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Review Article

Solid Dispersion: A Tool to enhance solubility of Poorly Water Soluble Drugs

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ABSTRACT

Solid dispersions have been used to increase the dissolution rates of poorly water soluble drugs. Many methods are used to prepare solid dispersions. This paper reports various solubility enhancement strategies in solid dispersion. The methods described are fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration process, spray drying technology, use of surfactant. The paper also shows study of characterization, selection of carriers, potential applications and limitations of these methods in solid dispersion.

Keywords: Solid Dispersion, solubility, Enhancement of Solubility, Selection

INTRODUCTION

When a drug is administered per orally in a solid dosage form such as tablets, capsules, it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. The bioavailability of many poorly water soluble drugs is limited by their dissolution rates. [1] An ideal dosage regiment in drug therapy of any disease is the one that attain desired bioavailability. Bioavailability may be defined as the rate and extend of drug absorption into the systemic circulation. [3] A drug with poor bioavailability is the one with

1. Poor aqueous solubility and slow dissolution rate in the biological fluids.
2. Poor stability of the dissolved drug at the physiological pH.
3. Inadequate partition coefficient and thus poor permeation through the biomembrane.
4. Extensive presystematic metabolism.

Three approaches in overcoming the bioavailability problems due to such causes are[2]

1. The pharmaceutics approach which involves **modification** of formulation, manufacturing process, or the physiochemical properties of the drug without changing the chemical structure.
2. The pharmacokinetic approaches in which the **pharmacokinetics** of the drug is altered by the modifying its chemical structure.
3. The biological approach whereby the route of the drug administration may be changed such as changing from oral to parenteral route. [3]

The second approach of chemical modification has a number of drawbacks of being very expensive and time consuming, require repetition of clinical study and long time for regulatory aspects. The attempts ,whether optimizing the formulation ,manufacturing process , or physiochemical properties of the drug , are mainly aimed at enhancement of dissolution rate as it is the major rate limiting step in the absorption of the most drugs.

The poor solubility of drug substances in water leads to low dissolution rate and thus to insufficient bioavailability.

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The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. In the other words the solubility can also define as the ability of one substance to form a solution with another substance[1]. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water.

There are several possibilities to enhance the solubility and dissolution rate like micronization, alteration in drug pH , Solid dispersion etc. [1, 2, 3,4].

METHOD FOR ENHANCEMENT OF SOLUBILITY AND BIOAVAILABILITY

There are various method by which the dissolution rate hence solubility of the drug can be enhanced. These are

Micronization [4]

The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of air attrition method. Examples of drug whose bioavailability have been increased by micronization include griseofulvin and several steroidal and sulfa drugs. [4]

Disadvantage: Micronization has several disadvantages; the most important disadvantage is limited opportunity to control important characters of final particles such as size, shape, morphology. Beside this micronization is a high energy process which causes disruptions in drug's crystal lattice. [3]

Use of surfactants [3, 4]

The surface active agents enhance dissolution rate primarily by promoting wetting and permeation of dissolution fluid into the solid drug particles. They are generally used in concentration below their critical micelle concentration (CMC) values since above CMC the drug entrapped in the micelle structure fails to partition in the dissolution fluid. Non ionic surfactant like polysorbates is widely used. Examples of drug whose bioavailability have been increased by use of surfactants in the formulation include steroids like spironolactone. [3]

Use of salt forms [4]

Salts have improved solubility and dissolution characteristics in comparison to the original drugs. Alkali metal salts of acidic drugs like penicillin and strong acid salts of basic drugs like atropine are more water soluble than parent drug. [4]

Disadvantage:

All poorly water soluble drugs are not suitable for improving their solubility by salt formation method.

Alteration in pH of drug microenvironment [4]

A majority of drugs are suffers from solubility problem. The aqueous solubility of such drugs can be increased by adjusting the pH. An increase in the pH the dissolution rate and solubility can be increase.

This can be achieved in two ways

a) in situ salt formation

b) addition of buffers to the formulation

e.g. buffered aspirin tablets [4]

Use of metastable polymorphs [5]

Polymorphism describes the existence of a drug in two or more crystalline form, each of which possesses a different space lattice arrangement but is chemically identical. There are two types of polymer

1. Enantiomeric polymorph is the one which can be reversibly changed into another form by altering the temperature or pressure

2. Monomeric polymorph, which is unstable at all temperature and pressure.

Metastable polymorphs is more soluble than the stable polymorph of a drug that exhibits polymorphism

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e.g. B form of chloramphenicol palmitate is more water soluble than the A and the C forms. [5,6]

Solute-solvent complexation [5]

Solvates of the drugs with organic solvents generally have higher aqueous solubility than their respective hydrates of the original drugs. Much higher solubility can be attained by freeze drying such a solute in solution with an organic solvent with which it is known to form a solvate .Such a process results in a powder of particles of submicron size

e.g. 1:2 griseofulvin benzene solvate . Care should take that solvent is nontoxic. [5]

Solvent deposition [4]

In this method, the poorly aqueous soluble drug such as nifedipin is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose by evaporation of solvent.

Selective adsorption on insoluble carriers [4]

A highly active adsorbent such as the inorganic clay like bentonite can enhance the dissolution rate of poorly water soluble drugs like indomethacin, griseofulvin and prednisone by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clays are – the weak physical bonding between the adsorbate and the adsorbent, and hydration and swelling of the clay in the aqueous media. [5]

Solid solution [4]

The three means by which the particle size of a drug can be reduces to submicron level are –

Use of solid solution.

use of eutectic mixtures and

Use of solid dispersions.

A Solid solution is a binary system comprising of a solid solute molecularly dispersed in solid solvent. Since the two components crystallize together in a homogeneous one phase system, solid solution are also called as molecular dispersion or mixed crystals. Because of reduction in particle size to the molecular level, solid solution show greater aqueous solubility and faster dissolution than eutectic and solid dispersions. They are generally prepared by fusion method whereby a physical mixture of a solute and solvent are melted together followed by rapid solidification. Such system, prepared by fusion is often called as melts. e.g. griseofulvin from such solid solution dissolved 6 to 7 times faster than pure griseofulvin. [4]

The mechanism suggested for enhanced solubility and rapid dissolution of molecular dispersion are: [5]

1. When binary mixture is exposed to water, the soluble carrier dissolve rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles and
2. When the solid solution ,which is said to be in a state of randomly arranged solute and solvent molecules in the crystal lattice , is exposed to the dissolution fluid, the soluble carrier dissolved rapidly leaving the insoluble drug stranded at almost molecular level .

Eutectic mixture [4]

These systems are also prepared by fusion method. Eutectic melts differ from solid solution in that the fused melt of solute – solvent show complete miscibility but negligible solid solubility. When the eutectic mixture is exposed to water, the soluble carrier dissolved leaving the drug in a microcrystalline state which solubilizes rapidly.

The method however cannot be applied to:

-drugs which fail to crystallize from the mixed melt,

-thermolabile drugs and

-Carriers such as succinic acid that decompose at their melting point.

Solid dispersion [5, 6]

These are generally prepared by solvent or co-precipitation method whereby both the guest

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solute and the solid carrier solvent are dissolved in a common volatile liquid solvent such as alcohols. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which results in amorphous precipitation of guest in a crystalline carrier. The basic difference between solid dispersion and solid solution is that the drug is precipitated out in an amorphous form in the former as opposed to crystalline form in the latter. The method is suitable for thermolabile substances but has number of disadvantages like

-higher cost of processing
-use of larger quantities of solvent
-Difficulty in complete removal of solvent.

Molecular encapsulation with Cyclodextrine [5]

The beta and gamma cyclodextrine and several of their derivatives are unique in having the ability to form molecular inclusion complex with hydrophilic drugs having poor aqueous solubility. These cyclodextrine molecules are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drugs as guest; the outside of the host molecule is relatively hydrophilic. Thus the molecularly encapsulated drug has greatly improved solubility and dissolution rate. There are several examples of drugs with improved bioavailability due to such a phenomenon –thiazide diuretics, barbiturates, and number of NSAIDs. [5]

A variety of devices have been developed over the years to enhance the drug solubility and dissolution rate. The solid dispersion method is one of the effective approaches to achieve this ideal goal particularly for the drug with poor aqueous solubility in which the drug is incorporated into a water soluble matrix. [6]

SELECTION CRITERIA OF DRUG [7]

The Biopharmaceutics Classification System (BCS) was introduced by the US Food and Drug Administration (FDA) to assess oral drug products. In this system, drugs are classified into four groups based on the ability of a given drug substance to permeate biological membranes and aqueous solubility. A given drug substance is considered 'highly soluble' when the highest dose strength is soluble in 250 ml water or less over a pH range 1 to 7.5, and is considered 'highly permeable' when the extent of absorption in humans is determined to be ≥90% of an administered dose (in solution), based on mass balance or related to an intravenous reference dose. For a rapidly dissolving tablet, ≥85% of the labeled amount of drug substance must dissolve within 30 minutes

According to BCS system, drugs are classified into four groups are as follow. [7]

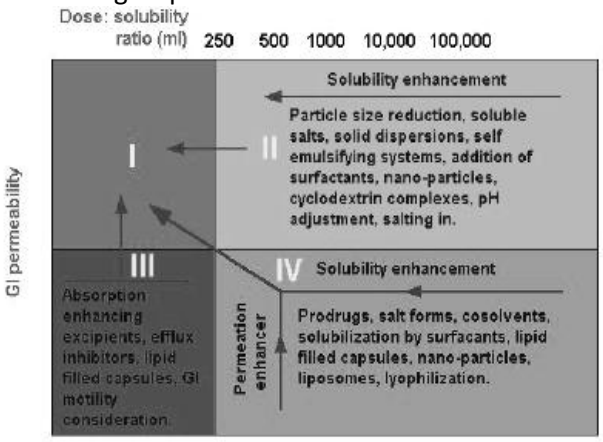

Figure 1: Possibilities of shifting the solubility-dissolution characteristics from a very poorly soluble drug to D: S within the range of values encountered in the human GI tract (D:S >250ml)

Class I consists of highly water-soluble drugs that are well absorbed from the gastrointestinal tract and, in general, have the preferred physicochemical properties. Drugs in Class I have high bioavailability after oral administration.

Class II consists of water-insoluble drugs that, when dissolved, are well absorbed from the gastrointestinal tract. The dissolution rate *in vivo* is usually the rate-limiting step in drug absorption. Commonly, drugs in this class have variable absorption due to the numerous formulation effects and *in vivo* variables that can affect their dissolution profile.

Class III consists of water-soluble drugs that do not permeate biomembranes readily.

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Class IV consists of water-insoluble drugs that, when solubilised, do not penetrate biomembranes readily. Unfortunately, most new chemical entities are water-insoluble lipophilic compounds or, in other words, Class II or even Class IV compounds. It can be quite challenging for a formulation scientist to develop usable pharmaceutical products from such compounds. Recently, a group of complexing agents called 'cyclodextrin' and other water-soluble polymers have been included into the formulators' armamentarium.

The solid dispersion method is one of the effective approaches to achieve this ideal goal particularly for the drug with poor aqueous solubility in which the drug is incorporated into a water soluble matrix.

Today 40% of all new chemical entities suffer from poor aqueous solubility. It is generally recognized that low solubility or dissolution rate often become a rate limiting step in absorption of poorly water soluble drugs from gastro intestinal tract and compromise oral bioavailability . [8]

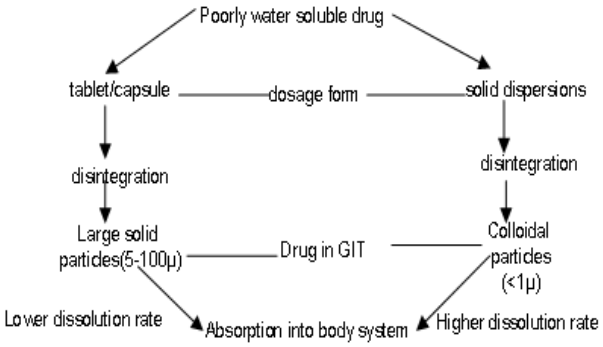
The solubility behavior of drugs remains one of the most challenging aspects in formulation and development. [9] The greater understanding of dissolution and absorption behavior of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products. Although salt formation, particle size reduction etc. have commonly been used to increase the dissolution rate of drug, there are practical limitations with these techniques and the desired bioavailability enhancement may not always be achieved. [10] Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such approach that has been shown significantly enhanced absorption of such drugs is to formulate solid dispersion. Once the solid dispersion is exposed to aqueous media and the carrier gets dissolved, the drug is released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs is expected to be high. Dispersion of drug within an inert carrier in the solid state is known as solid dispersion system. Chiou and Riegelman defined the term solid dispersion as **"a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures"** [10]

Advantages of Solid Dispersion [11]

1. Increase the dissolution of drugs
2. Increase the absorption of drugs
3. Increase in the enhancement of the bioavailability of the poorly water soluble drugs.

SOLID DISPERSION TECHNOLOGY [12,13]

Solid dispersion technology can be used to improve the *in vitro* and *in vivo* dissolution properties of slightly water soluble drugs and to control dissolution rate of slightly water soluble drugs. Solid dispersion is a product formed by converting a fluid drug carrier combination into solid state. Solid dispersion systems have being considered over last 25 years as a means of increasing the solubility, dissolution and absorption of poorly water soluble drugs.



Schematic representation of the bioavailability enhancement of poorly Water soluble drug by solid dispersion technique

Figure 2:

The basic mechanisms responsible for increasing **solubility** of drugs are [12]

• Wetting of drug improved by direct contact of the drug with the hydrophilic matrix.

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- Polymorphic forms
- Reduced particle size or particle agglomeration
- Formation of higher energy states
- Formation of amorphous states – the drug has higher energy in the amorphous state than crystalline state, through which the saturation concentration is increased.
- Soluble complex formation in microenvironment
- Super saturation phenomenon – the saturation concentration around small particle is higher than around particles.

The concept of solid dispersion was introduced by Seguchi and Obi [13] in 1961as a practical method for solubility and bioavailability enhancement of poorly water soluble drugs. This method involved the formulation of eutectic mixtures of drugs with water soluble carriers by the melting of their physical mixtures. [13]

The mechanism suggested for enhanced solubility and rapid dissolution of dispersion is when the dispersion is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles. For conventional capsules and tablets, the dissolution rate is limited by size of primary particles formed after the disintegration of dosage form. In this case an average particle size of 5um is usually the lower limit, although higher particle size is preferred for ease of handling, formulation and manufacturing. On the other hand, if a solid dispersion is used, a portion of drug dissolves immediately to saturate the gastrointestinal fluid and excess drug precipitates out as colloidal particles or oily globules of submicron size. Because of such early promises in bioavailability enhancement of poorly water-soluble drugs, solid dispersion has become one of the most active areas of research in pharmaceutical field. [13]

Method of Preparation of Solid Dispersion [14, 15]

Two basic methods are used to prepare solid dispersions

A) Melting (fusion) method.

B) Solvent evaporation method.

A) Melting (fusion) method [14]

The drug and carrier should be miscible in the molten state is the basic requirement of this method. In this method physical mixture of drug and carrier is heated directly until it melts. The molten mixture is then cooled and solidified rapidly in an ice bath. The resulting solid mass is then crushed, pulverized and sieved. The technique was first used by Seguchi and Obi who prepared sulphathiazole–urea solid dispersion.[14] The basic reason for increase in solubility is that, as the melt is rapidly quenched there is supersaturation of the drug where the drug molecules are arrested in solvent matrix by instantaneous solidification, usually rapid solidification is achieved by cooling on stainless-steel plates as it favors rapid heat loss.

The disadvantages of this method are

1) Decomposition of either drug or carrier during heating at high temperature.

2) Evaporation of drug or carrier which are volatile.

3) Thermal instability and immiscibility.

However, various modifications are being done in the basic process due to the thermal instability and immiscibility. They are-

Spray drying technique [15]

Spray congealing of melt from a modified spray drier onto cold metal surfaces and is used for dispersions containing mannitol and phenylbutazone. The manufacture of milk powder was one of the first applications of spray drying when the method was developed in 1920. Today, spray drying finds great utility in pharmaceutical industry because of the rapid drying and specific characteristics such as particle size and shape of the final product. In addition, it is simple and cost effective, as it is 30-50 times less expensive than freeze-drying. It is an established method that is initiated by

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atomizing suspensions or solutions into fine droplets followed by a drying process, resulting solid particles. The process allows production of fine, dust free powder as well as agglomerated one to precise specifications. The operating conditions and dryer design depends upon the drying characteristics of the product and require powder specifications.

Hot melt extrusion [14, 15]

Drug carrier mix is typically processed with twin–screw extruder; the drug carrier mix is simultaneously melted, homogenized, extruded and shaped as tablets, granules, pellets, sheets or powders. Advantage of this method is Drug carrier mix is subjected to an elevated temperature for about 1 minute which enables drug that are somewhat thermo labile to be processed. **Fig.3** [15]

This method has already been used successfully to prepare Solid Dispersion of itraconazole and hydroxypropylmethylcellulose (HPMC) , indomethacin , lacidipine , nefidipine , piroxicam, tobutamide and polyvinylpyrrolidone (PVP) , itraconazole and HPMC , Eudragit E 100 or a mixture of Eudragit E 100-PVP vinyl acetate to improve solubility and dissolution rate of poor water soluble drugs. [18]

Disadvantage

High shear forces resulting in high local temperature in extruder may be a problem for heat sensitive materials.

Hot spin melting [15]

Drug and carrier are melted together over an extremely short time in a high speed mixer and in the same apparatus, dispersed in air or inert gas in a Cooling tower.

Example - Testosterone, Progesterone and dienogest

Fusion-solvent method

In this method small quantity of organic solvent is used to dissolve the drug, the solution is added to molten carrier and resulting solution is evaporated to dryness.

2) Solvent method [16]

In this method both the guest molecule and the carrier are dissolved in common organic solvent followed by total removal of solvent to constant weight. Ta Chibani and Nakumara were the first to prepare dispersion of beta-carotene and PVP by this method [16] the evaporation method was then taken up by Myerson and Gibaldi, by dissolving both

Griseofulvin and PVP in chloroform and then evaporating the solvent they were able to achieve a solid dispersion, the release rate of griseofulvin from solid dispersion was 11 times higher than that of micronized drug. [16] Temperature for solvent evaporation is usually in range of 23-65ºC. The solvent can also be removed by freeze drying or by spray drying. This method is suitable for thermolabile materials.

An important prerequisite for the manufacture of solid dispersion using solvent method is that both the drug and the carrier should be sufficiently soluble in the solvent

Disadvantages of solvent method [16]

1. High cost of processing
2. Large quantity of solvent required
3. Difficulty in complete removal of solvents
4. Possible adverse effect of remaining solvent on stability of drug
5. Selection of volatile common solvent.
6. Difficulty of reproducibility of crystal forms

3) Lyophillization Technique [15]

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophillization 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. G.V.Betageri et al, Yalcin Topalogh et al, M E Badry et al and M Fathy have successfully investigated the potential

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applications of lyophilization in manufacturing of Solid Dispersion. [15]

4) Melt Agglomeration Process [17, 18]

This technique has been used to prepare solid dispersion, wherein the binder acts as a carrier. In addition, solid dispersion are prepared either by heating binder, drug and
excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of Solid Dispersion by melt agglomeration. Since these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. [17] In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particle.

POLYMERS USED IN SOLID DISPERSION [19]

Two main polymers have been used in solid dispersion method notably, polyethylene glycol (PEG) and polyvinylpyrolidone (PVP).

Polyethylene Glycol [19]

The term polyethylene glycol essentially refers to compounds that are obtained by reacting ethylene glycol with ethylene oxide. Their molecular weights range form 200 to 300,000. Polyethylene Glycols whose molecular weights are above 300,000 are commonly termed polyethylene oxides. Polyethylene glycols of molecular weights between 200 to 600 are clear. Viscous liquid at room temperature whereas those between 900 to 8,000 white, waxy solids. As the molecular weight increases, the water solubility decreases. In the preparation of solid dispersions, low molecular weight polymers of this
Compounds are used. Polymers of molecular eights ranging from 200 to 20,000 have been used extensively. It would be expected that the effect of molecular weight of the effect of molecular weight of the PEG on the rate of dissolution and solubility would increase of decrease in one dilution is influenced by several factors such as the weight fraction of PEG.

Polyvinyl Pyrrolidone [19, 20]

Polyvinylpyrrolidone (PVP) has a mean molecular weight ranging from about 10,000 to 7000,000. it is soluble in various solvents including water, ethanol, chloroform and isopropyl alcohol. PVP melts at a very high temperature, above 270 ^{o}C, where it becomes decomposed. PVP is therefore not suitable for preparation of solid dispersion by the fusion method but only for preparation of solid dispersion by solvent method. Typical molecular of PVP that are used for preparation of solid dispersion are in the range of 10,000 to 70,000.

PROBLEMS ASSOCIATED WITH PROCESSING AND STABILTY OF SOLID DISPERSION SYSTEMS [21]

Destabilization of solid dispersion system results in decreased dissolution rate, due to a number of factors. For example, solid dispersion systems may be destabilized through physical treatment such as pulverization and aging.

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Upon melting a drug and PEG, unpulverizable, sticky, detestable or glassy solids may form after cooling. Pulverization has resulted in the conversion of amorphous drugs in solid dispersion to crystalline forms. Melts containing 5-50% griseofulvin in PEG dispersion immediately after preparation were shown to be amorphous. When the melt was allowed to cool and pulverized, crystallinity was induced in 10-50% griseofulvin dispersion in PEG. Serajuddin et al. avoided the problem of pulverization by encapsulation the solid dispersion directly in hard gelatin capsules by the melt-filling technique. [21] Although crystallization did not occur in the dispersion with the lowest amount of drug, it did occur in the others with the increasing amount of drug.

Aging is the major problem associated with the stability of solid dispersions. Dissolution rates have been shown to decrease with age for a number of solid dispersion formulations. As the dispersion ages, crystallite and crystallite sizes increase leading to an increase in the amount of crystalline drug. An increase in the amount of crystalline drug in turn results in decrease in dissolution rate with age.

CHARACTERIZATION OF SOLID DISPERSIONS [20]

A number of methods have been used to characterize solid dispersions including

(1) Thermal methods of analysis – differential thermal and thermamicroscopial.

(2) Powder x-ray diffraction;

(3) Microscopically studies, including the use of polarized light and the scanning electron microscope.

(4) Spectroscopic methods, especially I.R.

(5) Dissolution rate determination.

(6) Thermodynamic investigations involving determinations of the heats of dissolution, H, and the melting points in order to calculate the resulting changes in entropy.

(7) Dynamic dialysis to characterize the formation of highly supersaturated solutions after dissolution of solid dispersions. [25]

The most important and frequently used methods among these are thermo analytical, powder x-ray diffraction and dissolution rate.

Thermomicroscopical Analysis [20]

This is a visual method of analysis using a polarized microscope with a state to determine the thaw and melting points of solids. Its advantages are the small amount of sample required (virtually one crystal) and direct observation of the changes taking place in the sample through the thaw and melt stages. However, it does not provide the thermodynamics of the melting process and in some instances it is not as sensitive as DTA. The technique has been used by others often to support DTA or DSC measurements.

Differential Thermal Analysis (DTA) [20]

This is an effective thermal method for studying the phase equilibrium of pure substances or solid mixtures. Differential heat changes that accompany physical and chemical changes are recorded as a function of temperature as the substance is heated at uniform rate. In addition to thawing and melting, polymorphic transitions, evaporation, sublimation, desolation, and other types of changes such as decomposition of the sample can be detected. DTA records energy changes occurring in the sample as it is being heated either exothermic or endothermic. However, for the interpretation of DTA thermo grams, prior knowledge of the type of reactions that may be occurring is essential. For instance, it is necessary to know whether the sample is undergoing polymorphic change, decomposition, or the sample is undergoing polymorphic change, decomposition, or desolation, DTA has been used routinely to identify different types of solid dispersion.

It has been shown by Borchardt and Daniels that the total heat of reaction, H, is proportional to the area under the DAT peak as described by, [20]

$$H = K \int \Delta T \, dT = KA$$

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Where, K is proportionality constant, ΔT is the temperature difference, A is area under DTA peak and t is the time.

Powder X Ray Diffraction [20]

X rays have been used in crystal structure studies in two different ways:

1) Single crystal x ray crystallography dealing with the determination of bond angle and inter atomic distance and

2) Powder diffraction dealing with the study of crystal lattice parameter, where the x ray diffraction intensity from a sample is measured as a function of the diffraction angle. Thus change in the diffraction pattern indicates change in the crystal structure. The relationship between the wavelength of the x ray, λ, the angle of diffraction,θ, and the distance between each set of atomic planes of crystal lattice, d, is given by Bragg's equation

$$M\lambda = 2d \sin \theta$$

Where M represents the order of diffraction.

SELECTION OF CARRIERS [21-24]

Since the carrier in the solid dispersion affects the dissolution rate of drug from the surface, the selection of carrier has an ultimate influence on the dissolution characteristics of dispersed drug therefore hydrophilic carrier results in a fast release of drug from dispersion and a poorly soluble or insoluble carrier leads to slower release of drug particles and thereby hampers the drug solution but can be used for sustained release of drug. Usually the carrier forms the bulk of solid dispersions. The commonly used carriers are

Sugars - Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol, Mannitol, Lactose

Acids - Citric acid, Tartaric acid, Succinic acid

Polymeric materials- PVP, PEG, CMC, HPMC, Guargum, Xanthangum, Sodium Alignate, Methylcellulose, Pectin, Hydroxyethylcellulose, Hydroxypropylcellulose,

Cyclodextrin, Galactomannan,

Miscellaneous- Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthines

The carrier presence not only prevents aggregation/agglomeration of individual drug particles exhibiting a high solid liquid interfacial tension but it also creates a microenvironment in which the drug solubility is high.

CONCLUSION

The solubility of drugs is a main factor affecting their dissolution rate and bioavailability of the drugs. Solubility enhancement of these drugs remains one of the most challenging aspects of drug development. Various methods have been developed for enhancing drug solubility and dissolution of the drugs. The solid dispersion method is one of the effective methods of solubility enhancement of poorly water-soluble drugs. Various methods described in this article are successfully used for the preparation of solid dispersion in laboratory.

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