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Review Article

SOLID DISPERSION: ITS TYPES AND MECHANISM OF ENHANCEMENT OF SOLUBILITY BY SOLID DISPERSION

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ABSTRACT

To improve dissolution of poorly water-soluble drugs and thus enhancing their bioavailability, the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state is used. This process is known as solid dispersion. It has engrossed significant interest as an efficient means of improving the dissolution rate. It happens due to dispersions of poorly water-soluble drugs with water-soluble carriers. The one of the most challenging aspects in formulation development is solubility behaviour of drugs. The number of poor water soluble compounds has radically increased. Compared to conventional formulations such as tablets or capsules, solid dispersions prepared by various methods can be used which have many benefits over the above conventional dosage form. For the preparation of solid dispersions, few of the aspects are to be considered such as; selection of carrier and methods of physicochemical characterization. In this review, an emphasis is put on solubility, various types of solid dispersions, BCS classification, carriers, solid dispersion techniques, mechanism to enhance dissolution in solid dispersion, characterization, advantages, disadvantages and the application of the solid dispersions.

KEYWORDS: *Solubility, Solid Dispersion, Carrier, Bioavailability.*

INTRODUCTION

The simplest and easiest way of administering drugs is through oral route. Over other types of dosage forms the oral dosage forms have many advantages like accurate dosage, less bulk, greater stability and easy production is possible. At present, to the formulation scientists in the pharmaceutical industry one of the most major challenges is formulation of poorly soluble compounds for oral delivery. Nearly 40% of identified potential new drug by pharmaceutical industry are poorly water soluble. Poor water soluble compounds. Large dose is required to produce desirable effect for the poor water soluble drug because they show decreased release rate and poor bioavailability but large dose may leads to toxicity of the drug. So the best option for increasing release rate is improvement of the solubility through formulation approaches [1].

When aqueous solubility of a drug is less than 100µg/ml, Poor dissolution: Intrinsic dissolution rate <0.1mg/cm2/min, High molecular weight: (>500), Self association and aggregation and high crystal energy (melting point >200°C is said to be poorly soluble [1].

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Factor Affecting Drug Absorption: [2]

Pharmaceutical factors: It includes physiological properties of drug substances and formulation factors. Physicochemical properties of drug substances.

- Drug solubility & dissolution rate
- Particles size & effective surface area
- Polymorphism
- Solvates & hydrates
- Salt form of drug
- Ionization state
- Drug pka & lipophilicity

Formulation Factors:

- Disintegration time
- Manufacturing variables
  - Method of granulation
  - Compression force
- Nature & type of dosage form
- Pharmaceutical ingredients
- Product age & storage conditions

Patient related factors i.e., physiological factors:

Membrane physiology:

- Nature of cell membrane
- Transport processes

Gastro-Intestinal motility:

- Gastric emptying rate
- Intestinal motility
- Drug stability in GIT
- pH of GIT
- Surface area of GIT
- Intestinal transit
- Blood flow to GIT.
- Effect of food

Solubility:

The solubility of substance is the amount that has passed into solution when equilibrium is attained between the solution and excess, *i.e.*, undissolved substance, at a given temperature and pressure. The substance to be dissolved is called as 'solute' and the dissolving fluid in which the solute is dissolved is called as 'solvent', which together form a 'solution'. Definition of different solubility terms is given in table1.

Table No. 1: Definition of different solubility terms [3]

Description forms (solubility definition)	Parts of solvent required for one part of solute	Solubility range (mg/ml)	Solubility assigned (mg/ml)
Very soluble (VS)	<1	>1000	1000
Freely soluble (FS)	1 to 10	100 -1000	100
Soluble	10-30	33-100	33
Sparingly soluble (SPS)	30-100	10-33	10
Slightly soluble (SS)	100-1000	1-10	1
Very slightly soluble (VSS)	1000-10000	0.1-1	0.1
Practically insoluble (PI)	>10000	<0.1	0.01

Techniques/Approaches for Solubility Enhancement of Poorly Soluble Drug: [4]

The techniques/approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general includes [5].

Chemical Modifications:

- Salt Formation
- Co-crystallization
- Co-solvency
- Hydrotropic
- Solubilizing agent
- Nanotechnology

Physical Modifications:

- Particle size reduction
- Modification of the crystal habit
- Complexation
- Solubilization by surfactants
- Drug dispersion in carriers i.e., Solid dispersions

Others:

- Supercritical fluid method
- Spray freezing into liquid and Lyophillization
- Evaporative precipitation into aqueous solution
- Hot melt extrusion
- Electrostatic spinning method
- Direct capsule filling
- Polymeric Alteration
- High- Pressure Homogenization
- Inclusion Complexes

Biopharmaceutical Classification System (BCS): The BCS was first devised in 1995 by Amidon and his co-workers. According to the BCS, drug substances can be classified as given in Table 2:

Table No. 2: Classification of drugs as per BCS system [1, 4]

Class I	**High Solubility, High Permeability**
Class II	Low Solubility, High Permeability
Class III	High Solubility, Low Permeability
Class IV	Low Solubility, Low Permeability

By increasing the solubility and dissolution rate of the class II drug in the gastro-intestinal fluids the bioavailability may be enhanced. Particularly for drugs with low gastrointestinal solubility drug release is a crucial and limiting step for oral drug bioavailability. It is possible to enhance their bioavailability and reduce side effects, by improving the drug release profile of these drug [1, 4].

Model list of Essential Medicines of the World Health Organization (WHO) has assigned BCS classification on the basis of data available in the public domain. Orally administered drugs out of 130 on the WHO list, 61 could be classified with certainty.

84% of these drugs belong to class I, 17% to class II, 39% to class III and 10% to class IV. The class II & class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility. Thus, a greater understanding of dissolution and absorption behaviour of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products [6].

Solid Dispersions:

Solid dispersion is process in which one or more active ingredients in an inert carrier or matrix at solid state are prepared by using different methods such as the melting (fusion), solvent evaporation and melting-solvent method. In a solid diluent or diluents the dispersion of a drug or drugs by traditional mechanical mixing is not included in this category. The solid dispersions may also be called solid-state dispersions [7].

Types of Solid Dispersions:

1. On the basis of carrier used [8]
2. On the basis of their molecular arrangement [9]

On the basis of carrier used: On the basis of carrier used solid dispersions can be classified into three generations:

First generation: Using crystalline carriers such as urea and sugars, first generation solid dispersions were prepared which were the first carriers to be employed in solid dispersions. They have the demerits of forming crystalline solid dispersions and did not release the drug as quickly as amorphous ones.

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 products based polymers such as hydroxylpropylmethyl-cellulose (HPMC), ethyl cellulose, and hydroxypropylcellulose or starch derivatives like cyclodextrins.

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.

On the basis of their molecular arrangement: Solid dispersions can be classified in following types:

Eutectics Systems: This mixture consists of two compounds which in the liquid state are completely miscible but in the solid state only to a very limited extent. By rapid solidification of the fused melt of two components these are prepared and that show complete liquid miscibility and minor solid-solid solubility as shown in Fig.1 [10].

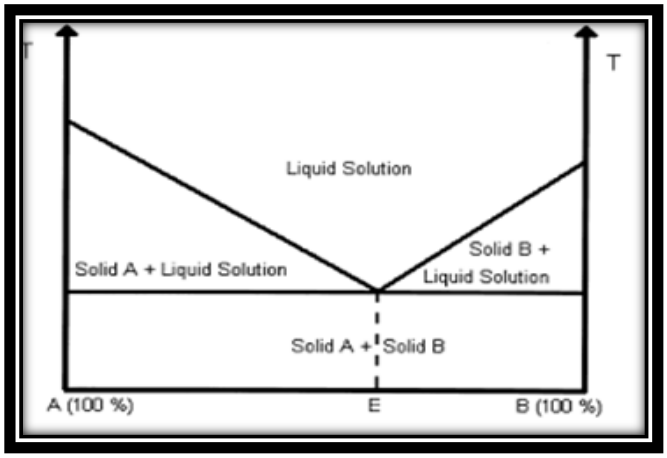

Fig. 1: Phase diagram of an Eutectic System

Thermodynamically, such a system is an intimately blended physical mixture of two crystalline components. When the mixture of A and B with a fix composition is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. When a mixture containing slightly soluble drug and carrier as an inert substance and highly water soluble is dissolved in an aqueous medium, the carrier will dissolve fast, releasing very fine crystals of the drug [4].

Amorphous precipitation in a crystalline carrier:

In the crystalline carrier the drug may also precipitate in an amorphous form instead of simultaneous crystallization of the drug and the carrier (eutectic system). The amorphous solid state is shown in Fig. 2. The high energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug [4].

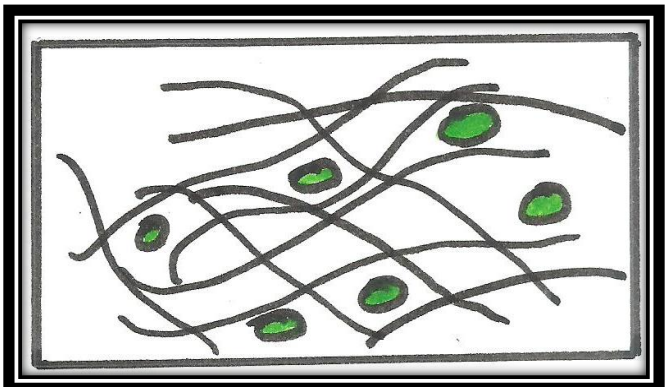

Fig. 2: Amorphous solid solution

Glass solutions and suspensions:

These are the homogeneous glassy system in which solute is dissolved in glass carrier. Glass suspensions are mixtures in which precipitated particles are suspended in glass solvent. Lattice energy is much lower in glass solutions and suspensions. Melting points of glasses is not sharp while they soften progressively on heating. Examples of carriers that form glass solutions and suspensions are citric acid, PVP, urea, PEG, sugars such as dextrose, sucrose, and galactose [10].

Solid Solutions:

In this system a homogeneous one phase system is formed when the two components crystallize together. The particle size of the drug is reduced to its molecular size in the solid solution. Thus, a faster dissolution rate is achieved in a solid solution than the corresponding eutectic mixture. Solid solutions can be classified as continuous or discontinuous according to the extent of miscibility of the two components. In continuous solid solutions, the two component are miscible in the solid state in all proportions [11].

Continuous Solid Solutions:

The components are miscible in all proportions in a continuous solid solution. Hypothetically, this means that stronger the bonding strength between the two components than the bonding strength between the molecules of each of the individual components [12].

Discontinuous Solid Dispersions: [2]

The solubility of each of the components in the other component is limited in the case of discontinuous solid solutions. A typical phase diagram (Fig.3) shows the regions of true solid solutions. One of the solid components is completely dissolved in the other solid component in these regions. The mutual solubility's of the two components start to decrease below a certain temperature. Goldberg reported that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.

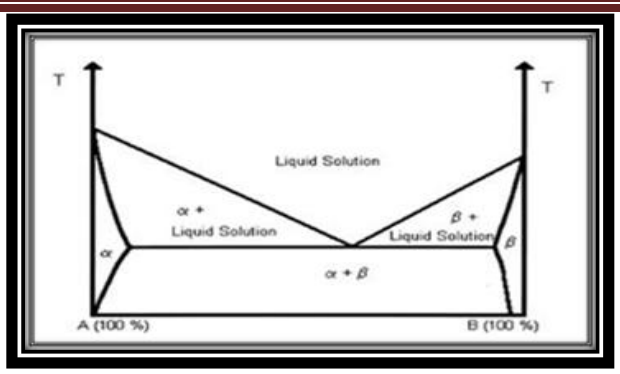

Fig. 3: Phase Diagram for Discontinuous solution

The solid solutions are classified as substitutional or interstitial according to the criterion of molecular size of the two components.

Substitutional crystalline solid solutions:

A substitutional crystalline solid dispersion is depicted in Fig. 4 in which the solute molecules substitute for the solvent molecules in the crystal lattice. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules. [2,10]

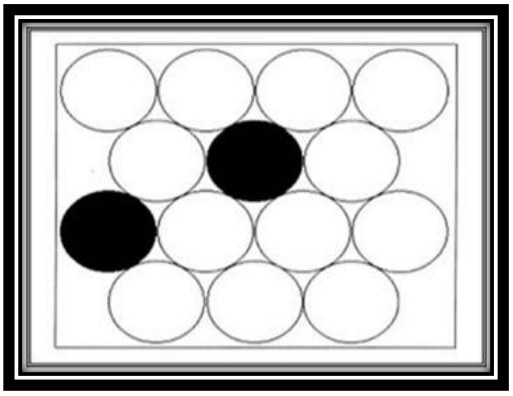

Fig. 4: Substitutional crystalline solid solution

Interstitial Crystalline Solid Solution: [2, 10]

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent in the crystal lattice as shown in Fig.5. The solute molecules should have a molecular diameter that is no greater than 0.59 times than that of the solvent molecular diameter and the volume of the solute molecules should be less than 20% of the solvent.

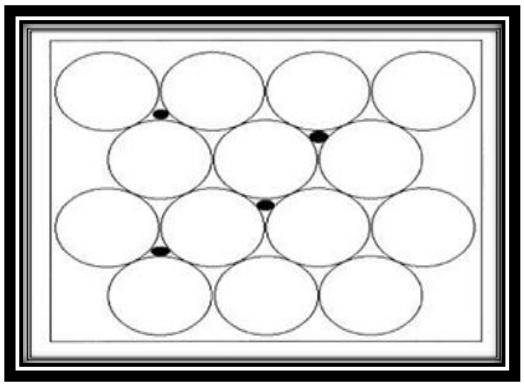

Fig. 5: Interstitinal Crystalline solid solution

Mechanism of Enhanced Dissolution in Solid Dispersion: [1, 2]

A number of factors may influence or increase the dissolution rate for solid dispersion. These factors include the following:-

Reduced Particle size or Reduced Agglomeration:

Both are related to reduction of particle size and increase in the exposed surface area of the drug. Size reduction has been considered to be result of eutectic or solid solution formation. It has also been suggested that to the dissolution medium as physically separate entities the presentation of particles may reduce aggregation. For solid dispersion many of the carriers used may have some wetting properties and may lead to reduce agglomeration and increase surface area by improved wetting.

Increased solubility or Dissolution rate of the drug:

The solubility of the drug may increase by using many of the carriers. Therefore carrier controlled the release of drug that is controlled by the carrier and is independent of drug properties. Secondly some system show release behaviour that is dependent on the properties of the drug rather than polymer.

From crystalline to amorphous state transformation/ Formation of high Energy State:

Amorphous drugs have the higher energy state, minimum stability and can be considered as cooled liquids. The energy required to transfer a molecule from crystal is greater than required for non-crystalline (amorphous) solid so they have grater aqueous solubility than crystalline forms. For example the solubility of amorphous state of novobiocin is 10 times more than crystalline form.

Wetting:

The liquid forms a film over the surface of the solid when a strong affinity exists between a liquid and solid. When this affinity is non-existent or weak the liquid has difficulty dispensing the air and there exist an angle of contact between the liquid and the solid. This contact angle results from an equilibrium involving three interfacial tensions [13].

Techniques for Solid Dispersions: [1]

Various methods of preparation solid dispersions are summarized as:

- Solvent evaporation
- Hot-melt extrusion
- Fusion method
- Solvent melt method
- Kneading technique
- Inclusion complexes
- Direct capsule filling
- Surface active carriers
- Particle size reduction
- Adsorption on insoluble carriers/fluidized bed system
- Solid deposition on super disintegrants
- Melt agglomeration method
- Dropping method

Advantages of Solid Dispersion: [2, 4]

The solid dispersions technique offers the following pharmaceutical advantages.

- Solid dispersion technique is useful to enhance solubility and bioavailability of poorly water soluble drugs.
- It is easier to produce and is more applicable
- It leads to increase in extent and rate absorption of a drug, hence rapid dissolution rate occurs.

- Transformation of liquid form of drug into solid form.
- Control of various parameters like molecular weight, composition, particle porosity and wettability can enhance the bioavailability of poorly water soluble drugs.
- It is easier to produce rapid disintegration oral tablets by solid dispersion.
- It is used to mask the bitter taste of drug.
- It is used to improve porosity of drug.

Disadvantage of Solid Dispersion: [2, 4]

The disadvantages of solid dispersion are enlisted below:

- It leads to the poor scale-up for the purpose of manufacturing.
- The polymers used in solid dispersion can absorb moisture and cause phase-separation, crystal growth and convert amorphous form into crystalline form. Thus result in decrease solubility and dissolution rate.
- It is laborious method of preparation.
- It causes reproducibility of physicochemical characteristics.

Applications Of The Solid Dispersion: [12, 13]

- The Solid dispersion systems were shown to provide the bio available oral dosage forms for the anti-cancer drugs, which could be substituted for the standard injections to improve the patient compliance & comfort.
- Solid dispersion also act as the functional carriers that offer the added benefit of the targeting the release of the highly soluble forms of the poorly water soluble drugs for absorption to an optimum site.
- The solid dispersion systems were also found to reduce the food effects on the drug absorption, thus by increasing the convenience of the drug therapy as it is the need for some drugs to be taken with food was eliminated.
- The solid dispersion formulations were demonstrated to accelerate the onset of action for the drugs such as NSAIDS [non-steroidal anti-inflammatory drugs] where immediate action is crucial in relieving acute pain and inflammation.
- The improved absorption efficiency was demonstrated for the solid dispersion systems that allows for the reduction in the content of the active agent per dose thus it decreases the cost associated with these drug therapies.
- The dry powder formulation consisting of the solid dispersion for use as inhalation is prepared in improving the immunosuppressive therapy in the lung transplant patients. Many problems can be avoided which includes use of local anaesthesia & irritating solvents. [14]

Limitations of Solid Dispersions:

- Laborious and expensive methods of preparation.
- Reproducibility of physicochemical characteristics.
- Difficulty in incorporating into formulation of dosage forms.
- Scale-up of manufacturing process.
- Stability of the drug and vehicle [8].

Selection of A Carrier:

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug. Materials used as carrier are given in table 2.

Table No. 2: Different carriers used in solid dispersion [6]

S. No.	Category	Carriers
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose
2	Acids	Citric acid, succinic acid
3	Polymeric materials	Polyvinyl pyrrolidine (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragitL100, eudragit E100, eudragit RL, eudragit RS
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans
6	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins

- Freely water-soluble with intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert.
- Heat stable with a low melting point for the melt method.
- Soluble in a variety of solvents.
- Able to preferably increase the aqueous solubility of the drug and
- Chemically compatible with the drug and not form a strongly bonded complex with the drug [15].

Generations of Carriers: [4, 15]

First generation carriers:

Example: Crystalline carriers: Urea, Sugars, Organic acids.

Second generation carriers:

Example: Fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins.

Third generation carriers:

Example: Surface active self emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14 [4].

Selection of Solvents: [15]

Solvent to be included for the formulation of solid dispersion should have the following criteria:

- Both drug and carrier must be dissolved.
- Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
- Ethanol can be used as alternative as it is less toxic.
- Water based systems are preferred.
- Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration.

Common solvents used are given in table 3.

Table No. 3: Different solvents used in solid dispersions [15]

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

Characterization:

Solid dispersion is characterised by using different techniques such as; Differential Scanning Calorimetry, Differential Thermal Analysis, Thermo-Microscopic Methods, X-ray Diffraction, Fourier Transform Infra Red Spectroscopy (FT-IR), Scanning Electron Microscopy (SEM) and dissolution studies.

Different techniques are:

Differential Scanning Calorimetry (DSC):

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

Differential Thermal Analysis (DTA):

In differential thermal analysis, the difference in temperature between the sample and a thermally inert reference material is measured as a function of temperature. With a corresponding deviation of sample temperature from that of the reference any transition that the sample undergoes results in liberation or absorption of energy by the sample. Whether the transition temperature is exothermic or endothermic is shown by plot of the differential temperature versus the programmed temperature. In constructing phase diagram of high reproducibility; a higher temperature range is permitted, greater resolution obtained is the main advantage of this technique. A sample size of less than 1 mg can be used [7].

Thermo-Microscopic Methods:

In this method to study the phase diagrams of binary systems hot stage microscope is used. The physical mixture or dispersion (approx1 mg) on a slide is heated at the rate of 1-5^{o}C per minute. The thaw and melting points are then recorded by visual observation. This method requires only a small amount of sample but it is limited to thermally stable compounds only. To characterize diflunisal-PEG solid dispersion this technique has been used [15].

X-ray Diffraction:

The X-Ray diffraction method is a very important and efficient tool in studying the physical nature of solid dispersions. Recently, it was used to study binary eutectic systems. The diffraction method is also particularly valuable in detecting compound or complex formation since its spectra or lattice parameters are markedly different from those of pure components. The biggest drawback of using the diffraction method to study dispersion systems is its frequent inability to differentiate amorphous precipitation from molecular dispersion if the lattice parameter of the solvent component is not changed [16].

Dissolution Studies:

Dissolution study is carried out to determine the rate and extent of dissolution. The dissolution study of solid dispersion was performed on the USP- type II paddle apparatus at 37±0.2^{0}C. Drug was dispersed in medium. Sample was taken time to time, filtered and analyzed for drug contents by measuring the absorbance at suitable wavelength using UV visible Spectrophotometer [16, 17].

Fourier Transform Infra Red Spectroscopy (FT-IR):

FT-IR spectroscopy can be employed to find the possible interactions between the drug and the carrier in the solid state on FT-IR spectrophotometer by the conventional KBr pellet method [17].

Scanning Electron Microscopy (SEM):

SEM is useful in ascertaining the morphology, particle size of solid particles and sometimes polymorphism of drugThe fine dispersion of drug particles in the carrier matrix may be visualized. The application of the electron microscope technique, however usually limited to chemicals with high resolution [18, 19].

CONCLUSION

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling. Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

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