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A REVIEW ON SOLID DISPERSION AND ITS APPLICATION

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ABSTRACT

The drugs have been classified into 4 categories by BCS classification system. Based upon permeability and solubility parameters. In formulation most of the drugs are poor solubility, due to this the bioavailability of the drug In vivo conditions is less. To improve the bioavailability of this type of drugs, the solubility is enhanced by various approaches in this research work we approach solid dispersion technology for improving the solubility of poorly soluble drugs and adopted by various preparation methods. This formulation is used in various drug delivery systems i.e. oral, tropical, parental, ocular, etc.....These formulations can be used to verity of drugs such as amorphous and crystalline substances. Recently, solid scale systems have received much interest as a way to resolve solubility issues because of their cost-effectiveness and technical simplicity compared to liposome's and other colloidal drug carriers. Solid dispersion have proven to be a better alternative over other approaches currently available for improving bioavailability of number of drugs with low solubility. Solid dispersion have been extensively developed for a wide range of drugs and have been evaluated for in vitroand in vivo applications by various routes. They have alsobeen used for drug targeting. In fact, the number of products based onsolid dispersion in the market and under clinical study is higher than that of othertechnology-based applications. A surprisingly large proportion of new drug candidatesemerging from drug discovery programs are water insoluble, and therefore poorly bioavailable, leading to abandoned development efforts. Solid dispersion is an effective way of improving the dissolution rate of poorly water soluble drug and hence it's bio availability.

The water soluble carrier used in preparation is solid dispersion enhance the dissolution rate of the poorly water soluble drug. The review article focus on the methods of preparation, advantage, dis-advantages,& characterization of the solid dispersion.

KEYWORD: Solid dispersion, type of solid dispersion, carrier, polymer, drug release, drug polymer interaction.

INTRODUCTION

The sparingly water-soluble drugs often show an erratic dissolution profile in gastrointestinal (GI) fluids, which consequently results in variable oral bioavailability.[1] To improve the dissolution and bioavailability of sparingly soluble drugs, researchers have employed various techniques, such as micronization, solubilization, salt formation, complexation with polymers, change in physical form, use of prodrug and drug derivatization, alteration in pH, addition of surfactants, and others.[2] Oral drug delivery is the easiest and simplest way of administering solid dosage form. Oral bioavailability of a drug depends on its solubility and/or dissolution rate. If these drugs are not completely released in the gastrointestinal tract, they will have a low bioavailability.[1-4] Drug release is a critical and rate limiting step for oral drug bioavailability, particularly for drugs possessing low gastrointestinal solubility and high permeability. Thus, attempts to increase the rate of dissolution of drugs having limited water solubility are frequently required.[5] Enhancement in the dissolution rate of such drugs is one of the most important concerning aspects of the pharmaceutical industries.[5-8] The low dissolution rate and low solubility of drug substances in water in aqueous G.I.T fluid frequently leads to inadequate bioavailability. The venture to improve the solubility and dissolution of hydrophobic drugs remain one of the trickiest tasks in drug development. Several methods have been introduced to triumph over this problem (Ford, 1986; Dressman et al., 2000). Micronization of drug is not ideal because micronized product has the propensity of agglomeration, which leads to reduced effective surface area for dissolution. But solid dispersion is the mainly promising method to formulators because of its simplicity of preparation, ease of optimization, and reproducibility (Chiou et al., 1971; Goldberg et al., 1966; Leuner et al., 2000).

Definition Of Solid Dispersion[9,10]

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 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

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.

Classification of Solid Dispersion[11-13]

Depending on the molecular arrangement, solid dispersions can be of the following types:

1. Eutectic mixtures

Solid eutectic mixtures are usually prepared by rapidly cooling the co-melt of the two components in order to obtain a physical mixture of very fine crystals of the two components.

2. Solid solutions

Depending on the miscibility, the two types of solid solutions are: Continuous solid solutions - In continuous solid solutions, the components are miscible in all proportions i.e. the bonding strength between the components is stronger than the bonding between the individual component. Discontinuous solid solutions - In discontinuous solid solutions, the solubility of each of the component in the other component is limited in nature. Depending on the distribution of the solvates in the solvendum, solid solutions can be of two types: Substitutional crystalline solution. These are those solid solutions which have a crystalline structure, the solute molecules substitute for the solvent molecules in the crystal lattice. Interstitial crystalline solid solution – These are those solid solutions in which the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice.

3. Amorphous solid solutions

In amorphous solid solutions, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent.

4. Glass solutions and glass suspension

A glass solution is a homogenous system in which the solute dissolves in the glassy solvent. The glassy state is characterised by the transparency and brittleness below the glass transition temperature. The term glass refers to a pure chemical or a mixture of pure chemicals in the glassy state.

TYPES OF SOLID DISPERSIONS

Solid dispersions can be broadly classified as:

On the Basis of Carrier Employed

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

a. First generation solid dispersions

Formulation of eutectic mixtures releases dug 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.

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 solublization.

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

c. Third generation solid dispersions

Recent advancement in solid dispersions constitute the third generation solid dispersions. They are either selfemulsifying 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.

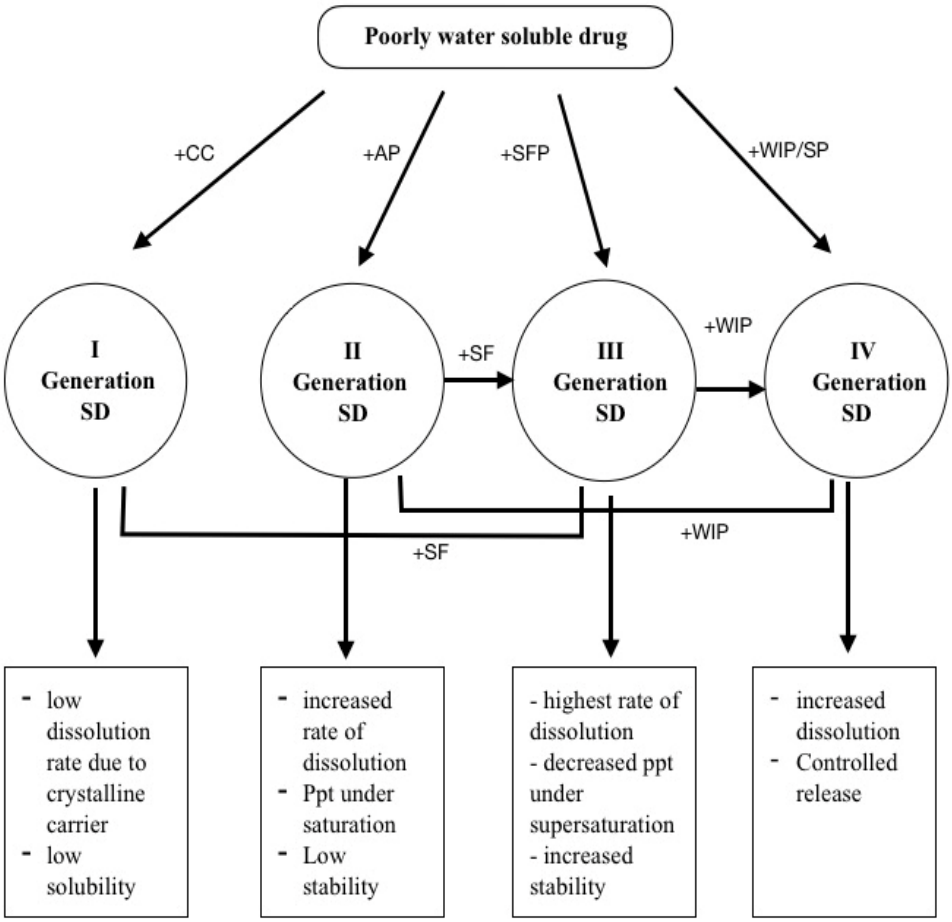


Fig 3: Classification of solid dispersion based on carriers.

Crystalline carrier; AP: amorphous polymers; SFP: surfactant polymer

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

d. Fourth generation solid dispersions

These are the most recent type of solid dispersions are Controlled Release Solid Dispersions(CRSD). They contain poosrly 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 EudragitO RS PO and EC are used to retard drug release.

METHODS FOR PREPARING SOLID SOLUTIONS[14,15]

Kneading Technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.

Solvent evaporation method

In this method, both drug and carrier are dissolved in organic solvent. After entire dissolution, the solvent is evaporated. The solid mass is ground, sieved and dried.

Ex. Solid dispersion of furosemide with eudragits was prepared by solvent evaporation method (Rasenack et al., 2003).

Co-precipitation method

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. When the formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex (Moyano et al., 1997).

Melting method

Drug and carrier are mixed using mortar and pestle. To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components. It is then cooled to acquire a congealed mass. It is crushed and sieved.

Ex. albendazole and urea solid dispersion was prepared by this method (Kalaiselvan et al., 2006).

Co-grinding method

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use.

Ex. chlordiazepoxide and mannitol solid dispersion was prepared by this method (Nokhodchi et al., 2007).

Gel entrapment technique

Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then drug for example is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved (Bhise et al., 2008).

Spray-Drying Method

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer (Bakatselou et al., 1991).

Lyophilization Technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative method to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion (Betageri et al., 1995).

Electrospinning Method

The electrospinning technology used for the polymer industry combines solid solution/dispersion technology with nanotechnology. In this procedure, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces prevail over the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are produced. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandrel (Deitzel et al., 2001). This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest and the cheapest this technique can be utilized for the preparation of solid dispersions in future (Zhang et al., 2007).

Dropping method

solution The dropping method, developed by Ulrich et al. (1997) to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods. For laboratory-scale preparation, a solid dispersion of a melted drug-

carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation (Bashiri et al., 2003).

Melt Extrusion Method

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g. sustained-release pellets (Karanth et al., 2006).

Melt Agglomeration Process

This technique has been used to prepare Solid Dispersion where the binder acts as a carrier. SD(s) are prepared either by heating the binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer (Tsinontides et al., 2004). A rotary processor has been shown to be alternative equipment for melt agglomeration because of easier control of the temperature and because higher binder content can be incorporated in the agglomerates (Vilhelmsen et al., 2005).

POLYMERS AS CARRIERS IN SOLID DISPERSIONS.[16,17]

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 associatedwith 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.

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, Tg (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.

Cellulose Derivatives

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

b. Hydroxy propyle cellulose

These are type of polymers show good solubility in wide range of solvents. It also includes water upto40-degree C. HPC enhances release rate with their increased composition in the formulation and also when low molecular weight HPC are used as carriers.

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.

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.

Polyvinylalcohol (PVA), crospovidone (PVP-CL), polvinylpyrrolidone-polyvinylacetate copolymer (PVPPVA)[18,19]

These three polymers belong to the polyvinyl group. Whereas polyvinylalcohol (PVA) and vinylpyrrolidone/vinylacetate (PVP-PVA) copolymers are both water soluble, crospovidone swells when dispersed in water. The use of PVA/PVP copolymers as carriers in solid dispersions has been shown to lead to enormous increases in the drug release rate. Studies with the cytostatic drug HO-221 showed that the PVA/PVP solid dispersed not only dissolved 25 times faster than the drug powder, but also enhanced the bioavailability in

beagles by a factor of 3.555. Even though crospovidone does not dissolve in water, it can also be used as a carrier to improve drug release rates. For example, a 1:2 ratio of furosemide to crospovidone led to an increase in the dissolution rate by a factor of 5.856, in comparison with either the drug powder or a physical mixture of furosemide with crospovidone.

Urea[20]

In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea8. Although urea is not often used as a carrier these days. In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 600065.

Sugar, polyols and their polymers[21]

Chitosan a derivative of the polysaccharide chitin which is formed by deacetylation at the N position has also been used as a carrier in solid dispersions. Both chitosan and its salt form, chitosan glutamate, were able to improve the release of nifedipine by a factor of two to three compared to the drug powder.

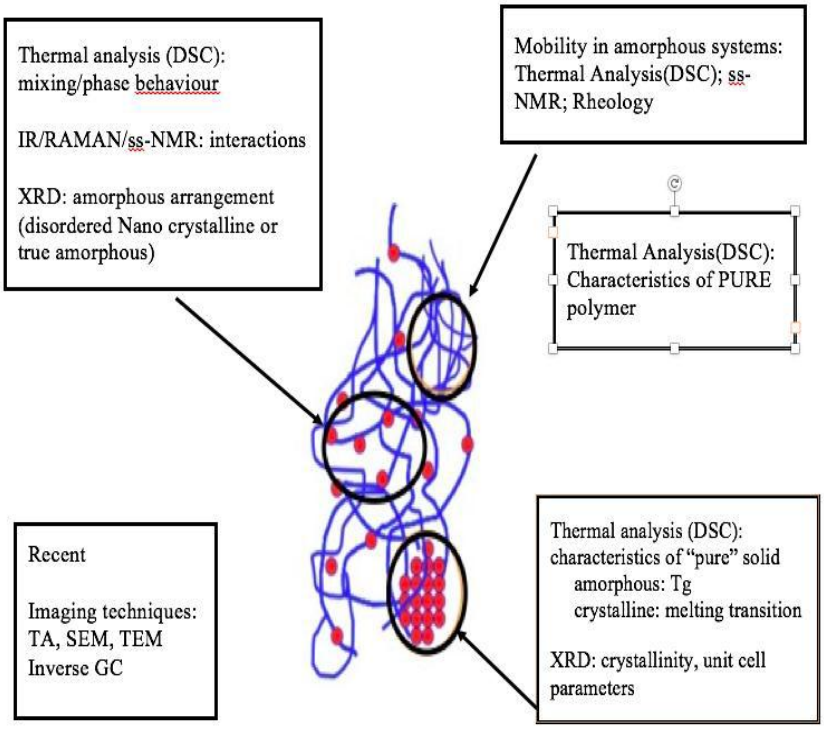
Emulsifiers[22]

Two mechanisms are possible here for release behavior of drug: improvement of wetting characteristics and solubilization of the drug. Bile salts and their derivatives are natural surfactants that are built from a steroidal skeleton in the liver and which are important to the emulsification of fats and oils in the diet. As with other surfactants, they can enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate.

Surface active agents[23]

Surface-active agents are substances that at low concentrations adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface and the interfacial tension. Surface-active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. The surface active carriers are said to be amphipathic in nature., surface active carriers may be included to improve the efficacy or the bioperformance of drug. The properties of surfactant are such that they can alter the thermodynamic activity, solubility, diffusion, disintegration, and dissolution rate of a drug.

Characterization of solid dispersion[24]



The most important methods which are use for characterization are thermo analytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug.

Methods for the characterization of solid dispersions are as following

1. Dissolution testing.
2. Thermo analytical methods: differential thermo analysis and hot stage microscopy.
3. Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change.
4. X-Ray diffraction.
5. Spectroscopic methods, e.g. IR spectroscopy, NMR spectroscopy.
6. Microscopic methods including polarization microscopy and scanning electron microscopy.

Advantages of Solid Dispersion[25-28]

1. Improving drug bioavailability by changing their water solubility has been possible by solid dispersion.

2. Increase in dissolution rate & extent of absorption and reduction in Pre systemic metabolism.

3. Transformation of liquid form of drug into solid form.

4. Solid dispersion results in particles with reduced particle size and thus the surface area are improved and increased dissolution rate is attained. Hence bioavailability is increased.
5. The carrier used in the solid dispersion plays a major role in improving the wettability of the particles. Improved wettability results in increased solubility thus improving the bioavailability.

Disadvantages of Solid Dispersion[29,30]

1. Major disadvantage is their instability. They show changes in crystallinity and a decrease in dissolution rate with ageing.
2. Temperature and moisture have more deteriorating effect on solid dispersions than on physical mixtures.
3. Difficulty in handling because of tackiness.
4. Drawback of solid dispersions is their poor scale-up for the purposes of manufacturing.

Applications of solid dispersion

1. It increases the solubility of poorly soluble drugs and thus increases the dissolution rate, which enhances the absorption and bioavailabilty of the drug.
2. For stabilization of the unstable drugs against various decomposition procedures like hydrolysis, oxidation etc
3. For reducing the side effect of certain drugs.
4. Masking of unpleasant taste and smell of drugs.
5. To avoid undesirable incompatibilities.
6. To obtain a homogeneous distribution of a small amount of drug in solid state.
7. Dispensing of liquid (up to 10%) or gaseous compounds in a solid dosage.
8. Formulation of sustained release dosage form
9. Reduction in the inactivation of drugs like morphine and progesterone in pre systemic circulation.

CONCLUSION[31-36]

Increasing the Bioavailability of a poorly soluble drug is a challenging aspect of drug development. Because of the poor aqueous solubility the drug possess dissolution problems due to which the in vivo absorption of the drug is reduced and thus the bioavailability is reduced, making the drug inappropriate for oral consumption and therefore solubility enhancement become necessary for such drug candidate. Solid dispersion is a most simple and efficient technique for increasing the aqueous solubility of a drug. The increase in

porosity also depends on the carrier properties, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate and increases the solubility of poorly water soluble drug. Solid dispersion has also been used to produce sustained release microsphere using tedious methods. New optimized techniques are also useful in the industries.

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