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Solid Dispersion: Different methods of enhancing solubility and classification of solid dispersion

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ABSTRACT

Solubility is one of the most significant parameters that affects the absorption and bioavailability of the drugs. Amongst the newly developed drugs 40% possesses low aqueous solubility, so it becomes a great challenge to enhance the solubility of such drugs in order to enhance the bioavailability. Solid dispersion is one of the solubility enhancing methods to enhance their bioavailability. The current article highlights the study of various methods of enhancing solubility and solid dispersion's advantages over them.

Keywords— Solid dispersion, Solubility, Hydrotropy

1. INTRODUCTION

One of the foremost difficult aspects pharmaceutical industries have long-faced is to boost the oral bioavailability of the poorly soluble medication. On an average 30-40% of newly discovered drug candidates are poor water soluble hence it becomes necessary to enhance the solubility of the poorly water-soluble drugs. ^[1]

2. SOLUBILITY

It is a phenomenon in which solute is being dissolved in the solvent to give the homogeneous system. It can be defined as the amount of solute that dissolves in the unit volume of solvent to form a saturated solution under the specified conditions of pressure and temperature. According to pharmacopeia general terms to describe the solubility range is given below. ^[2]

Table 1. Solubility range

Definition	Parts of solvent requires 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



Fig. 1: Bio pharmaceuticals Classification System

2.1 Solubility process

The breaking of bonds of solute which are either intermolecular or inter-ionic bonds and the solvent molecule separation in order to provide space for the solute molecule in solvent and the interaction between solute and solvent molecules called as the solubilization process. [3][4]

In 1995 BCS was introduced which was elaborated as the Biopharmaceutics Classification System, according to this system the APIs were divided into the four classes if you look at their permeability and aqueous solubility. [5]

2.2 Methods for enhancement of solubility

There are various techniques used for increasing the solubility of the poorly water soluble drugs and more on improving bioavailability of such drugs.

2.2.1 Particle size reduction: It is pretty much understood that on particle size reduction there is increase in the surface area of the particle and intrinsically the solubility is related to the particle size, increased surface area leads to the enhancement in the dissolution rate. Particle size reduction can be achieved by various machines such as jet mill, rotor stator colloidal mill, ball mill, etc. The major disadvantage of this method is control important characteristics like shape, size, surface charge etc. [6]

2.2.2 Nanosuspension technology: In aqueous vehicle pure drug particles are dispersed in which suspended particles possesses diameter of less than 1µm in a biphasic system. Surfactants stabilizes nano-sized drug particles in a colloidal dispersion. Drugs which are soluble in the aqueous media as well as in lipid media both type of drug's solubility can be improved with the nanosuspension technology. There are four principle techniques developed in recent years for preparing the nanosuspensions. [7]

(a) Wet milling.

(b) Homogenization.

(c) Emulsification and solvent evaporation.

(d) Supercritical fluid method.

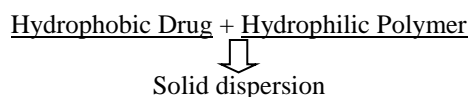
2.2.3 Surfactant: Surface tension is lowered between the two liquids, gas liquids or solids by the surfactants. Solubility of enrofloxacin has been improved upto 26 times than the original drug. There are various surfactants used such as lauroyl macroglycerides, castor oil, etc. [8]

2.2.4 Salt formation: In order to increase solubility of acidic or basic drugs salt formation is one of the most common method and the dissolution rate is also increased so. Salts of the acidic and basic drugs generally have higher solubility than their corresponding acidic or basic forms. The aqueous solubility of acidic or basic drugs as a function of pH dictates whether the compound will form suitable salt or not and if it forms then what could be their physicochemical properties. [9]

2.2.5 PH adjustment: Applying the pH change to some of the poorly water soluble drugs might be helpful in improving their solubility, the buffer capacity and the tolerability are considerable in this technique. [10]

2.2.6 Hydrotrophy: This technique was used to increase the aqueous solubility of poorly water soluble drugs, the term was first coined in 1916 by Carl Neuberg but the practical implemented in 1976. The poor aqueous solubility of drug is increased by the large amount of the 2° solute. The major advantage of this technique is that there is no use of organic solvents thus avoids the problem of residual toxicity, error due to volatility, cost etc. The complete removal of water is not possible if there is use of water as solvent. [11][12]

2.2.7 Solid dispersion: Solid dispersion represent group of solid products which consists of at least two different components, in solid dispersion the two components generally are the hydrophobic drug and the hydrophilic carrier. The carrier may be either crystalline or amorphous forms. [13]



3. HISTORY

Sekguchi and obi in 1961 introduced a unique approach named solid dispersion in order to decrease particle size and increase the dissolution rate. They used urea as water soluble carrier for preparation of eutectic mixture of sulfathiazole which is a poorly water soluble drug. In 1965 Nakamura and Tachibana reported a novel method of preparing aqueous colloidal dispersions of β-carotene by using water soluble polymers such as PVP. They dissolved drug and polymer in common solvent then the solvent is evaporated completely. When the co-precipitate were exposed to the water a colloidal dispersion was obtained. Levy and Kanig afterward notes that there is possibility of using solid solution in which the selected drug is dispersed molecularly in a soluble carrier. In a series of reports in 1965-1966, Goldberg *et al* showed detailed experimental and theoretical discussion of the advantages of solid solutions over the eutectic mixtures. In 1966 Mayersohn and Gibaldi verified that dissolution rate of griseofulvin could be markedly enhanced when dispersed in PVP by the same solvent method. Simonelli *et al* thoroughly discussed the mechanism of increased dissolution rate which were dispersed in the polyvinylpyrrolidone carriers. [14] [15]

4. CLASSIFICATION OF SOLID DISPERSIONS

Solid dispersions are classified on the basis of two categories viz. on the basis of carrier used and on the basis of their solid state structure.

4.1 On the basis of carrier used

There are four generations of the solid dispersions if we classify them on basis of their used carrier.

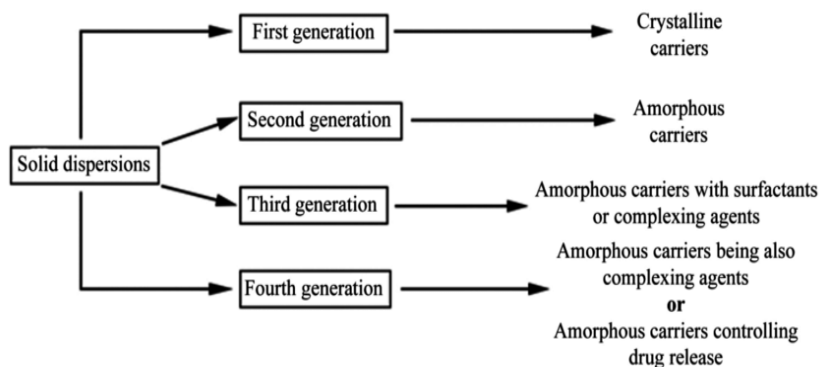


Fig. 2: Different generations of solid dispersions

4.1.1 First generation: First generation represents to the crystalline solid dispersions, first solid dispersion was prepared by the Sekiguchi and obi, and they prepared the eutectic mixture of sulfathiazole using urea as a carrier. In such type of solid dispersions crystalline drug is being dispersed in the crystalline carrier. The melting of the drug is higher than the melting point of the eutectic mixture, while carrier and drug both have same melting point. Eutectic mixture is always preferable because both drug and the carrier will crystalline simultaneously in a cooling process, which will show well dispersed drug in the carrier and there will be an significant enhancement in the dissolution rate of drug from the actual API's dissolution rate. Drug molecule of the crystal lattice can replace the carrier molecule of the crystalline solid solutions, or in the solvent molecule they can occupy the interstitial spaces in crystal lattice. [16][17]

4.1.2 Second generation: Apart from the first generation the second generation solid dispersions are consist of amorphous carriers which mostly polymers. The amorphous solid dispersions can be separated into the two group's amorphous solid solutions and in amorphous solid suspensions in consideration of the physical state of the drug. Both drug and carrier miscible in each other to form a homogeneous mixture in spite this amorphous suspension shows two different phases. There will be formation of amorphous carrier suspensions if drug shows limited carrier solubility and extremely high melting point. [18]

4.1.3 Third Generation: Subsequent supersaturation state of drugs of amorphous solid dispersions may lead to precipitation and decrease the drug concentration in vitro in vivo. Bioavailability of drugs will be negatively affected. This phenomenon is very common; particularly with sugar glass based solid dispersions. As the surfactants and emulsifiers are introduced into the solid dispersions this seems to be helpful not only in improving the dissolution profile but also the chemical and physical stability of drug. [19]

4.1.4 Fourth generation: In the fourth generation the solid dispersion is of controlled release solid dispersion (CRSD) type in which the poorly water soluble drugs having the short biological half-life. There are two main targets of the CRSD: [20]

- Solubility enhancement
- The extended release of drug the controlled manner

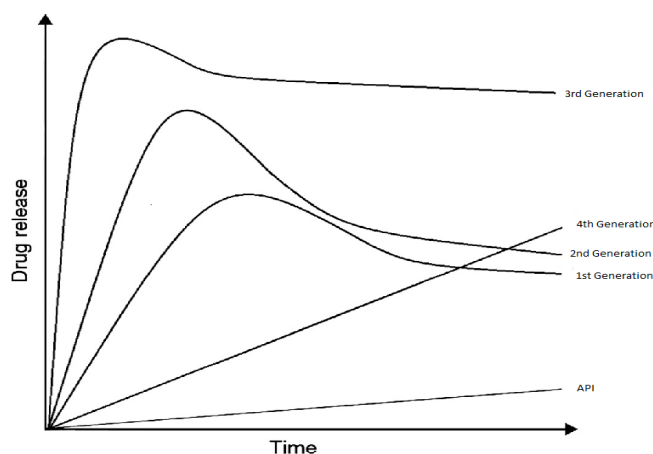


Fig. 3: Dissolution profile comparison of four generations of solid dispersions in supersaturated conditions

4.2 On the basis of their solid state structure

On the basis of solid state structure the solid dispersion can be divided into the two main categories: Drug and polymer exhibiting immiscibility in fluid state and Drug and polymer exhibiting miscibility in fluid state.

4.2.1 Drug and polymer exhibiting immiscibility in fluid state: If there is immiscibility of drug and polymer in their fluid state then it is expected that there will be no miscibility of fluid mixture upon the solidification. There are two possibilities if the immiscibility occurs: [21]

- **Crystalline solid dispersions:** In this system on solidification either one of the drug or polymer or both drug and polymer will crystallize and as a result of this crystalline solid dispersions will be formed.
- **Amorphous solid dispersions:** In this case of immiscibility neither drug nor polymer will crystalline upon solidification and such type of solid dispersions are called as amorphous solid dispersions.

4.2.2 Drug and polymer exhibiting miscibility in fluid state: Structure of solid dispersion may be get affected if the drug and polymer show miscibility in fluid state and upon solidification it might go into the phase separation.

- **Eutectic mixtures:** Sekiguchi and obi were the first to describe the eutectic mixtures in 1961 in which drugs and polymer are mixed in the molten state and upon cooling they crystallize into two different components with zero miscibility. ^[22]
- **Solid solutions:** When solute shows the nonstoichiometric incorporation into the crystal lattice of solvent then there will be formation of solid solutions. Solid solutions can be classified according to the solute present in crystal lattice or the way by which solute molecules are circulated. In general, the terminology “solid solution” refers to the system that contains a crystalline carrier. Solid solutions consist of just one phase in comparison to the liquid solutions where a number of components are required. The solid solutions can be divided into the further four categories. ^[23]
 - (a) Continuous solid solutions
 - (b) Discontinuous Solid solutions
 - (c) Substitutional crystalline solid solutions
 - (d) Interstitial Crystalline Solid solutions
- **Glass solutions:** In glass solutions there is dispersion of the solute molecule molecularly into the amorphous carrier. Therefore one phase homogeneous system is formed in the glass solutions, however there will be irregularity in the dispersion of the solute molecule due to the high viscosity of glass solutions as compare to the liquid solutions and through mixing homogeneous distribution can be obtained in the glass solutions. ^[24]
- **Glass suspensions:** There will be phase separation if miscibility is observed of an amorphous drug in an amorphous carrier which is limited and there will be increase in the drug content.

5. METHODS OF PREPARATION OF SOLID DISPERSION

- (a) Melting method
- (b) Solvent Evaporation method
- (c) Melting Solvent method
- (d) Melt Extrusion method
- (e) Lyophilization technique
- (f) Melt agglomeration process
- (g) Spray drying method

6. ADVANTAGES OF SOLID DISPERSION

- It useful in enhancing the solubility of drugs who possesses low solubility and bioavailability.
- It is helpful in reducing the particle size.
- It improves the porosity and wettability of drug.
- It is helpful in producing rapidly disintegrable oral tablets.
- Helpful in stabilizing unstable drugs.
- It can be used in dispensing of liquid or gaseous compounds.
- Helpful in transforming liquid form of drug into solid form.
- It is easier to produce and more applicable. ^{[25][26]}

7. DISADVANTAGES OF SOLID DISPERSION

- There is poor scale up for the purpose of manufacturing.
- It causes reproducibility of physicochemical characteristics. ^[27]

8. APPLICATION OF SOLID DISPERSION

- The Solid dispersion systems were shown to offer the bio obtainable oral dose forms for the anti-cancer medication, which might be substituted for the standard injections to boost the patient compliance and comfort.
- Solid dispersion is useful in increasing the onset action of various drugs such as NSAIDs where quick action is required to get rid of pain and inflammation.
- Solid dispersion is found helpful in reducing the pre-systemic inactivation of the drugs like morphine and progesterone.
- With solid dispersion it is possible to attain homogeneous distribution of drugs which present in small amount (solid state).
- Undesirable incompatibilities can be avoided with the use of solid dispersion.
- Side effect of certain drugs can be reduced. ^{[28][29]}

9. SELECTION OF SOLVENTS

To get included in the solid dispersion formulation the solvent should possess following properties/criteria.

- Carrier and drug both must get dissolved.
- Water based system are more preferable.
- Solvents which are toxic should be avoided because they possess risk of residual level after properties.
- Alternative less toxic solvents can be used e.g. ethanol. ^[30]

Table 2: Different solvents used in solid dispersion

Solvent	Melting point (°C)	Boiling point (°C)	Vapour pressure at 25 °C (pKa)
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
Water	0	100	3.16
Chloroform	-63	62	26.1
DMSO	19	189	0.08
Acetic acid	17	118	1.64

9.1 Selection of carriers

Carrier should have following properties in order to get involved in solid dispersion formulation and should be suitable to increase dissolution rate of drug. [31]

- Carrier should be nontoxic.
- It should be pharmacologically inert.
- It should be soluble in water freely.
- Should be soluble in numerous solvents.
- Carrier should be able to increase the aqueous solubility of drug molecule.
- It should not form complexes with drug.
- Should be chemically compatible with drug.

Table 3: Different carriers used in solid dispersion [31]

S no.	Category	Carriers
1.	Acid	Citric acid, succinic acid
2.	Polymeric materials	PVP, PEG, HPMC, Methyl cellulose, cyclodextrins, hydroxyl propyl cellulose, pectin.
3.	Sugar	Dextrose, sucrose, galactose, sorbitol, xylitol, lactose.
4.	Surfactants	Polyoxyethylene stearate, poloxamer 188, tweens, spans.
5.	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane.

10. CHARACTERIZATION OF SOLID DISPERSION

Various technique used for characterization of solid dispersion such as:

- Differential scanning calorimetry
- Differential thermal analysis
- Thermomicroscopic methods
- X-ray diffraction
- FTIR
- Scanning electron microscopy
- Dissolution studies

10.1 Differential Scanning Calorimetry (DSC)

DSC can be used by quantifying the heat associated with melting (fusion) of the material to determine crystallinity. DSC is a well-known technique that measures the flow of heat into or out of a material according to time or temperature.

10.2 Differential Thermal Analysis (DTA)

Difference in sample temperature and reference material used thermally is evaluated in DTA as a function of temperature. The sample temperature deviation from the reference and transition that the sample undergoes results in sample energy release or absorption. Differential temperature plot vs. programmed temperature indicates whether exothermic or endothermic transition temperature. Less than 1mg sample size can be used. [13]

10.3 Thermo-microscopic methods

In this technique, warm stage microscope is used to explore the phase diagrams of binary systems. A slide heats the physical mixture or dispersion (approx 1 mg) at a rate of 1-5 ° C per minute. Then visual observation records the thaw and melting points. This technique needs only a tiny sample quantity but is restricted to compounds that are thermally stable. This method was used to characterize diflunisal-PEG strong dispersion. [31]

10.4 X-ray diffraction

The technique of X-Ray diffraction is a very significant and effective instrument to study the physical nature of solid dispersions. It has been used recently to study binary eutectic systems. The technique of diffraction is also particularly useful in the detection of compound or complex formation as its spectra or lattice parameters differ significantly from those of pure parts. The major drawback of using the diffraction technique to study dispersion processes is its regular inability to distinguish amorphous precipitation from molecular dispersion unless the solvent component's lattice parameter is altered. [32]

10.5 Fourier Transform Infra-Red Spectroscopy (FTIR)

Using the standard KBr pellet technique, FT-IR spectroscopy can be used to detect possible relationships between the drug and the carrier in solid state on FT-IR spectrophotometer. [33]

10.6 Scanning Electron Microscopy (SEM)

SEM is useful in determining morphology, solid particle size and sometimes drug polymorphism the fine dispersion of drug particles can be visualized in the carrier matrix. Use of the electron microscope method is generally restricted to high-resolution chemicals. [34]

10.7 Dissolution studies

Dissolution research is conducted to determine the dissolution rate and magnitude. The strong dispersion dissolution analysis was conducted at $37\pm 0.20^\circ\text{C}$ on the USP-type II paddle device. In medium, the drug was distributed. The sample was taken from time to time, filtered and analyzed for drug content using a UV visible spectrophotometer to measure the absorbance at the appropriate wavelength. [32] [33]

11. CONCLUSION

Solid dispersion is one the useful techniques can be employed for improving the solubility of poorly water soluble drugs. There are several types of solid dispersion discussed in this article, various advantages and disadvantages have also been discussed. There are several methods of preparing the solid dispersions which varies from simple to advanced techniques. So it can be concluded that solid dispersion is a useful technique and further can be developed in pharmaceutical industry.

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