Recent Review on Solid Dispersion of Hydrotropes

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Abstract

The augmentation of oral bioavailability of poorly water-soluble drugs remains one of the most demanding aspects of drug development. Although salt formation, co-solubilization and particle size reduction have been used to increases dissolution rate, oral absorption and bioavailability of some drugs . Solubility is those physiological factor which affecting absorption of drugs and its therapeutic effectiveness. The low dissolution rate and low solubility of drug substances in water & in aqueous G.I.T. fluid leads to insufficient bioavailability. The improves solubility and dissolution of hydrophobic drugs remains one of the trickiest tasks in drug development.

Keywords- *solid dispersion, Hydrotropes, Solubility, Dissolution rate.*

Introduction- The bioavailability of a water soluble drug is limited by its dissolution rate, which in turns is collected by the surface area which available for dissolution. The dissolution rate is often the effect of particle size of any drug and its biological activity is well identified. Trituration, grinding, ball milling, fluid energy micronization and controlled precipitation is methods of reducing particle size and increasing surface area[1].The solubilization of drugs in organic solvents in aqueous media by use of surfactants and co-solvents leads to liquid formulations which are frequently unwanted from patient's suitability and commercialization. Although particle size reduction is mainly used to increase dissolution rate, it is a useful limit to size reduction achieved by some methods e.g. controlled crystallization, grinding, pearl milling etc. The uses of very fine powders in dosage form may also be difficult because of handling difficulty and poor wettability due to charge improvement [2].

From conventional tablets and capsules, the dissolution rate is restricted by the size of major particles created after degeneration of dosage form. In this case, 5 micrometer is average particle size that is usually the lower limit, although higher particle sizes are most preferable for ease of handling, formulation and manufacturing. In other words, if a solid dispersion or a solid solution is used, a small portion of drug dissolves to saturate gastrointestinal fluid[3].

The solid dispersion was prepared by water soluble carrier is spongy and cheap mass which is harder to handle, mainly in the capsule-filling and tablet making development. e.g. pulverization, sieving.

From Noyes-Whitney equation, it gives some hints as dissolution rate of even very poorly soluble compounds might be improved to diminish the limitations to oral availability:

$$dC/dt = AD(Cs-C)/h$$

Where dC/dt = dissolution rate, A is surface area, D is diffusion coefficient, Cs is solubility of compound in dissolution medium, C is concentration of drug at time t and h is the thickness of the diffusion medium[4].

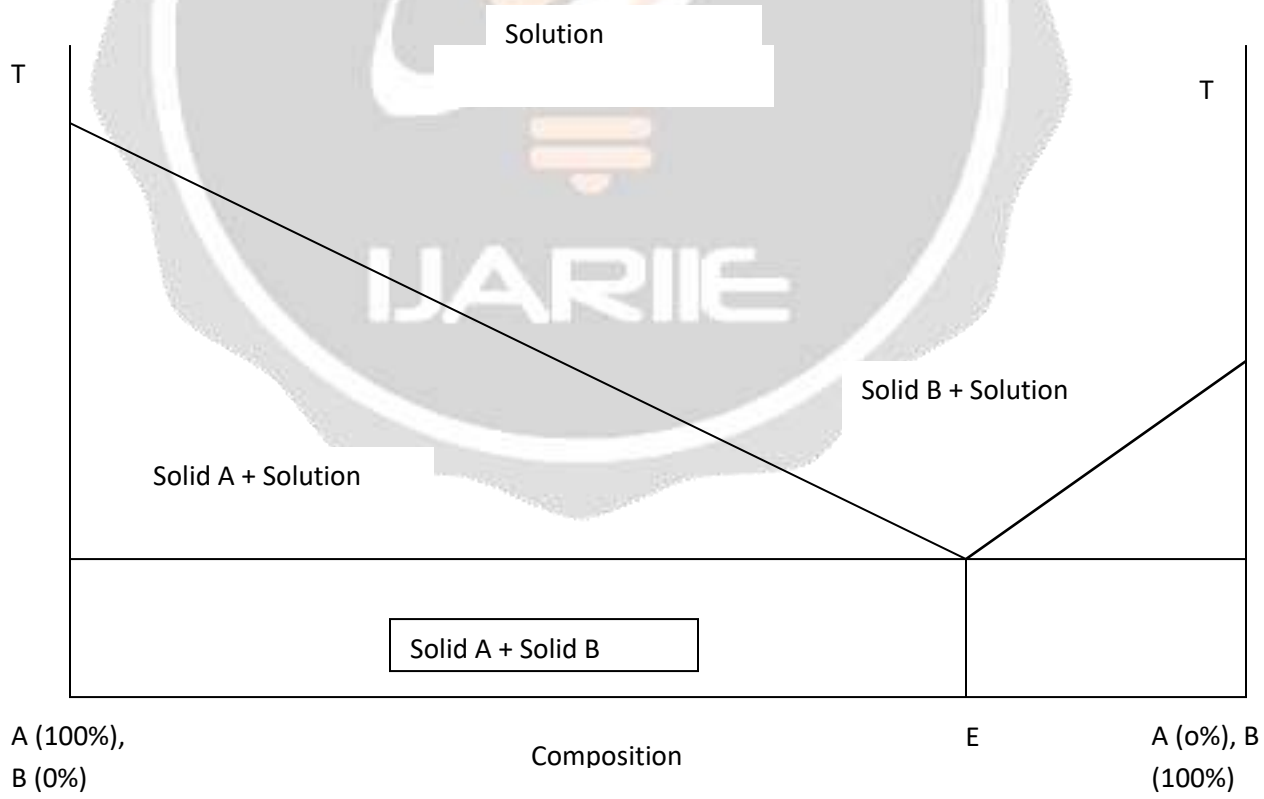
"**Solid dispersion** is that technology which dispersing one or more active ingredients in an inert matrix in the solid stage to get an increased dissolution rate or sustained release of drug, its properties and improved stability".

Types of solid dispersion:-

1. **Simple Eutectic mixer**
2. **Solid solution**
3. **Glass solution**
4. **Compound formation**
5. **Amorphous precipitation**

1. Simple Eutectic Mixture:-

Eutectic mixture is those type of mixture which is highly water- soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline compounds. Melt fusion method is used to prepared this eutectic mixture. [5].



Hypothetical Phase Diagram of Eutectic Mixture

2. Solid Solutions:-

Solid solution contains solid solute mixed in solid solvent. This systems is prepared by solvent evaporation method, whereby solute and carrier guest is dissolved in a common volatile solvent like alcohol.

Solid solution can be classified on the basis of crystalline structure of the solid solution.

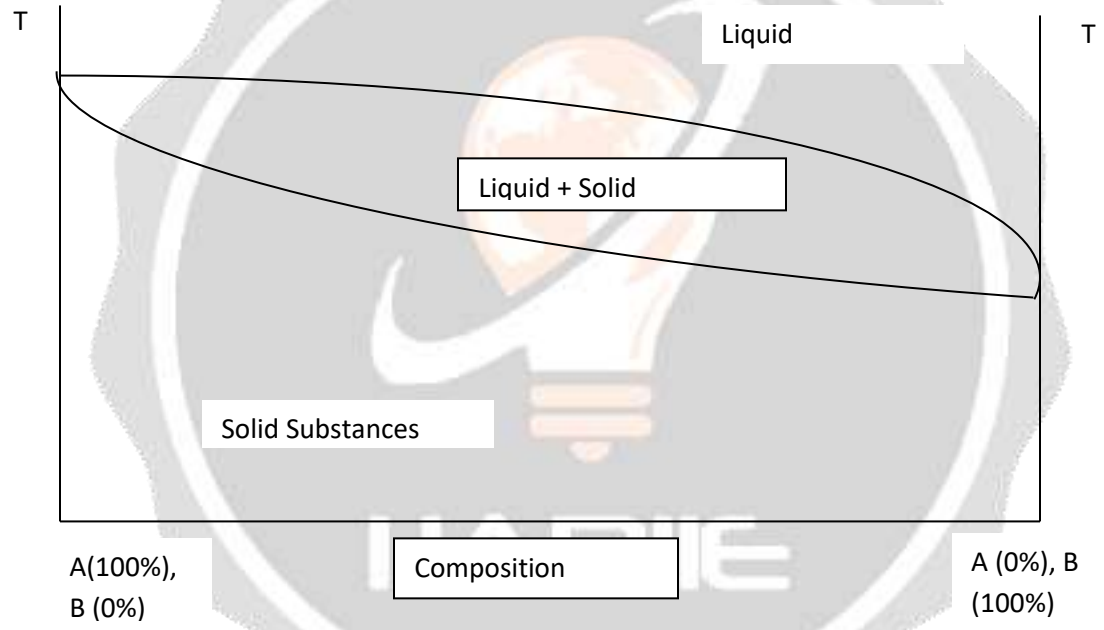
a) Continuous solid solutions

b) Discontinuous solid solutions

c) Substitution solid solutions

d) Interstitial solid solutions

a) Continuous Solid Solutions:

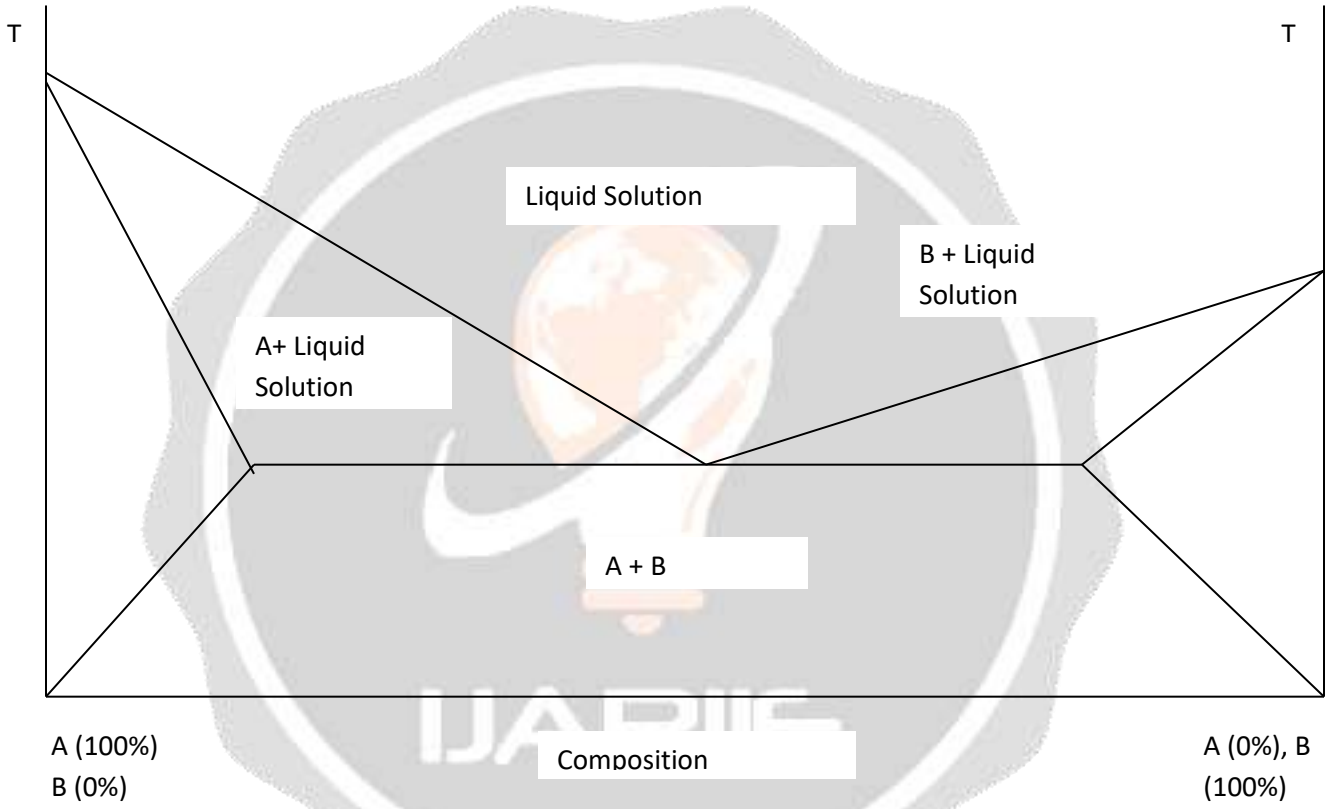


Hypothetical Phase Diagram of Continuous Solid Solutions

b) Discontinuous Solid Solutions:-

This system is as similar as continuous solid solution; it contains a limited solubility of a solute in a solid solvent. Each component dissolves some other component to a certain degree above the eutectic temperature. When the temperature is down, the solid solution regions become narrower.

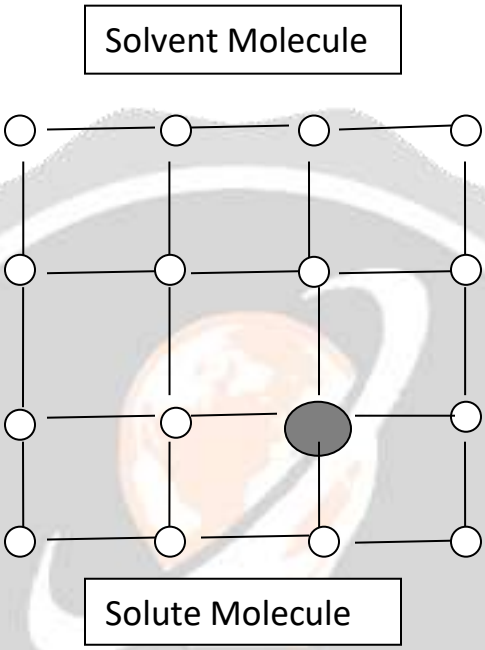
The limited solid solution and free energy of stable solution is also lower from the pure solvents [6]



Hypothetical Phase Diagram of Discontinuous Solid Solution

c) Substitutional Solid Solution:-

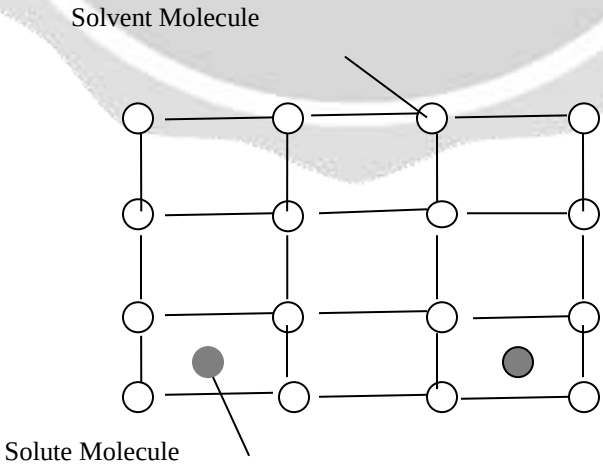
In this type of solid solution, the solute molecule substitutes keeps in form of solvent molecules in the crystal lattice of the solid solvent. It is also known as continuous or discontinuous solid solution. The size and static factors of the solute molecules plays important role in the formation of solid solution.



Substitutional Solid Solution

d) Interstitial Solid Solution:

In solid solutions, the solute (guest) molecule contains the interstial space of the solvent (host) lattice. It presents only a discontinuous (limited) solid solution. The size of the solute will be critical in order to fit into the interstices.



Interstitial Solid Solution

3. Glass Solution:-

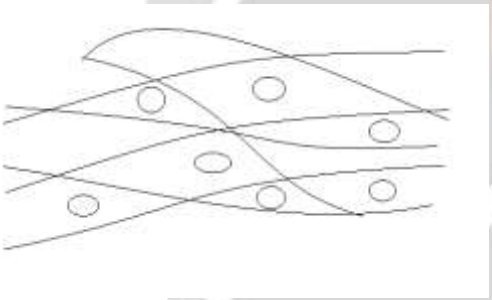
In Glass solution, it is a homogenous type of solution which a glassy or a vitreous carrier solubilizes drug molecules in its matrix. Polyvinylpyrrolidine (PVP) dissolves organic solvents which undergo to create a glassy state upon evaporation of the solvents. [7].

4. Compound or Complex Formation:-

In Compound or complex formation, it is two type of components in a binary system during solid dispersion preparation. The accessibility of drugs from complex or compound depends on the solubility, association constant and intrinsic absorption rate of complex formation.

5. Amorphous Precipitation:

In Amorphous precipitation, it occurs drug precipitates as an amorphous form in the inert carrier. The equivalent crystalline form of drug in this system generally produced lowest dissolution rates than the higher energy state of drug.[8].



Amorphous Precipitation

MECHANISM OF DISSOLUTION RATE ENHANCEMENT-

Dissolution rate enhancement is that mechanism which release from solid dispersion. In solid dispersion system, the increase in drug dissolution rate can be recognized to a number of factors like particle size, crystalline or polymorphic forms and testability of drug. The main significant reasons for improvements in dissolution from these systems are as follows:

- **Reduction of Particle Size:-**
  - Particle size is reduced in solid solution and amorphous precipitation.
  - It may be enhanced dissolution rate due to increase in the surface area.
  - It is explain that the presentation of particles to dissolution medium as physically break up may reduced aggregation.
- **Solubilization Effect:-**

- Carrier material has dissolved; it may be a solubilization effect on the drug.
- Solubility and dissolution enhancement of poorly soluble drug is connected to the ability of carrier matrix to improved local drug solubility as well as wettability [9].

❖ **Wettability and Dispersibility:-**

- Carrier materials can enhancing effect on the wettability and dispersibility of the drug due to the use of surfactant, which reduced interfacial between hydrophilic drug element and aqueous solvent segment.
- Both are rising the effective surface area exposed to the dissolution medium.
- They hold up agglomeration of particles, which can decrease the dissolution rate.

❖ **Conversion of Polymorphic Nature of Solute:-**

- A molecule is necessary to transfer for energy state from crystal lattice.
- Non-crystalline (amorphous) solid is lower than pure crystalline solid.
- Amorphous state shows elevated dissolution rate than crystalline solid solution.
- Reduced lattice energy can result in faster dissolution rate and better stability [10].

SELECTION OF CARRIER

Selection of carrier is most important steps in the formulation and development of solid dispersion. A material consists following individuality to a suitable carrier for increasing dissolution rate:

- ❖ Intrinsic rapid dissolution properties and freely water soluble.
- ❖ Non-toxic character and pharmacologically inertness.
- ❖ Thermal stability is consider with low melting point for melt method.
- ❖ Solubility should exceed through vitreous state for solvent evaporation method.
- ❖ It is ability to increase the aqueous solubility of the drug [11].

METHODS FOR PREPARING SOLID SOLUTIONS

❖ **Kneading Technique:-**

- In this technique, water is used to permeate from carrier and changed to a paste.
- Then drug is added completely and kneaded for particular time.
- Then kneaded mixture is dried and accepted through specific sieve if necessary.
- Solvent evaporation method was proceed.

- organic solvent is used to dissolve both drug and carrier.
- After dissolution, complete solvent is evaporated.
- The solid mass is settled down, sieved and dried. E.g. Solid dispersion of furosemide was prepared by solvent evaporation method.[12]

❖ **Melting Method:-**

- Drug and carrier are mixed together by using mortar and pestle.
- After sometime, a homogenous mixture is found and then the mixture is heated at eject melting point. It is permitted to cool and congealed mass is prepared.
- The mass is crushed and sieved [13].

❖ **Spray-Drying Method:**

- Drug is dissolved in solvent form and specific quantity of carrier is dissolved in water.
- Both solution are mixed with sonication method.
- A suitable method is produce clear solution.
- Spray dryer is use to spray the solution [14].

POLYMERS USED IN SOLID DISPERSIONS-

A selection of polymers is used as carriers for different formulation of solid dispersion.

Some polymers are used in solid dispersions as follows:

A) Polyethylene Glycols (PEG):-

The term polyethylene glycols is those polymers which are obtained by reacting ethylene glycol with ethylene oxide. In this manufacture of solid dispersion, molecular weight of 1500-20,000 is more preferable.[15]

B) Polyvinyl Pyrrolidone (PVP):-

PVP have molecular weights between 10,000 to 700,000. It is easily soluble in Solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not suitable for preparation of solid dispersions prepared by melt metod.[16]

C) Cyclodextrins:

Cyclodextrins are mainly used to improve solubility, chemical protection, taste masking and improved handling by the exchange of liquids into solids by entrapment of hydrophobic solute in hydrophilic cavity of CD. [17]

D) Phospholipids: Phospholipids are main important structural components of cell membranes. Phosphotidylcholine was isolated from egg yolk and brain. In phosphatidyl ethanolamine and phosphatidyl serine, the choline moiety can replace by ethanolamine and serine respectively. [18]

Conclusion- Knowledge with solid dispersions over the last few decades indicates that this is very productive approach for improving the release rate and oral bioavailability of hydrophobic drugs. The improvements in the manufacturing techniques for solid dispersion have been made in the last few years.

Another advantage of solid dispersions over other approaches is that many of the carriers that can be applied are extensively used in the pharmaceutical industry as excipients, no toxicity studies are required.

ACKNOWLEDGEMENT- Authors would like to thanks **Department of pharmacy, Shri JJT University, Rajasthan**, Department of pharmacy, Teerthanker Mahaveer University, Moradabad and Department of Quality assurance, Bacfo Pharmaceuticals Pvt. Ltd., Noida for providing necessary guidance and facilities during manuscript preparations.

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