ISSN: 0975-766X
CODEN: IJPTFI
Available through Online
Review Article
www.ijptonline.com

SOLID DISPERSION TECHNIQUES FOR ENHANCEMENT OF SOLUBILIZATION AND BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUGS- A REVIEW

Mr. Vinod T. Wagh [1]*, Dr. R. D. Wagh[2]
[1]Suresh Gyan Vihar University, Mahal, Jagatpura, Jaipur, 302025.
[2] Principal, A. R. A. College of Pharmacy, Nagaon, Dhule, 424005.
Email: wagh.vinod517@gmail.com

Received on 02-02-2015 *Accepted on 28-02-2015*

Abstract

A success of formulation depends on how efficiently it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules especially in oral formulation. But most of the time it becomes challenging to formulate poorly water soluble drugs. Nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs. Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the in vivo efficacy. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. The solubility and dissolution properties of drugs play an important role in the process of formulation development. Problem of solubility is a major challenge for formulation. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate/prepare solid dispersions. In this review we concentrated on improvement of the solubility of poorly water soluble drugs by preparing solid dispersion using various methods.

Keywords: Solubility, bioavailability, physical and chemical method, solid dispersion, carriers, dissolution.

Introduction

Almost More than 90% drugs are orally administered. Drug absorption, sufficient & reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on Solubility of that compound in aqueous medium[1]. More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of

active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble[2].Drug absorption, sufficient and reproducible bioavailability and pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances. Orally administered drugs on the Model list of Essential Medicines of the World Health Organization (WHO) are assigned Biopharmaceutical Classification System (BCS) on the basis of data available in the public domain. According to BCS

Class-I- Drugs having high solubility and high permeability

Class-II- Drug having low solubility and high permeability

Class-III- Drugs having high solubility and low permeability

Class-IV- Drugs having poor solubility and poor permeability

The rate and extent of absorption of class II & class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility[3]**.**

Due to this major reason Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility. Solubility is the characteristic physical property referring to the ability of a given substance, the solute, to dissolve in a solvent[4].

Solvent: The component which forms major constituent of a solution & is capable to dissolve another substance to form a uniformly disperse mixture at the molecular level**.**

Solute: A substance that present in small quantity & dissolves in solvent[5].

Solubility Definitions-"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."[6]

In the other words, "solubility can also define as the ability of one substance to form a solution with another substance."[7]

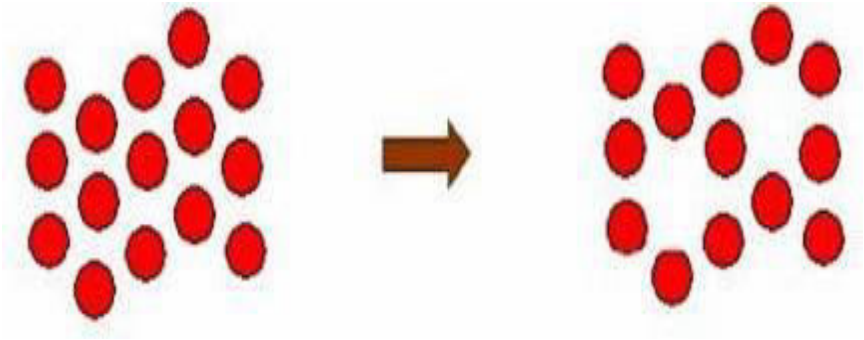
Solubility Definition[8]

Definition	**Parts of solvent required for one part of solute**
Very Soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30

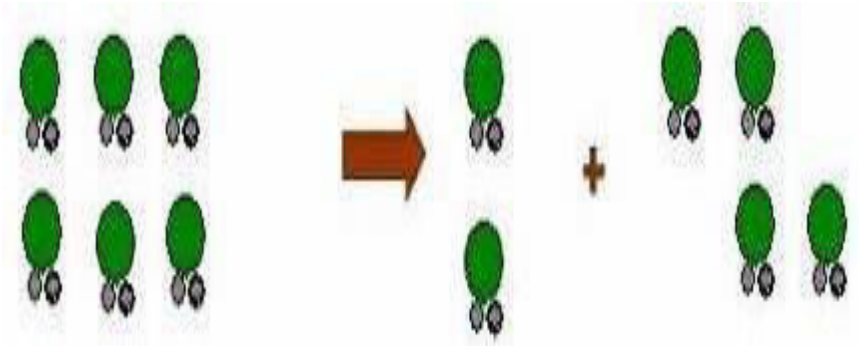
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

Process of solublization: The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion[9].

Step 1: Holes opens in the solvent.



Step2: Molecules of the solid breaks away from the bulk.



Step 3: The freed solid molecule is integrated into the hole in the solvent.

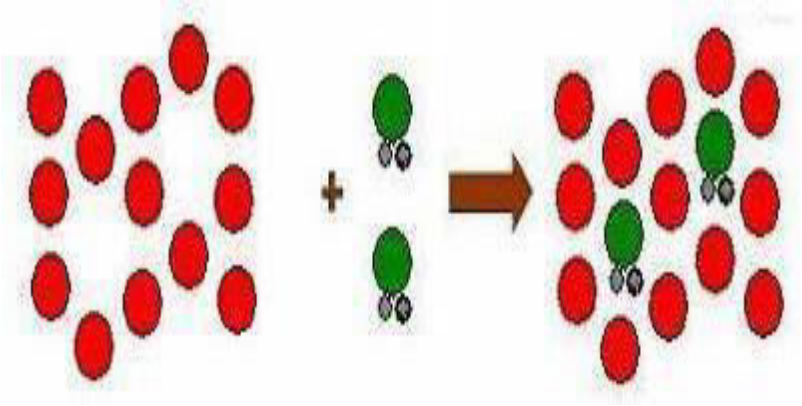


Figure- Process of solublization

Factors affecting Solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system [10].

Particle Size:

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by [11].

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where,

S is the solubility of infinitely large particles

S_0 is the solubility of fine particles

V is molar volume

γ is the surface tension of the solid

r is the radius of the fine particle

T absolute temp in degree kelvin

R universal gas constant

Pressure:

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility[12]**.**

Nature of the solute and solvent:

While only 1 gram of lead chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubility's of these two substances is the result of differences in their natures[13]

Temperature:

Generally, an increase in the temperature of the solution increases the solubility of a solid solute[14].

Molecular size:

The larger the molecule or the higher its molecular weight the less soluble the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent[15].

Polarity: Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction.All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces[16].

Polymorphs:

The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities[17].

NEED OF SOLUBILITY ENHANCEMENT

The better characterization of biochemical targets increasingly drives drug development; these targets are generally cell-based and access to them in these models is relatively straightforward. This has led to the widely discussed proliferation of highly active compounds that have physicochemical characteristics that are poorly suited to delivery to a whole organism: at the head of this list of undesirable characteristics is poor water solubility[18].

According to recent estimates, nearly 40% of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties. Solubility is one of the important parameter to achieve desired concentration of drug in

systemic circulation for pharmacological response to be shown. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules[19].

Bioavailability – is measurement of the extent of therapeutically active drug that reaches systemic circulation & is available at the site of action. It is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for non intravenous routes of administration[20].

Poor aqueous solubility is caused by two main factors[21]

1) High lipophilicity and

2) Strong intermolecular interactions which make the solubilisation of the solid energetically costly.

TECHNIQUES OF SOLUBILITY ENHANCEMENT [22]

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are.3

1) PHYSICAL MODIFICATIONS

A. **Particle size reduction**

- Micronization
- Nanosuspension
- Sonocrystalisation
- Supercritical fluid process

B. **Modification of the crystal habit**

- Polymorphs
- Pseudopolymorphs

C. **Drug dispersion in carriers**

- Eutectic mixtures
- Solid dispersions
- Solid solutions

D. **Complexation**

- Use of complexing agents

E. **Solubilization by surfactants:**

- Microemulsions
- Self microemulsifying drug delivery systems

2) CHEMICAL MODIFICATIONS

3) OTHER METHODS

- Cocrystalisation
- Cosolvency
- Hydrotrophy
- Solvent deposition
- Selective adsorption on insoluble carrier
- Use of soluble prodrug
- Functional polymer technology
- Porous microparticle technology
- Nanotechnology approaches

Definition of solid dispersion:

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 or in crystalline particles .Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Solid dispersions should preferably be designated according to their molecular arrangement[23].

Carriers for Solid Dispersions[24]

1. Acids – Citric Acid, Tartaric Acid, Succinic Acid.

2. Sugars – Sucrose, Dextrose, Sorbitol, Maltose, Galactose, Xylitol.

3. Polymeric Materials – Polyvinylpyrollidone, PEG 4000 & 6000, Carboxymythyl cellulose, Hydroxypropylvcellulose, Guar gum, Xanthan gum, Sodium Alginate, Dextrin, Cyclodextrin.

4. Surfactants – Polyoxyethylene stearate, poloxamer, Deoxycholic acid, Tweens

and Spans, Gelucire 44/14, Vitamine E TPGS NF

5. Miscellenous – Urea, Urethane, Hydroxyalkyl Xanthene, Pentaerythritol[25]

Mechanism of Increased Dissolution Rate by Solid dispersion[26]

1. Reduction in particle size.

2. Solublization effect (use of carriers).

3. Increased wettability and dispersibility by carriers

4. Formation of metastable dispersion with reduced lattice energy for faster dissolution.

CLASSIFICATION OF SOLID DISPERSION[27]

1. Simple Eutectic Mixtures

2. Solid Solutions

3. Glass Solution & Glass Suspension

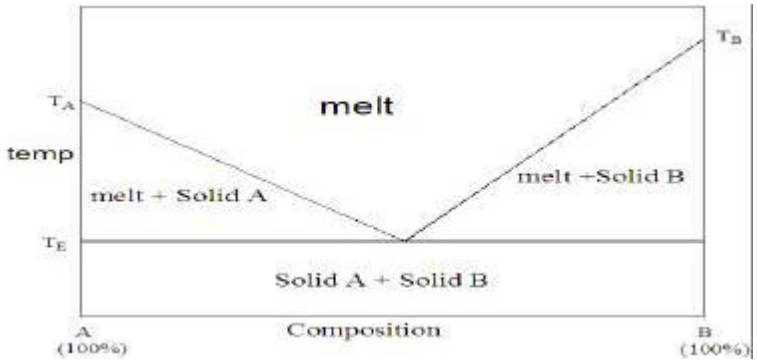
4. Amorphous precipitation In Crystalline Carrier

5. Compound Or Complex Formation

6. Combination Of Previous Five Types(usually combination of 2-3 methods)

1. Simple Eutectic Mixtures:

It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution. Thermodynamically it is intimately blended mixture of two crystalline components[28]

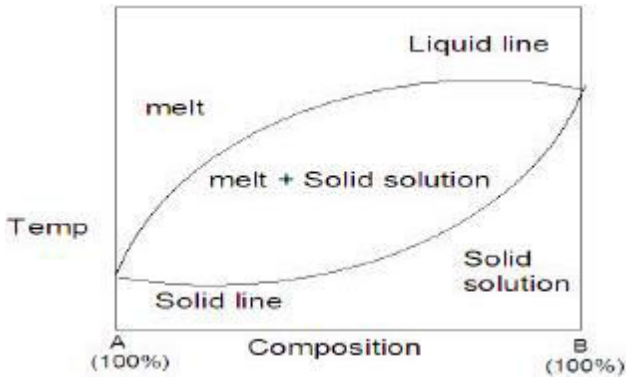


2. Solid Solution:

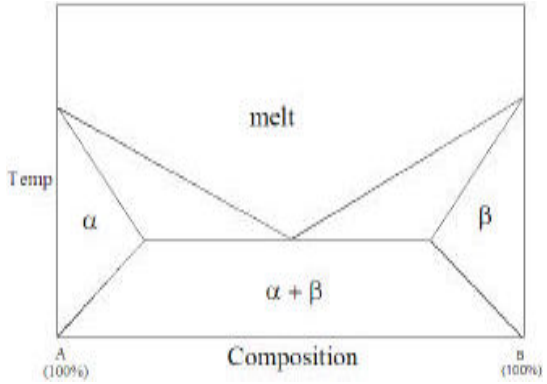
Two components crystallize together in homogenous one phase system. Particle size of drug in solid solution is reduced to its molecular size. Solid solutions shows faster dissolution rate than eutectic mixtures.

Classification of solid solutions, according to extent of miscibility of two components;

a) Continuous Solid Solution – Two solids miscible in solid state in all proportions

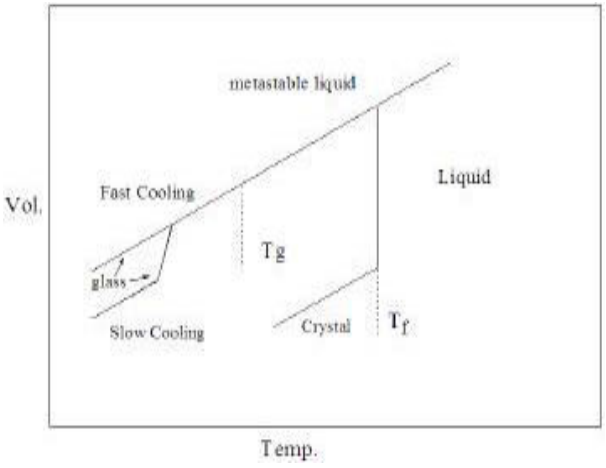


b) Discontinuous Solid Solutions – Exist at extremes of composition



3. Glass Solution & Suspensions:

Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended in glass solvent. Different characteristics of glassy state are transparency, brittleness below the glass transition temperature[30].



Tg – glass transition temp.

Tf – M.P. of material

4. Amorphous Precipitation in Crystalline Carrier:

It is postulated that drug with propensity to super cooling has more tendency to solidify as an amorphous form in presence of carrier. This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form[31].

Advantages of solid dispersion[32]

- Solid dispersion is used for the improvement of the bioavaibility of poorly water soluble drugs.
- Enhance the dissolution of drug.
- Reduce presystamic metabolism this may be due to carrier inhibit the enzyme responsible for biotransformation of drug.
- Through use of the solid dispersion, the liquid form of drug can be transformed to the solid form.
- Solid dispersions are in the solid state hence preferred by patients as compare to the solubilization products are in the liquid state.
- Solid dispersion better than other particle size reducing techniques to enhance the solubility ,because the other size reduction techniques reduces the size to a limit approximately 2-5 µm which does not cause enough enhancement in drug solubility or drug release in small intestine and to improve the bioavaibility.
- The problem of solid powder such as less size of particle shows poor mechanical properties (include high adhesion and poor flow properties) can be overcome by use of solid dispersion.
- The extended release solid dispersion can also be prepared.

Common methods used for preparation of solid dispersion

- Fusion method.
- Solvent method.
- Melting solvent method.
- Solvent-deposition method.

- Melt agglomeration process.
- Solvent evaporation method
- Crystallization in aqueous solvent
- Use of adsorbent
- Kneading Method
- Supercritical Fluid Method
- Lyophilization method
- Extruding method
- Spray drying
- Electrospinning

Fusion method[33]

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method.

Advantages

- The main advantage of direct melting method is its simplicity and economy.
- In addition melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier.

Solvent method[34]

The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties.Using the solvent method, the pharmaceutical engineer faces two challenges. The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution and solid dispersions are obtained.

Advantages

- The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

Supercritical fluid methods[35]

Supercritical fluid methods are mostly applied with carbon dioxide, which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution.

Advantages

- The supercritical anti-solvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize and form particles.
- The general term for this process is precipitation with compressed anti- oven. More specific examples of PCA are Supercritical Anti Solvent when supercritical CO2 is used, or Aerosol Solvent Extraction System, and Solution Enhanced Dispersion by Supercritical fluids.

Melting solvent method[36]

In this method drug is first dissolved in a suitable liquid solvent Solution is then incorporated directly into the melt of polyethylene glycol obtainable below 70oe, without removing the liquid solvent. It has been shown that 5-10% (w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property.

Advantages

- In this method that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

Melt agglomeration method[37]

This technique has been used to prepare where in the binder acts as a carrier. In addition, are prepared either by Heating binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient 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. 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.The mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

Characterization of solid dispersion system

Many methods are available that can contribute information regarding the physical nature of solid dispersion system. A combination of two or more methods is required to study its complete picture.

- Thermal analysis.
- Spectroscopic method.
- X-ray diffraction method.
- Dissolution rate method.
- Microscopic method.
- Thermodynamic method.
- Modulated temperature differential scanning calorimetry
- Environmental scanning electron microscopy
- Dissolution testing

Thermal Analysis Techniques[38, 39]

Thermal analysis comprises a group of techniques in which a physical property of a substanceis measured as a function of temperature, while the substance is subjected to a controlled temperature programme. In deferential thermal analysis, the temperature difference that develops between a sample and an inert reference material is measured, when both are subjected to identical heat treatments. The related technique of deferential scanning calorimetry relies on deference's in energyrequired to maintain the sample and reference at an identical temperature. Length or volume changes that occur on subjecting materials to heat treatment are detected in dilatometry; X-ray or neutron difraction can also be used to measure dimensional changes. Both thermogravimetry and evolved gas analysis are techniques which rely on samples which decompose at elevated temperatures. The former monitors changes in the mass of the specimen on heating,

whereas the latter is based on the gases evolved on heating the sample. Electrical conductivity measurements can be related to changes in the defect density of materials or to study phase transitions.

X-ray crystallography[40, 41]

X-ray crystallography is a method of determining the arrangement of atoms within a crystal, in which a beam of X-rays strikes a crystal and diffracts into many specific directions. From the angles and intensities of these diffracted beams, a crystallographer can produce a three dimensional picture of the density of electrons within the crystal. From this electron density, the mean positions of the atoms in the crystal can be determined, as well as their chemical bonds, their disorder and various other information. Since many materials can form well as various inorganic, organic and biological molecules X-ray crystallography has been fundamental in the development of many scientific fields. In its first decades of use, this method determined the size of atoms, the lengths and types of chemical bonds, and the atomic-scale differences among various materials, especially minerals and alloys.

Spectroscopy[42, 43]

Spectroscopy was originally the study of the interaction between radiation and matter as a function of wavelength (λ). In fact, historically, spectroscopy referred to the use of visible light dispersed according to its wavelength, e.g. by a prism. Later the concept was expanded greatly to comprise any measurement of a quantity as a function of either wavelength or frequency.

Thus it also can refer to a response to an alternating field or varying frequency (ν). A further extension of the scope of the definition added energy (E) as a variable, once the very close relationship for photons was realized.

Differential scanning calorimetry (DSC) [44, 45]

All spray-dried samples and starting materials were analyzed in triplicate. DSC measurements perform using DSC equipped with a refrigerated cooling system. Dry nitrogen at a flow rate of 50 ml/min was used to purge the DSC cell. Open aluminum pans were used for all measurements. The mass of the empty sample pan and the reference pan was taken into account for the calculation of the heat flow.

The sample mass varied from 1 to 6 mg. The enthalpic response was calibrated with an Indium standard and the temperature scale was calibrated with Octadecane, Indium and Tin. The heat capacity signal was calibrated by comparing the response of a sapphire disk with the equivalent literature value at 80 °C.

Scanning electron microscopy[46, 47]

The morphology of the spray-dried ternary solid dispersions can be characterized with a Philips XL30 ESEM FEG environmental scanning electron microscope operating at 25 kV accelerating voltage and a vacuum. The samples were sprayed on double-sided carbon tape that was mounted on conventional SEM stubs.

Dissolution testing[48, 49]

Dissolution experiments can be performed in triplicate on the binary and ternary dispersions. The tests were performed according to the USP 24 method 2 in a Hanson SR8plus dissolution apparatus. To simulate the dissolution of a weak basic compound in the stomach, 500 mL of simulated gastric fluid without pepsin was used as dissolution medium at a temperature of 37 °C and a paddle speed of 100 rpm. An amount of the spray-dried powders, corresponding to drug dose of 100 mg, was added to the dissolution medium. Five-milliliter samples were taken and immediately replaced with fresh dissolution medium at 5, 10, 15, 30, 45, 60, and 120 min. These samples were filtered with 0.45 μm Teflon filters. The first 2 ml were discarded. The remainder was diluted with methanol (1/2) to avoid precipitation, and analyzed with HPLC[10] .

Applications of solid dispersion[50]

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 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

Conclusion

A drug administered in solution form is immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. Although salt formation, particle size reduction etc. have commonly been used to increase dissolution rate of the drug, there are practical limitation with these techniques the desired bioavailability enhancement may not always be achieved. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. Solid dispersion is mainly used to mask the taste of the drug substances, and to prepare rapid disintegration oral tablets. Solid dispersion has also been used to produce sustained-release microspheres using tedious methods such as water-in-oil emulsions. Above Review shows that, it is now possible that to increase the solubility of poorly soluble drugs with the help of Solid Dispersion Technique effectively. Also this method is practically simple than other methods.

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Corresponding Author:

Mr. Vinod T. Wagh [1]*,

Email: *wagh.vinod517@gmail.com*