World Journal of Pharmaceutical research

Volume 3, Issue 1, 1841-1860. Review Article ISSN 2277 – 7105

ROLE OF SOLID DISPERSION IN IMPROVING SOLUBILTY AND DISSOLUTION RATE: A COMPREHENSIVE REVIEW

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Article Received on
19 December 2013
Revised on 17 January 2014,
Accepted on 15 February 2014

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ABSTRACT

Poor water solubility is the major drawback for the various types of drugs and many approaches have been introduced for the solubility enhancement of such drugs. Solid dispersions have been known to be one amongst the recent means of improving the dissolution rate by enhancement of solubility, and hence the bioavailability of poorly water soluble drugs. According, to – Chiou and Riegeman Solid dispersions are "The dispersion of one or more active ingredients in an inert carrier or matrix, where the active ingredients could exist in finely crystalline, solubilised or amorphous state." solid dispersion is a very useful method for pharmaceutical point of view because of its capability to solve the solubility problems by using solid dispersion method. The present article reviews the basic concept about solid dispersion, various types of solid dispersion, and criteria of solvent Selection, the methods of preparation, characterization, their advantages, limitations, applications, future prospect and various types of marketed preparations.

Key words: solid dispersion, solubility enhancement, selection of carrier.

INTRODUCTION

Many potential drug candidates are characterized by a low oral bioavailability. Often poor drug dissolution/solubility rather than limited permeation through the epithelia of the gastrointestinal tract are responsible for low oral bioavailability [1]. Thus aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption

and thus the in vivo efficacy. [2] Drugs with low aqueous solubility have low dissolution rates and hence suffer from oral bioavailability problems. [3]

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. [4]

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent as given in table 1. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion [5]. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. [6]

There are various techniques available to improve the solubility of poorly soluble drugs, such Micronization, Nanosuspension, Modification of the crystal habits, Eutectic mixtures, Solid dispersions, Micro emulsions, Self micro emulsifying drug delivery systems, cyclodextrin inclusion and lipid based delivery systems etc. solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. In case of solid dispersion drug disperse in the matrix generally a hydrophilic matrix and a hydrophobic drug, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. [5]

HISTORY

In 1961, the concept of solid dispersion first emerged .Solid Dispersions were proposed to increase the dissolution and oral absorption of poorly-water soluble drugs .As early as in

1961, Sekiguchi et al. developed the concept of solid dispersion of poorly water soluble drugs.

Definition	Definition Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

Therapeutic efficacy of a drug depends on the bioavailability of the drug which in turn depends on the solubility of the drug candidate. For the absorption of the drug at absorption site it must be present in the aqueous state. Thus, the Release of drug is a crucial step for the oral bioavailability of the drug. Basically poorly water soluble drugs with the low gastrointestinal solubility and high permeability (BCS class II) and drugs with low solubility and permeability (BCS class IV) observe the problem of oral solubility and hence bioavailability. Improvement in the release profile of such drugs it is possible to enhance the solubility and thereby the bioavailability of the drug. According to the monograph of European Pharmacopoeia, about 40% of drugs have aqueous solubility of less than 1mg/ml and 32% have an aqueous solubility less than 0.1mg/ml. although aqueous solubility of more than 1% (1g/100ml) does not show any potential. However, the 1% solubility limit is an arbitrary guideline and in no way represents a universal limitation in terms of solubility and absorption relationship. [7, 8]

Definition of Solid Dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. [9]

Advantages of solid dispersion

1] Solid dispersion technique is useful to enhance solubility and bioavailability of poorly water soluble drugs [10].

2] It is easier to produce and is more applicable [11].

3] It leads to increase in extent and rate absorption of a drug, hence rapid dissolution rate occurs.

4] Transformation of liquid form of drug into solid form [12].

5] Control of various parameters like molecular weight, composition, particle porosity and wettability can enhance the bioavailability of poorly water soluble drugs.

6] It is easier to produce rapid disintegration oral tablets by solid dispersion.

7] It is used to mask the bitter taste of drug.

8] It is used to improve porosity of drug [13].

DISADVANTAGE OF SOLID DISPERSION:

The disadvantages of solid dispersion are enlisted below:

1] It leads to the poor scale-up for the purpose of manufacturing [10].

2] 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.

3] It is laborious method of preparation.

4] It causes reproducibility of physicochemical characteristics [14].

Selection of a carrier

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

1. Freely water-soluble with intrinsic rapid dissolution properties.
2. Non-toxic and pharmacologically inert.
3. Heat stable with a low melting point for the melt method.
4. Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
5. Able to preferably increase the aqueous solubility of the drug and
6. Chemically compatible with the drug and not form a strongly bonded complex with the drug. [15, 16]

Solvent

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

1. Both drug and carrier must be dissolved.

2. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
3. Ethanol can be used as alternative as it is less toxic.
4. Water based systems are preferred.
5. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration. [11]

METHOD OF PREPARATION OF SOLID DISPERSIONS

Melting Method (Fusion Method)

The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. However many substances, either drugs or carriers, may decompose or evaporates during the fusion process which employs high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier. [17, 18]

Melt –agglomeration method

In Melt-Agglomeration method is used to prepare solid dispersion in which solid dispersion is prepared in conventional high shear mixtures and binder itself act as a carrier. [19]In this a mixture of drug, carrier and Excipients are heated to a temperature above the melting point of the carrier using a high shear mixer. The equipment used for Melt-Agglomeration is Rotary Processor and is used to produce stable solid dispersion.

Solvent Evaporation Method

In this method, the first step is formation of solution containing physical mixture of the drug and carrier dissolved in a common solvent and second step involves the removal of solvent resulting in the formation of solid dispersion. First, to dissolve both the drug and the carrier in a common solvent and secondly, to evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic drug in the highly water soluble carrier polyvinylpyrrolidone. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods

like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65°C. [20]

Alternative Strategies

Super critical fluid technology

Supercritical carbon dioxide was used as a solvent to load chlorpheniramine maleate (CPM) into Eudragit polymers (E) for controlled release. CPM was loaded into E in ratio of 1:10 using supercritical carbon dioxide as the solvent at various pressures (780 to 5000 psi), temperatures (22°C to 55°C), processing time (0 to12 hours), and the drug polymer ratio (1:1 to 1:10) to form solid dispersions. This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursor's dyes and bio molecules such as proteins and peptides. From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug-loaded biopolymer micro-particles for pharmaceutical applications has been studied intensively by a number of researcher groups CFs either as solvent: rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). [21]

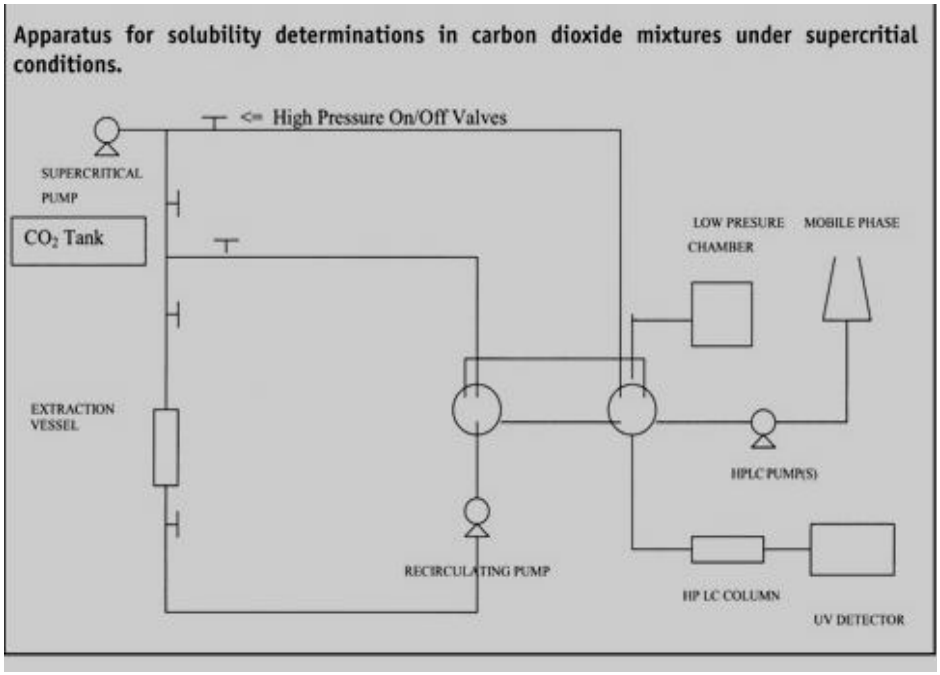

Fig 1 Schematic diagram for super critical fluid technology

Lyophilisation Technique

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. Lyophilisation 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. [22]

Melt Extrusion Method

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185°C from feeder to die. The extrudates are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory-cutting mill and sieve to exclude particles >355µm. [23]

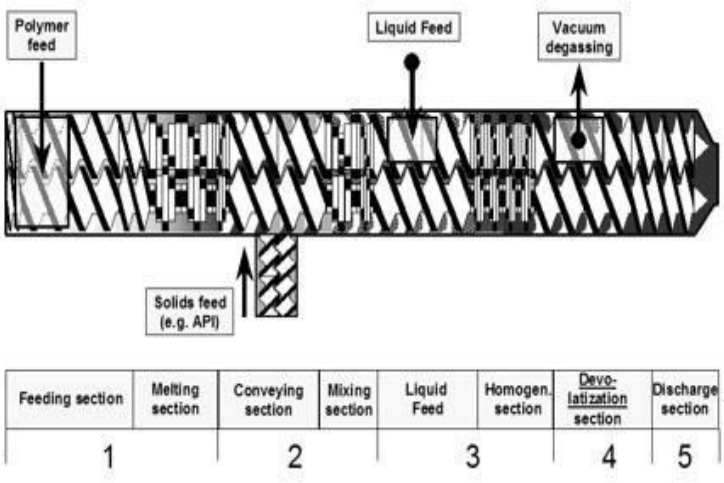

Fig 2 Extruder for the preparation of solid dispersion

Co-precipitation

This technique is widely used for improving the dissolution characteristics of poorly water soluble drugs. In this method, drug and carrier are mixed in an organic solvent [24]. On precipitation, drug and carrier are separated and separation is mainly depends upon solubility properties of drug and the carrier. In this method, required quantity of drug and carrier were

added in a solvent to obtain a clear solution. The solution was dried at room temperature and then placed in incubator for 12 hours [25]. At last, it was passed through a sieve.

Spraying on Sugar Beads using Fluidized Bed Coating

The approach involves fluidized bed coating system, where-in a drug-carrier solution is sprayed onto the granular surface of Excipient or sugar spheres to produce either granule ready for tableting or drug- coated pellets for encapsulation in one step. This method has been applied for both controlled-and immediate-release solid dispersions. [26] For e. g., Itrakonazole coated on sugar sphere, is made by layering onto sugar beads a solution of drug and hydroxypropylmethylcellulose (HPMC) in an organic solvent of dichloromethane and ethanol.

The use of Surfactant

The utility of the surfactant systems in solubilisation is well known. Adsorption of surfactant on solid surface can modify their hydrophobisity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilisation, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions. Two of the important surface-active carriers used are Gelucire 44/14and Vitamin ER-alpha- tocopheryl polyethylene glycol 1000 succinate (TPGS). In which Gelucire44/14 has commonly been used in solid dispersion for the bioavailability enhancement of drugs. A commonly used surfactant, Polysorbate 80, when mixed with solid PEG, has also been reported to be an alternative surface-active carrier. [27, 28]

Freeze-drying

In freeze drying technique drug and carrier are dissolved in a common solvent, which is immersed in liquid nitrogen. Then this solution is lyophilized. [29] Freeze-drying is most suitable technique for incorporating drug substance in stabilizing matrices. In this method, during the formation of solid dispersion, drug is exposed to minimal thermal stress and phase separation risk is reduced.

Electrostatic Spinning Method

This technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology. [30] This technology is now applied in the pharmaceutical field. [31]Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. [32] Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (biodegradable and non-biodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct incorporation of the materials into a capsule. Itraconazole/HPMC nano fibers have been prepared using this technique. [33]

(c) Kneading method

A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved. Ex-furosemide and crospovidone solid dispersion was prepared by this method. [34]

Spray-drying

It is one of the most widely used techniques in the preparation of solid dispersion. In this method drug and carrier are dissolved or suspended and the solvent is removed by spraying it into a stream of heated air. [35] Van Drooge prepared a solution of Diazepam and povidone and then sprayed into liquid nitrogen and then lyophilized. It is 40-50 times less expensive then freeze –drying, so it is cost-effective and simple.

Dropping method

This method was first developed by Bulau and Ulrich in 1977. It facilitates the crystallization of different chemicals and formation of round particles from melted solid dispersion. It is used for laboratory scale preparation as follows: Solid dispersion of melted drug-carrier is dropped on to a cooling plate for solidification into round particles. [36] Factors such as size of pipette and viscosity of melt determine the size and shape of particles. It is very important to

adjust the temperature, when the melt is dropped on to the plate for solidification into spherical particles as viscosity is highly temperature dependent.

TYPES OF SOLID DISPERSIONS

Simple eutectic mixture

When a mixture of A and B with composition E 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. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability. [18, 37]

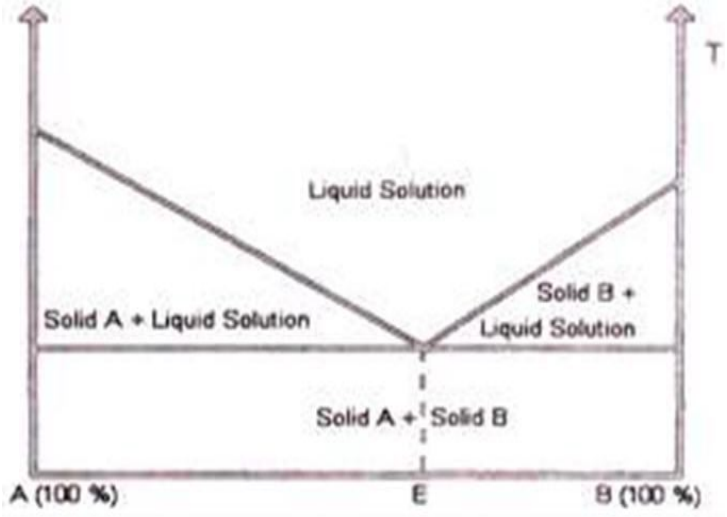

Fig. 3 phase diagram for a eutectic system

Solid Solutions: According to their miscibility two types of solid solution are;

Continuous Solid Solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

Discontinuous Solid Solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram, show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubility's of the two components start to decrease. According to Goldberg that the term solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. [37]

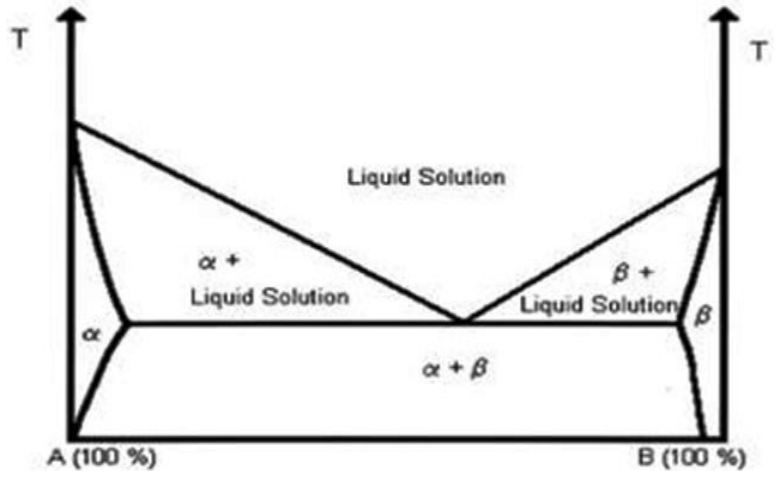

Fig 4 phase diagram for discontinuous solid solution

According to the way in which the solvate molecules are distributed in the solvent, the two types of solid solutions are

Substitutional Crystalline Solutions

A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which the solute molecules substitute for 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. [38]

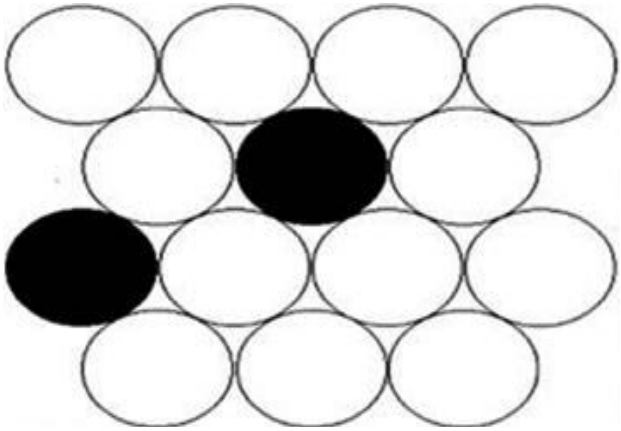

Fig 5 substitutional crystalline solid solution

Interstitial Crystalline Solid Solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent. [39]

Amorphous Solid Solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carrier's urea and sugars such as sucrose, dextrose and galactose, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol and various cellulose derivatives have been utilized for this purpose. [40]

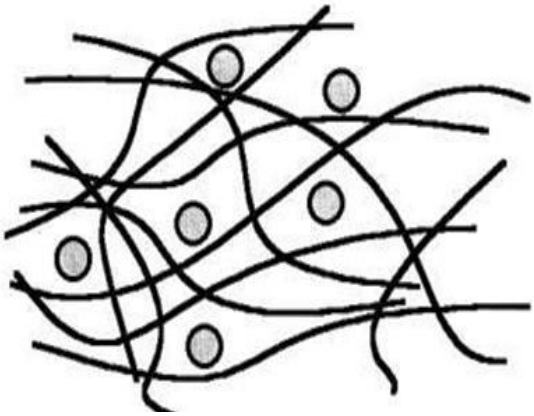

Fig. 6 amorphous solid solution

Glass Solutions and Glass Suspensions

Chiou and Riegelman first introduced the concept of formation of a glass solution as another potential modification of dosage forms in increasing drug dissolution and absorption. A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature Tg. [39, 40]

Mechanism of Increased Dissolution Rate

The main reasons postulated for the observed improvements in dissolution of these systems are as follows: [41]

a) Reduction of particle size

In case of glass, solid solution and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to an increase in both the surface area solubilisation.

b) Solubilisation effect

The carrier material, as it dissolves may have a solubilization effect on the drug. This was shown to be the case for acetaminophen and chlorpropamide in urea as well as for numerous other drugs. Any agglomeration or aggregation of the particles, which can slow the dissolution process.

d) Metastable Forms

Formation of metastable dispersions with reduced lattice energy would result in faster dissolution rates. It was found that the activation energies for dissolution for furosemide was 17 K Cal per mol, whereas that for 1:2 furosemide: PVP co precipitate was only 7.3 K Cal per mol.

c) Wettability and dispersibility

The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media.

Evaluation & Characterization of Solid Dispersion

Physical appearance

Includes visual inspection of solid dispersions

Microscopy

A] Scanning Electron Microscopy: It is very useful in determining the particle size and morphology of drug particles. [11]

B] Optical Microscopy: Stage Micrometer and Calibrated Ocular Micrometer are used in Optical Microscopy and is used for particle size analysis of powder [42] E. Various number of particles are measured and their mean diameter can be calculated.

Drug carrier compatibility

This study is done to determine the interactions if any between the drug and carrier and to determine the formation of inclusion complexes. Methods used for this purpose are [43]

(a) Fourier Transform Infra Red (FTIR) Spectroscopy

Infra red studies was carried out to rule out interaction between drug and carrier used in Formulation of solid dispersion by potassium bromide disc method using Infra red spectrophotometer.

(b) Differential Scanning Calorimetry

Differential scanning calorimetry was performed by Differential scanning calorimeter 60 shimadzu to obtain suitable thermo grams. The accurately weighed sample was placed in an aluminium pan and an empty aluminium pan was used as reference. The experiment was performed under nitrogen flow, at a scanning rate 300C/min. In range of 50-3500C.

Percent Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation. [5]

PY (%) = [Practical Mass (Solid dispersion) / Theoretical Mass (Drug+ Carrier) ×100

Phase-solubility studies

In phase –solubility studies an excess amount of drug is added to the specific carrier containing Increasing concentration [42]. It is shaken at 37 degree Celsius for 48 hours in thermostatically controlled water –bath. Then the solution is filtered through a cellulose nitrate membrane filter. The filtrate is diluted and analyzed spectrophotometrically [11].

Aqueous solubility studies

It was carried out to determine solubility drug alone in aqueous medium and also in presence of carriers .This was done by dissolving excess drug in different flasks containing different Concentration of carrier in distilled water. The flasks were shaken thoroughly for 6 hours and kept aside for 24hours.The suspensions were filtered, diluted suitably and absorbance was measured a suitable wavelength. [44]

Drug content

In this method definite amount of solid dispersion is taken and dissolved in a suitable solvent

in which drug is freely soluble, then after appropriate dilution concentration are measured by UV Spectrophotometers. [45]

Dissolution Studies

Dissolution studies are the most significant evaluation parameter for any solid dosage form. Dissolution study is carried out to determine the rate and extent of dissolution. The dissolution study of solid dispersion was performed in 500ml at 37ºC by the USP- II paddle apparatus at 75 rpm. Drug was dispersed in medium. Aliquots of 5 ml from the dissolution medium were withdrawn at different time interval and replenished by an equal volume of fresh dissolution medium. The samples were filtered through whatman filter paper and analyzed for drug contents by measuring the absorbance at suitable wavelength using Shimadzu 1700 UV/visible Spectrophotometer. [11]

Stability studies

This study is used to determine the stability of solid dispersion on storage for a long period of time. [46] Various methods are used to evaluate the stability studies of solid dispersion are:

1) Isothermal Calorimetry
2) Dynamic Vapour Sorption
3) Saturated Solubility Studies
4) Humidity Studies
5) DSC (Tg, temperature recrystilization)

APPLICATIONS OF SOLID DISPERSION IN PHARMACEUTICAL FIELD

Apart from absorption enhancement, the solid dispersion technique may have numerous Pharmaceutical applications which should be further explored it is possible that such a technique be used

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.
- Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds. [11, 47]

CURRENTLY MARKETED SOLID DISPERSION PRODUCTS

The commercial applications of solid dispersion are limited. Only a few Products have been marketed such as: [42, 48]

1] Solufen (Ibuprofen)

2] Gris-PEG (Griseofulvin)

3] Prograf (Tacromilus)

4] Sporanox (Itraconazole)

5] Crestor (Rosuvastatin)

6] Intelence (Etravirine)

7] Cesamet (Nabilone)

Future prospects

One major focus of future research will be identification of new surface-active carriers and Self - emulsifying carriers for solid dispersion. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may the inadequate drug solubility in carriers, so a wider choice of carriers will increase the success of dosage form development. Attention must also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self - emulsifying. Carriers are lipidic in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP3-based drug metabolism and p-glycoprotein-mediated drug efflux will require careful consideration [49] In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed towards the development of extended release dosage forms. It may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsule filling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use, it is expected that the research in these two areas will progress simultaneously and be complementary to each other.

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