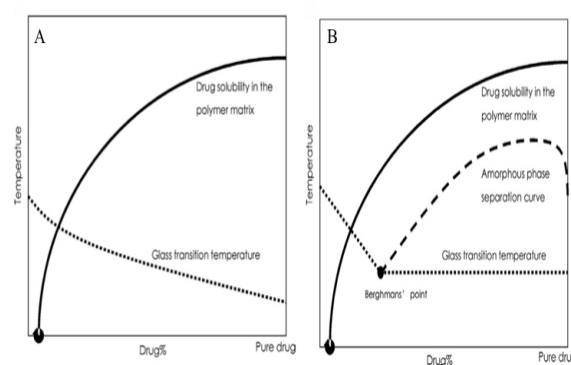


Fig 15: Possible temperature-composition phase diagrams.

(A) the situation where an amorphous phase separation curve does not intersect with glass transition temperature curve and (B) the situation where the amorphous phase separation curve intersects with Tg curve.

7.1.c. Storage stability

Ideally a molecular dispersion should be kinetically stable at its storage temperature as it essential for dissolution. At normal storage temperature and desirable drug loading (>20%), drug exceeds its equilibrium solubility in polymer matrix. However, the dispersion can be stable kinetically if the phase separations are frozen below the glass transition temperature. Here we consider instability from the point of view of drug crystallization. Drug molecules are dispersed randomly among the polymer segments and thus for a drug to form stable crystal nuclei a certain amount of polymer must diffuse away. (fig 16).

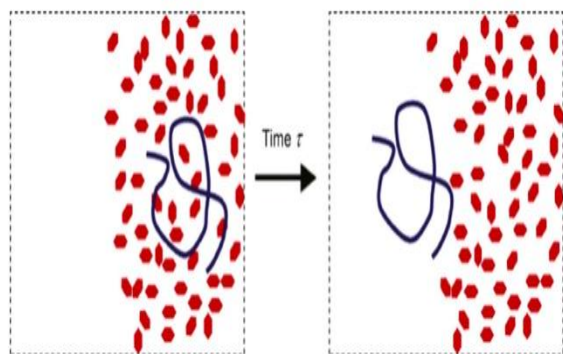


FIG 16: Illustration of polymer chain is diffusing out of a drug domain.^[36]

The stability of SD structure is attributed to the high viscosity of the polymer at glass state. Thus, for systems at higher temperature in the molten state, the diffusion of both drug and polymer are fast and phase separation can occur quickly. As water is a very effective plasticizer, the absorption of moisture significantly decreases the glass transition temperature of a solid dispersion and consequently enhances the mobility of drug and polymer. Therefore, polymers that are resistant to the absorption of water, where the T_g remains >70 degree C even after storage in a relative humidity of 75%, are the first choice for the preparation of stable solid dispersions.

7.2. Drug Polymer Interaction in Dissolution

Ultimate success of a solid dispersion is determined by its performance in dissolution after oral administration. The general strategy behind almost all solubilization technologies is the so called “spring-and-parachute” concept. For a solid dispersion, this means that the drug should first dissolve along with the soluble polymer matrix to create a supersaturated solution (“the spring”) after which supersaturation is maintained long enough for drug absorption (“the parachute”) to take place.

- (A) Particles dissolve rapidly and release drug into a highly supersaturated solution; subsequently drug precipitates as amorphous and/or crystalline particles onto which polymer adsorbs as a stabilizer;
- (B) drug and polymer are gradually released while drug remains amorphous in the undissolved particles; and
- (C) Drug and polymer are gradually released but drug is present as crystals in the undissolved particles especially near their surfaces. The free drug concentration is dependent on the solubility of either amorphous or crystalline drug which in turn depends on the drug/polymer ratio, polymer dissolution rate and drug crystallization rate.

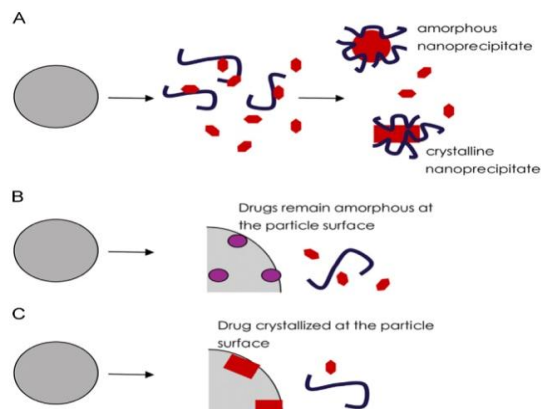
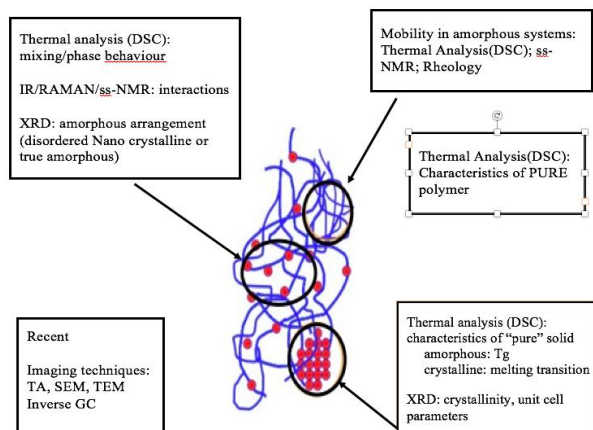


Fig 17: The three possible scenarios of drug diffusion from solid dispersion.

Depending on the type of solid dispersion, dissolution can occur in three possible ways (fig17). When the drug loading is low, the drug and polymer in the solid dispersion dissolve rapidly (fig17a) after which drug is continuously absorbed and can undergo precipitation in the presence of polymer and endogenous compounds such as bile acids, phospholipids and mucin. Solid dispersion particles may dissolve slowly either because of high drug loading or the nature of the polymer resulting in a more sustained release profile.

As water continuously penetrates into solid dispersion particles, phase separation eventually occurs. If drug crystallization is still inhibited by the polymer matrix in this situation, the drug may form amorphous aggregates (Fig. 17B) and the free drug concentration in the dissolution media will be equal to the solubility of amorphous drugs. However, if the drug is present in a crystalline state in the solid dispersion particles (Fig. 6C), the free drug concentration in the solution decreases to that of the solubility of drug crystals, i.e., the dissolution advantage of the solid dispersion is lost.

8. CHARACTERIZATION OF SOLID DISPERSIONS^[37]



CONCLUSION

Solid dispersions can therefore be used to improve solubility of poorly water soluble drugs. The polymers used are easy to handle and their application and their mechanism in formulating an optimized SD can be well understood. This review provides a comprehensive coverage of the formulation characteristics of solid dispersions and the mechanism of interaction taking place in Solid dispersions.

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