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A REVIEW ON SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG USING NATURAL CARRIER

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ABSTRACT

Many water insoluble medications present in class 2 and it is portrayed by low solvency and high porousness. Dissolvability of medication can be upgrading by expanding of disintegration rate. Numerous solubilization methods are accessible for expanding of solvency just as porousness like micronization, coacervation, complexation, strong scattering, and cosolvent. Ineffectively solvent and disintegration profile makes issue in drug industry for improvement of measurement structure. Strong scatterings are the most alluring technique for improving of bioavailability of ineffectively water dissolvable medications. Decrease of molecule size prompts expansion in wettability and porosity of medications. Porosity and wettability works on the dissolvability and disintegration rate.

Keywords: Solubility, solubility enhancement, dissolution and techniques

INTRODUCTION

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. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. So that salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs but there are practical limitations of these techniques. The salt formation is not applicable for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved due to the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media using surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability **[1]**.

Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly water soluble drugs. To overcome the solubility problem discussed above, many authors formulated solid dispersions using number of various polymers and methods. In spite of tremendous research activity on solid dispersions since 1961, their commercial application is limited. Only a few products have been marketed so far. One aspect of solid dispersion technology on which most workers in the field would agree is that the number of marketed products arising from this approach has been disappointing. Research for alternative carriers has been increasing to suit for the industrial applications as well as to reduce the production cost and toxic effects. Recently, many natural polymers have been evaluated for their uses in formulation of solid dispersion. Cost effective pharmaceutical excipients are always desirable **[1]**.

Pharmaceutical excipients developed from natural sources are economic. Present day consumers look for natural ingredients in food, drugs and cosmetics as they believe that anything natural will be more safe and devoid of side effects. Natural excipients show lack of toxicity, easy availability and economic considerations in pharmaceutical industry as compared to their synthetic counterparts. Naturally, derived excipients have shown promising results in the modification of drug release from the formulations.

1.1. Solubility:

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent as given in table. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion **[2]**.

Table 1.1: Terms Used for Approximate Solubility's

Definition	Parts of solvent required for one part of solute
Very Soluble	<1
Freely Soluble	1-10
Soluble	10-30
Sparingly Soluble	30-100
Slightly Soluble	100-1000
Very Slightly Soluble	1000-10000
Insoluble	>10000

1.1.1. Possible Causes for Poor Oral Absorption: Any drug is said to be poorly soluble when:

Aqueous solubility<100µg/ml

High crystal energy (melting point >200 0C)

Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm2/min,

High molecular weight: (>500), Self association and aggregation

Noyes-Whitney equation (1) illustrates how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral bioavailability:

dC/dt *h = AD. (Cs - C) ---------------- (1)

Where, dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, Cs is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t, h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

1.2. BCS classification: The BCS was first devised in 1995 by Amidon *et al.*

According to the BCS, drug substances can be classified as belonging to one of four classes:

Class 1: high solubility and high permeability

Class 2: low solubility and high permeability

Class 3: high solubility and low permeability

Class 4: low solubility and low permeability

Especially for class II substances according to the Biopharmaceutical Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects **[3]**.

1.2.1. Class Boundaries Used In BCS:

- A drug substance is considered highly soluble when the highest dose strength is soluble in £ 250 ml water over a pH range 1 to 7.5.
- A drug is considered highly permeable when the extent of absorption in humans is determined to be 90% of an administered dose, based on the mass balance or in comparison to an intravenous dose.
- A drug product is considered to dissolve rapidly when 85% of the labeled amount of substance dissolves within 30 minutes, using USP apparatus I or II in a volume of £ 900 ml buffer solution **[4].**

1.3. Solid dispersion

Solid dispersion was introduced in the early 1970s, refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

Chiou and Reigelman first defined solid dispersion in 1971 as “dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent or melting solvent method”. Dispersions prepared by fusion process are often termed as melts, e.g., nimisulide- PEG 4000 and those obtained by the solvent method are frequently referred to as coprecipitates or coevaporates, e.g., coprecipitates of furosemide crosspovidone **[5]**.

1.3.1. Meritorious features and pitfalls of solid dispersion

The homogenous distributions of small amount of drug(s) at solid state, provided in solid dispersions tend to have numerous advantageous applications viz.

- More acceptable to patients than solubilization product, since solid dispersion rises to solid oral dosage forms instead of liquid as solubilization products
- Enhancement of the active agent bioavailability to a desirable extent
- Avoiding polymorphic changes and the consequent bioavailability problems

- Transformation of liquid or gaseous form of the drug in to solid form is possible
- Homogeneous distribution of small amount of drug at solid state is possible to attain **[6].**

Despite their numerous meritorious features, solid dispersions during formulation development have some limitations too, viz.

- Reproducibility of its physico-chemical properties
- Poor stability of dosage from
- Laborious and expensive method of preparation
- Aggregation, agglomeration and air adsorption during formulation
- Decrease in dissolution rate with aging ford
- Difficulty in pulverization and sifting because of their tacky and soft nature **[7]**

2.0. CLASSIFICATION OF SOLID DISPERSION

Solid dispersions are classified by various ways viz. on the basis of carrier used and on the basis of their solid state structure,

2.1. On the basis of carrier used

2.1.1. First generation

First generation solid dispersions were prepared using crystalline carriers such as urea and sugar, which were the first carriers to be employed in solid dispersion. They have the disadvantage of forming crystalline solid dispersion, which were thermodynamically more stable and did not release the drug as quickly as amorphous ones.

2.1.2. Second generation

Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers such as povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates as well as natural product based polymers such as hydroxylpropylmethyl-cellulose (HPMC), ethyl cellulose, and hydroxypropoylcellulose or starch derivates like cyclodextrins.

2.1.3. Third generation

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self emulsifying properties. Therefore, third generation solid dispersions appeared. The use of surfactant such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer 407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability **[6,7]**

2.2. On the basis of solid state structure

2.2.1. Drug and polymer exhibiting immiscibility in fluid state

If a drug and polymer are immiscible in their fluid state, it is expected that they would not exhibit miscibility on solidification of the fluid mixture.

Such systems may be regarded as similar to their corresponding physical mixtures and any enhancement in dissolution performance may be owing to modification in morphology of drug and/or polymer due to physical transformation (i.e., solid to liquid state and back), intimate drug– polymer mixing, and/or enhanced surface area. Formation of crystalline or amorphous solid dispersions can be biased by the rate of solidification of mixture and the rate of crystallization of drug and/or polymer **[8]**.

2.2.2. Drug and polymer exhibiting miscibility in fluid state

If the drug and polymer are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, thereby influencing the structure of solid dispersion **[9].**

2.2.2.1. Eutectic Mixtures

Eutectic mixture was first described as solid dispersions in 1961 by Sekiguchi & Obi. Eutectic mixtures are formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. When a drug (A) and a carrier (B) are co-melted at their eutectic composition defined by point 'e', as shown schematically in **Figure 1.1**, the melting point of the mixture is lower than the melting point of either drug or carrier alone. At the eutectic composition (e), both drug and carrier exist in finely divided state, which results in higher surface area and enhanced dissolution rate of drug. This was first reported for sulfathiazole-urea **[10-11]** Other examples of eutectic mixture include acetominophen-urea **[12]** and the dispersion of griseofulvin and tolbutamide in polyethylene glycol (PEG) 2000 **[13]**.

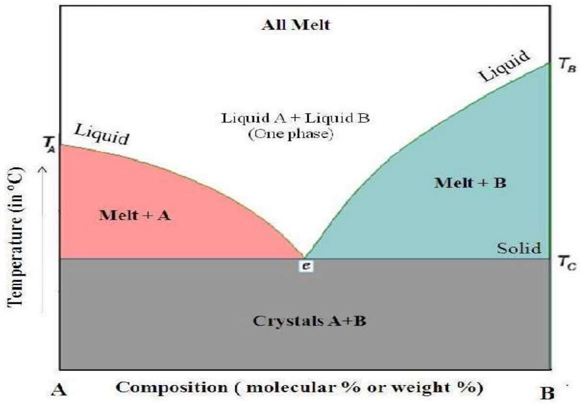

Figure 1.1: Phase diagram of a eutectic mixture

2.2.2.2. Crystalline Solid Dispersion

A crystalline solid dispersion (or suspension) is formed when the rate at which drug crystallizes from drug–polymer miscible mixture is greater than the rate at which drug–polymer fluid mixture solidifies.

2.2.2.3. Amorphous Solid Dispersion

If the drug–polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then drug is kinetically trapped in its amorphous or a “solidified-liquid” state. These types of dispersions have the risk of potential for conversion to a more stable and less soluble crystalline form.

2.2.2.4. Solid Solution

Solid solution is a solid dispersion that is miscible in its fluid as well as solid state. These solid solutions may be either of amorphous or crystalline type. In amorphous solid solutions as the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. Amorphous solid solutions have improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility. Crystalline solid solution may result when a crystalline drug is trapped within a crystalline polymeric carrier. Poorly soluble drugs have been incorporated in carrier molecules using crystal inclusion and crystal doping techniques, although the usage of such technologies has not yet gained widespread application in pharmaceutical product development.

According to extent of miscibility of the two components, solid solutions are continuous or discontinuous type. In continuous solid solutions, the two components are miscible in the solid state in all proportions. The components that are immiscible at intermediate composition, but miscible at extremes of composition are referred to as discontinuous solid solutions.

According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional and interstitial. In the substitutional solid solution, the solute molecule substitutes for the solvent molecule in the crystal lattice as shown in **Figure 1.2**. In this case, the molecular size of the two components should not differ by more than 15%. An interstitial solid solution is obtained when the solute (guest) molecule occupies the interstitial space in the solvent (host) lattice. For this to occur, the solute molecule diameter should be less than 0.59 than that of solvent molecule. Therefore, the volume of the solute molecule(s) should be less than 20% of the solvent molecule(s). Examples include solid solutions of digitoxin, methyltestosterone, predinsolone acetate and hydrocortisone acetate in the matrix of PEG 6000. They all exhibit faster rate of dissolution.

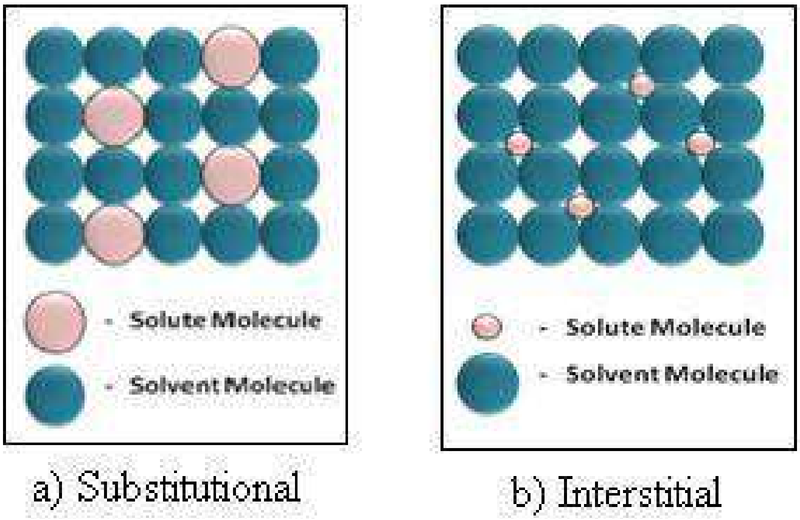

Figure 1.2: Schematic representation of substitutional and interstitial solid solutions

3.0. MECHANISM OF BIOAVAILABILITY ENHANCEMENT

The enhancement in dissolution rate because of solid dispersion formation, relative to pure drug, varies from as high as 400 fold to less than two fold. The increase in dissolution rate can be attributed to myriad factors and it is very difficult to show experimentally that any one particular factor is more important than the other. Solid dispersions increase the dissolution rate of poorly water soluble drugs by one of the following mechanisms.

- Reduction in particle size
- Improvement in wettability and dispersibility
- Changing crystalline form of drug to amorphous form
- Reduction in aggregation and agglomeration of drug particles.

4.0. SELECTION OF CARRIER(S)

The properties of the carrier have a profound influence on the dissolution characteristics of the dispersed drug. A carrier ought to meet the following prerequisites for being suitable for increasing the dissolution rate of a drug. It should be

- Freely water soluble with rapid dissolution properties
- Nontoxic and pharmacologically inert
- Heat stable with a low melting point for the melt method
- Soluble in a variety of solvents
- Preferably enhancing the aqueous solubility of the drug
- Chemically compatible with the drug
- Forming only weakly bounded complex with the drug

The various carries for solid dispersion are enlisted in **Table 1.2**

Table 1.2: Carriers used in the preparation of solid dispersion

Chemical class	Examples
Acids	Citric acid, Tartaric acid, Succinic acid
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
Polymer Material	Polyvinyl pyrolidone, PEG 4000,PEG 6000, Sodium alginate, Carboxy methylcellulose, Guargum, Xanthan gum, Methyl cellulose
Surfactant	Polyoxyethylene stearate, Polaxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14,Vitamin E TPGS NF
Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxylakyl xanthenes.

5.0. METHODOLOGIES

The core steps involved in the formation of solid dispersion between a drug and polymer are:

1. Transforming drug and polymer from their solid state to fluid or fluid-like state through processes such as melting, dissolving in solvent or cosolvent, or subliming.
2. Mixing the components in their fluid state.
3. Transforming the fluid mixture into solid phase through processes such as congealing, solvent removal, and condensation of sublimed mixture.

Basically, there are two methods of preparing solid dispersions, fusion and solvent processes. In case of thermolabile drugs or those with high melting points, a modified method is employed known as melting solvent method. The latter method is limited to drugs with low therapeutic doses, i.e. below 50 mg. However, for the preparation of solid dispersions, several methods have been reported in literature, which are:

5.1 Fusion method

In this method, the carrier is heated to a temperature just above its melting point and drug is incorporated in to the matrix. If the drug has high solubility in the carrier, the drug could remains "dissolved" in the solid state, yielding a solid solution. The melt is solidified in an ice bath under rigorous stirring, pulverized and then sieved. Rapid congealing is desirable, because it results in supersaturation of drug as a consequence of entrapment of soluble molecule in the solvent matrix by instantaneous solidification.

The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling.

Advantages

- It is more convenient and economical method for drugs stable at temperature below 1000C
- Technically it is an easier method if the drug and carrier are miscible in the molten state
- It precludes the use an organic solvent there by circumventing the enigmas of its removal from the dispersion
- Dissolution for dispersions obtained by melting technique are much faster than those prepare during solvent techniques

Drawbacks

- High melting carrier cannot be used
- Thermal degradation or instability may result at the melting point
- Decomposition may take place, often dependent upon composition, fusion time and rate of cooling
- Evaporation or sublimation and polymeric transformation of the dispersion component may take place
- Solidified melt may be tacky and unhandable Immiscibility between drug and carrier results in irregular crystallization that causes obvious problems during formulation

5.2. Solvent Evaporation Technique

Tachibana and Nakamura first reported this method in 1965. This technique involves dissolving the drug and the carrier in a suitable organic solvent or a combination of solvents to get a clear solution. As the solvent is being removed, supersaturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The solvent is then evaporated directly on a water bath or hot plate or using a rota-vapour. The resulting solid dispersion is stored in the desiccator under vaccum and pulverized to obtain the desired size fraction. The important prerequisite for the manufacturing of solid dispersion using the solvent method is that both drug and the carriers are sufficiently soluble in the solvent. Solid dispersion prepared by solvents removal process termed by Bates as coprecipitates. A basic process of preparing solid dispersion of this type consists of dissolving the drugs and the polymeric carrier in a common solvent, such as ethanol, chloroform, or a mixture of ethanol and dichloromethane.

Advantages

- High melting carries can also be utilized
- Thermal decomposition of drug and carriers associated with the fusion method can be avoided

Drawbacks

- Larger volumes or organic solvent have to be used which makes the process slightly expensive
- Removal of the solvent is difficult
- Residual solvent can have possible adverse effect
- Difficulty of reproducing crystal forms
- Supersaturation of the solute cannot be attained unless the system goes through a highly viscous phase, Selection of common solvent is difficult

6. IMPORTANCE OF NATURAL CARRIERS IN SOLID DIISPERSION

Research for alternative carriers has been increasing to suit for the industrial applications as well as to reduce the production cost and toxic effects. Recently, many natural polymers have been evaluated for their use in new applications. Many carriers used in solid dispersions also cause problems due to their hygroscopic nature. Hence, continuous search for new carriers and new techniques is going on which will be useful for large scale manufacturing. Many polymers have limitations in enhancing solubility of poorly water soluble drugs due to their high viscosity. Use of polymers with low viscosity and high swelling capacity offers better alternative for these types of polymers. Use of natural polymer is more beneficial because of their low cost, biocompatibility, and biodegradability. Most of these polymers are hydrophilic in nature, and after absorbing they swell and form a viscous gel layer around the dosage form resulting into delayed/ sustained drug release. The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug.

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug:

1. Soluble in water for fast release or insoluble for sustained release.
2. Physiologically inert.
3. Melting point should be not more than 200^0C.
4. Thermal stability up to its melting point.
5. Non-toxic, non-irritant.
6. Chemically compatible.

Natural gums, polysaccharides and their derivatives represents group of polymers widely used in pharmaceutical dosage forms. Polysaccharides are the choice of materials among the hydrophilic polymers used, because they are non-toxic & acceptable by the regulatory authority. Natural gums like Guar gum, Xanthan gum, Locust bean gum etc when used in optimum concentration lead to increase in dissolution rate due to low viscosity and high swelling capacity which offers better alternative for these types of polymers. The dissolution rate of drugs from the formulations containing viscous carriers is generally low due to the formation of gel layer on the hydrated surfaces, which prevents the drug release during dissolution.

This can be overcome during tablet formulation by adding disintegrants. Pulverization of the product is also another important draw back with the high viscosity carriers, which can be overcome by using decreasing order of polymer/drug ratio during formulation. However, it is reported that the swelling ability of the carrier improves dissolution rate of poorly water soluble drug. As the viscosity of the carrier reduces the dissolution rate, it is useful to modify the gum in such a way that its swelling ability remains same and viscosity reduced. This can be achieved by heating.

Cyclohexdrins, carbohydrates and other miscellaneous carriers also play important role in dissolution enhancement of poorly water soluble drugs, for example skimmed milk, silica gel, gelatin and egg albumin etc **[14, 15]**.

7. CONCLUSION

Solid dispersions are useful method for improving of solubility by increasing of dissolution characteristics. Many poorly water soluble drugs are available in pharmaceutical industry which needs to improve of solubility parameter. Most of the dosage forms are taken by orally which creates the problem in bioavailability. Many additional techniques are also available for solubility enhancement like micronization, Nanonization, supercrystal fluid recrystallization, use of surfactant, evaporation precipitation, Sono-crystallization, Nanomorph technology and solid dispersion. Carriers are plays active role in solid dispersions.

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