WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 07, 665-692. Review Article ISSN 2277–7105

A REVIEW ON SOLID DISPERSIONS

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Article Received on
10 Feb. 2018,
Revised on 02 March 2018,
Accepted on 22 March 2018
DOI: 10.20959/wjpr20187-11718

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ABSTRACT

Enhancement of solubility, dissolution rate and bioavailability of the drugs in drug development of hydrophobic drugs is a great challenge. Over the years a variety of solubilization techniques have been studied and widely used, as more than 40% of the newly developed drugs are poorly water soluble in pharmaceutical field. To improve such solubility issues, solid dispersion technique is widely used. The solubility behaviour of the drugs remains one of the most challenging aspects in formulation development. Solid dispersions are generally prepared with a drug which is having poor aqueous solubility and with a water soluble hydrophilic carrier. Solid dispersions, defined as the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state and an efficient technique to improve dissolution of poorly water-soluble drugs to enhance their bioavailability. So, solid dispersion technique is an efficient tool for increasing the oral bioavailability and dissolution rate of a range of hydrophobic drugs. This article reviews preparation of solid dispersion like selection of carrier, classification, characterization, their advantages, limitations and applications.

KEYWORDS: Solubility, solubilization techniques, Solid dispersions.

1. INTRODUCTION

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products.

However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.

Solubility also plays a major role for other dosage forms like parentral formulations as well. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.

More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important rate limiting parameter to achieve desired concentration in systemic circulation for pharmacological response. Poor solubility is a major challenge for formulation scientist.

The improvement of drug solubility thereby its oral bioavailability remains one of the most challenging aspects of drug development process especially for oral drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form.

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II and class IV substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. As for BCS class II and class IV drugs rate limiting step is drug release from the dosage form and solubility in the

gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drug.

The negative effect of compounds with low solubility include poor absorption and bioavailability, insufficient solubility for IV dosing, development challenges leading to increasing the development cost and time, burden shifted to patient (frequent high-dose administration).

1.1. Techniques to Overcome Poor Solubility[1]

The description of a technology as 'solubility enhancing' can be misleading, since although the phenomenon of super-saturation is real, the techniques used do not increase the solubility of insoluble compounds. More accurately, they present the drug in a form which is optimal to its absorption, given its solubility limitations. It is also important to be aware that water solubility also requires the specification of temperature and pH; many important drugs only exhibit aqueous solubility under certain physiological conditions, and these need to be meet at the site of absorption. This topic focuses on the technologies that have arisen to meet the challenge posed by insoluble compounds and the ways in which these technologies have made a difference. The techniques that are used to overcome poor drug solubility are discussed under following major headings.

Techniques for Solubility Enhancement

I. Chemical Modifications

1. Salt Formation
2. Co-crystallization
3. Co-solvency
4. Hydrotrophy
5. Solubilizing agent
6. Nanotechnology

II. Physical Modifications

1. Particle size reduction

a. Micronization

b. Nanosuspension

2. Modification of the crystal habit

a. Polymorphs

b. Pseudopolymorphs

3. Complexation

a. Use of complexing agents

4. Solubilization by surfactants

a. Microemulsions

b. Self microemulsifying drug delivery system

5. Drug dispersion in carriers

a. Solid dispersions

b. Solid solutions

c. Eutectic mixtures

I. Chemical Modifications

1. Salt formation: is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Ex: Aspirin**,** Theophylline, Barbiturates.

2. Co-crystallization: New approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. A co-crystals may be defined as crystalline material that consist of two or more molecular (and electrical neutral) species held together by non-covalent forces. It can be prepared by evaporation of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt and slurry preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds.

3. Co-solvent: It is well-known that the addition of an organic co-solvent to water can dramatically change the solubility of drugs. Weak electrolytes and non polar molecules have poor water solubility and it can be improved by altering polarity of the solvent. Solvent used to increase solubility known as co-solvent. It is also commonly referred to as solvent blending.

4. Hydrotropy: It designates to increase in solubility in water due to presence of large amount of additives. It improves solubility by complexation involving weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, urea) and solute. Ex. Sublimation of Theophylline with Sodium acetate and Sodium alginate.

5. Solubilising agents: The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. PEG 400 is improving the solubility of hydrochlorothiazide.

6. Nanotechnology approaches: Nanotechnology will be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometres (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has very low effective surface area for dissolution and next step taken was nanonisation.

II. Physical Modifications

1. Particle size reduction: The techniques of size reduction using various milling processes are well established and these practices are a standard part of formulation development. This can be done mainly by Micronization and Nanosuspension. As particle size decreases, surface area of particle increases resulting in increase in solubility.[2] Sometimes Sonocrystallisation technique is also used for particle size reduction.

2. Modification of crystal habit: Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability. Similarly amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase in surface area. Order for dissolution of different solid forms of drug Amorphous >Metastable polymorph >Stable polymorph.

3. Complexation: Complexation is the association between two or more molecules to form a non bonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Ex. of complexing agents are; chelates- EDTA, EGTA, molecular complexes- polymers, inclusion complexes cyclodextrins.

4. Solubilisation by surfactants: Surfactants are molecules with distinct polar and non polar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitter ionic or non-ionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of

solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension but increases solubility of drug within an organic solvent.

2. SOLID DISPERSIONS

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960's.[3]

i) Definition

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.[4]

ii) Advantages of solid dispersions[5, 6]

1. Solid dispersion technique is useful to enhance solubility and bioavailability of poorly water soluble drugs.
2. Rapid disintegration of oral tablets.

Drug is formulated with hydrophilic carrier (e.g. PEG) as a solid dispersion to increase its aqueous solubility and dissolution. Then superdisintegrant (e.g. croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self-medication even without the aid of water.

3. As a formulation vehicle

Solid dispersions can be used as formulation vehicle to facilitate the preclinical safety and early clinical studies on new chemical entities with very low aqueous solubility. It provides a means to rapidly assess the safety and efficacy profile of the drug substance that may be otherwise difficult to obtain.

4. Particles with reduced particle size

Solid dispersions represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and

highly soluble carriers, thus a high surface area is formed, resulting in an increased dissolution rate and consequently improved bioavailability.

5. Particles with improved wettability

Enhancement of drug solubility is related to the drug wettability. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts when used, significantly increase the wettability of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

6. Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, results in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release rate.

7. Drugs in amorphous state

The enhancement of drug release can usually be achieved if the drug is in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that if drugs precipitate it is as a metastable polymorphic form with higher solubility than the most stable crystal form..

8. It is easier to produce.
9. Transformation of liquid form of drug in to solid form.
10. It is used to mask the bitter taste of drug.

iii) Disadvantages of solid dispersions

1. The major disadvantages of Solid dispersion are related to their instability.
2. Several systems have shown changes in crystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility.
3. Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness.

4. Usually solid dispersions are prepared with water soluble low melting point synthetic polymers such as polyvinyl pyrrolidone, mannitol or polyethylene glycol. These polymers show superior results in drug dissolution enhancement, but the amount of these polymers required is relatively large, around 1:2 to 1:8 (drug/ polymer) ratio.

5. Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization.

6. It is laborious method of preparation.

iv) Limitations of solid dispersion systems

Despite extensive expertise with solid dispersions, there are some problems which limit the commercial application of solid dispersions. The primary reason is the poor predictability of solid dispersion behavior due to a lack of a basic understanding of their material properties.

1) There is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also of a vital concern, because it may increase drug mobility and promote drug crystallization.
2) Most of the polymers used in solid dispersions can absorb moisture, which may result in the phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate.

2.1. Classification of Solid dispersions[7]

Researchers have classified SD on various basis, but it can be broadly classified into following ways.

A. On the Basis of Carrier Employed

Usually various type of hydrophilic carriers are used to prepare SD. These carriers or polymers affects the final properties of SD system like, its state, drug release kinetics, dissolution profile, stability profile etc. Therefore considering the above facts on the basis of hydrophilic carriers used, SD may be further subdivided into three types.

i) First Generation Solid Dispersion (FGSD)

The first experiment of enhancing the solubility of poorly water soluble drug was demonstrated in 1961 by Sekiguchi and Obi. They proposed the possibility of eutectic

mixture formation which releases the drug as microcrystal's and ultimately enhances the solubility. In series to that success ful SD of drugs like sulphathiazole and chloramphenicol was prepared using urea and sugar as crystalline carrier systems. Therefore SD which are formulated by using crystalline carriers are designated as "FGSD". The crystalline carriers which are usually employed are as follows: urea, sugar, mannitol, sorbitol, galactose, xylitol, sucrose etc. but the major drawback is that they are thermodynamically unstable therefore does not release drug as faster as compared to amorphous forms.

ii) Second Generation Solid Dispersion (SGSD):

The limitation like hasten drug release profile are prone to thermodynamic instability of FGSD, hence gave birth to the development of SGSD. In contrast to FGSD, these totally rely on "amorphous carrier systems"; therefore known as SGSD. Amorphous carriers are generally polymeric carriers which are further sub classified into.

- Natural product based polymer: include cellulose derivatives, like hydroxyl propyl methyl ellulose (HPMC)[58], ethyl cellulose (EC), hydroxyl propyl cellulose (HPC), cyclodextrin etc.
- Fully synthetic polymer: include poly vinyl pyrrolidone (PVP), polyethylene glycol (PEG) etc. SGSD is a single phase homogeneous system in which drug is dispersed at molecular level to provide a supersaturated state. This SGSD facilitate the reduction of size upto molecular level which enhances the wettabillity and causes a increment in solubility profile.

iii) Third Genration Solid Dispersion (TGSD)

TGSD is the recent advancement in SD technique. These constitute of either self-emulsifying or surfactant assisted amorphous carrires. Addition of surfactant not only enhances the solubility but also avoid the recrystallization problem associated with SD. The surfactant which usually employed are: inulin, inutec, compritol 888ATO, gelucire 44/14, poloxamer 407 etc.

B. On Basis of Number of Component Employed

On basis of number of components utilize SD can be subclassified into binary and ternary SD. When only two components i.e. drug and carrier are used they are known as binary SD, for ex sulphathiazole with urea or dimenhydrinate in ethyl cellulose. When SD is prepared by employing drug, carrier and a suitabale surfactant it is known as ternary SD, for example furosamide-PEG6000- MCC, and nalidixic acid-PEG6000-SLS.

C. On the Basis of Structure of SD

i) Eutectic

Eutectic mixture can be simply defined as "system consist of two compound which are completely miscible in liquid state but to only a very limited extent in solid state". As depicted in (Fig. 1), when a drug (P) and carrier (Q) are co-melted at their eutectic composition shown by point (S). The melting point of system is lower than either of drug or carrier system alone. At eutectic point (S) both drug and carrier exist in a finely divided state; which may lead to increased surface area followed by increased dissolution rate and hence increased B.A of drug. Carriers that are usually employed for formation of a eutectic mixture are polyethylene glycol (PEG) and polyoxypropylene.

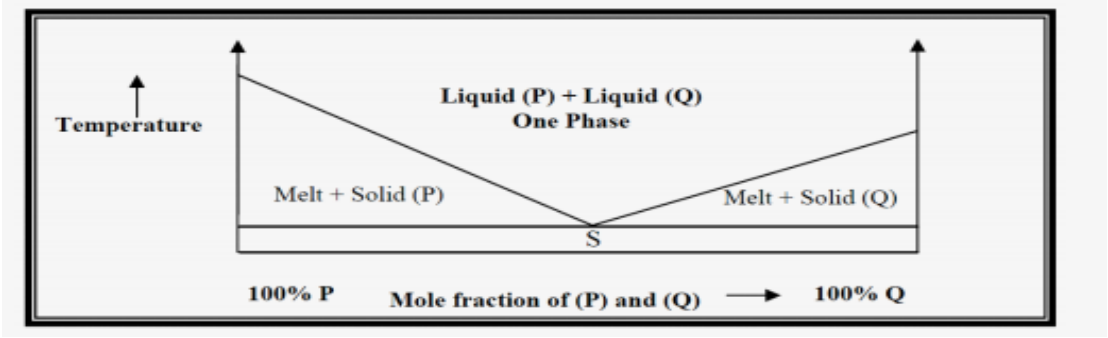

Fig 1: Phase diagram of simple eutectic mixture. At eutectic composition (S) both drug and carrier solidify simultaneously as mixture of finely divided crystalline solid component.

ii) Solid Solution

This is a type of SD that is miscible in fluid as well as in solid state. They are comparable to liquid solution consisting of just one phase irrespective of number of components. In solid solution the size of drug particle reduced to its absolute minimum level i.e. at "molecular level "and thus enhanced the solubility of drug. It can be further sub classified on the basis of entrapment of drug in solid solution.

a) Substitutional solid solution.

b) Interstitial / amorphous solid solution.

a) Substitutional solid solution: On the basis of entrapment of drug molecule solid solution can be termed as "Substitutional solid solution"; when drug particle replace the carrier molecule as shown in (Fig. 2). It happens when the particle size of carrier system is

comparable to that of drug molecule and approximately it can bear a difference of 15% in particle size.

b) Interstitial /Amorphous solid solution: In this solid solution drug molecule occupy interstitial spaces or voids between carrier molecules. In such solid solution molecular size of drug play a crucial role that the size should not be greater than 0.59 of the solvent molecule as depicted in (Fig. 2). Furthermore the volume of solvent molecule should be less than 20% of solvent molecule.

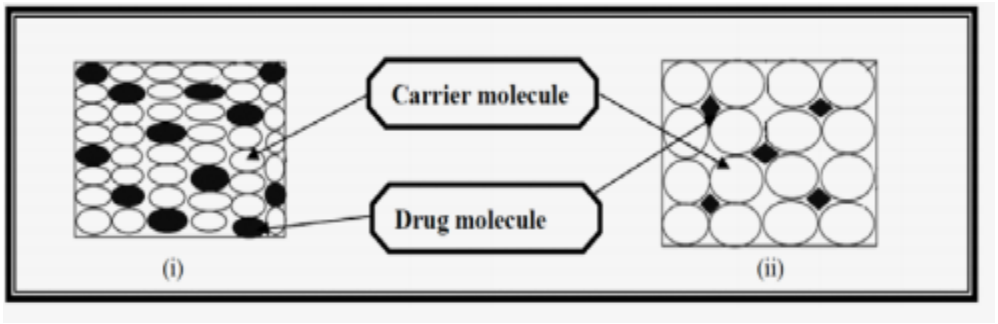

Fig 2: Substitutional and Interstitial solid solution.

iii) Glass solution

Glass solution is a homogeneous system which consists of solid solute dissolved in a solid solvent. Mixed / heterogeneous groups of crystal are formed because both components crystallize simultaneously. Thus the system is expected to have better solubility profile then eutectic mixture.

iv) Glass Suspension

A glass suspension is a homogenous system in which the drug molecule is suspended in a glassy carrier. For both glass solution and glass suspension; the glassy state is characterized by transparency and brittleness below the glass transition temperature. These glasses possess very low lattice energy, which results in a system with very low melting point. Therefore this reduction in lattice energy causes solubility enhancement of NCE.

2.3. Methods of Preparation of Solid Dispersions[8]

Various methods have been developed for preparation of solid dispersions, these methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de mixing (partially or complete), and formation of different phases is observed. Phase

separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted.

Various preparation methods are

1. Solvent evaporation method
2. Modified solvent evaporation method
3. Melting/Fusion method
4. Solvent-melting method (Melt evaporation)
5. Kneading method
6. Co-grinding method
7. Co-precipitation method
8. Spray drying method
9. Gel entrapment technique
10. Direct-capsule filling
11. Lyophilization technique
12. Electro spinning method
13. Super critical fluid (SCF) technology
14. Dropping solution method.

1. Solvent evaporation method

In this method, the physical mixture of the drug and carrier were dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, some disadvantages are associated with this method such as.

- The higher cost of preparation
- The difficulty in completely removing liquid solvent.
- The possible adverse effect of traces of the solvent on the chemical stability
- The selection of a common volatile solvent.
- The difficulty of reproducing crystal form.
- In addition, a super saturation of the solute in the solid system cannot be attained except in a System showing high.

2. Modified solvent evaporation method

Drug is dissolved in organic solvent at its saturation solubility with continuous stirring for some time. Polymer is suspended in sufficient amount of water (up to wet mass of polymer). The drug solution is poured at once into polymer suspension. The entire solvent is evaporated. The mass obtained is dried.

3. Melting /Fusion method

This method 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. The modification in the method can be done by pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures. Advantage of melting method is that it is economic and solvent less process, however this method is not suitable for the drug or carrier which is unstable at fusion temperature or evaporates at higher temperature. Some of the means to overcome these problems could be by 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. E.g. Albendazole and urea solid dispersions were prepared by this method.

4. Solvent melting method

Accurately weighed drug is dissolved in organic solvent. The solution is incorporated into the melt of mannitol and cooled suddenly and mass is kept in desiccators for complete drying. The solidified mass is crushed, pulverized and passed through sieve. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose (less than 50 mg).

5. Kneading Technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.

6. Co-grinding method

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Eg. Chlordiazepoxide and mannitol solid dispersion was prepared by this method.

7. Co-precipitation method

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

8. Spray-Drying Method[5, 8, 9,10]

It is one of the most widely used techniques in the preparation of solid dispersions. 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. Spray drying is an efficient technology for solid dispersion manufacturing because it permits extremely rapid solvent evaporation resulting in fast transformation of an API-carrier solution to solid API-carrier particles. Spray drying was basically consisting of four steps i.e. atomization, drying, evaporation, and separation of dried powder. It was a closed-system process in which a solution of both drug and carrier system was subjected as a fine droplet with the help of atomizer to a chamber which is maintained at a specific condition of temperature and pressure. During these circumstances the solvent rapidly evaporates from the surface of the fine droplet and result in development of fine granules of narrow size distribution. Especially for this technique usually we employed the "organic solvent"; which rapidly evaporates on slight rise in temperature and also has good solvent capacity for large number of drug molecules and carrier systems. The ultimate structure of final Solid dispersions as well as its size, dissolution, stability is greatly affected by various process parameters and the geometry of equipment. Spray drying, a process typically used in the production of coarser (up to 500 m) for food, pharmaceutical, and industrial powders. It can also be used to prepare micro-particulate powders for NCE, excipients, pulmonary and bio therapeutic particle engineering, the drying of crystalline

active pharmaceutical ingredients (APIs), and encapsulation. It is 40-50 times less expensive than freeze –drying, so it is cost-effective and simple. Spray drying is one of the most common techniques used to prepare solid dispersions due to the possibility of continuous manufacturing, ease of scalability, good uniformity of molecular dispersion and cost-effectiveness in large scale production with high recoveries (more than 95%). Solid dispersion products prepared by spray drying are commercially available such as Incivek and Intelence.

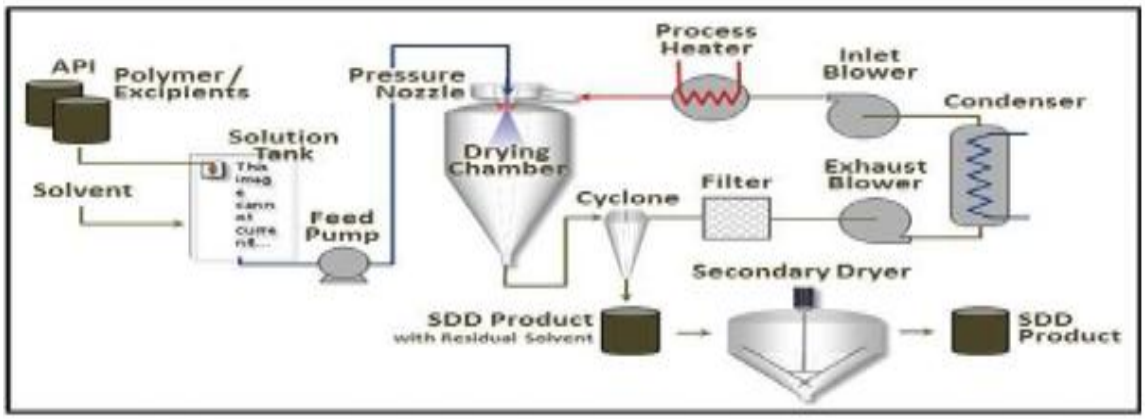

Fig 3: Schematic overview of spray drying process.

9. Gel entrapment technique

Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then drug is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved.

10. Direct capsule filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug.

11. Lyophilization Technique

Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization 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.

12. Electro spinning

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. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Columbic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited If the viscosity increases, the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

13. Supercritical fluid method

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. The use of processes using SCF reduces particle size, residual solvent content, without any degradation and often results in high yield.

14. Dropping solution method

The dropping method, developed to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods. For laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation.

2.4. Suitable properties of a carrier for solid dispersions[5, 11]

The carrier used in solid dispersions must be inert and non-toxic. Selection of carrier for solid dispersions depends on the following properties.

a) Water solubility: Water solubility improves wettability and dissolution.
b) Glass transition point: A high glass transition point improves stability of the formulation.
c) Water uptake: Minimal water uptake by the carrier produces a stable formulation.
d) Melting point: A low melting point of the carrier is required for a stable formulation.
e) Solubility parameters: The carrier should have solubility parameters similar to the drug and must be capable of forming a solid solution.

2.5. Selection of Carriers used in Solid dispersions

The selections of carrier have a profound effect on dissolution characteristics of a drug. So, a water soluble carrier leads to faster release of drug from the matrix and a water insoluble carrier leads to slower release of drug from the matrix.

It should fulfill the following criteria for improving the dissolution characteristics of a drug:

- It does not form a strongly bonded complex with the drug.
- It should be chemically compatible with the drug.
- It should be soluble in a number of solvents.
- It should be pharmacologically inert.
- It should be nontoxic.
- It should be able to increase the aqueous solubility of drug.

2.6. Classification of Carriers

Carriers can be classified in different ways.

In one way they can be classified as.

i) First generation carriers

These include - Sugars, organic acid, and urea.

ii) Second generation carriers

These includes – Starch derivatives like cyclodextrins, Cellulose derivatives like ethyl cellulose, hydroxyl propyl cellulose, hydroxyl propyl methylcellulose and fully synthetic polymers like polyethylene glycols, povidone, polymethacrylates.

iii) Third generation carriers

These includes-Tween 80, poloxamer 408, Gelucire 44/14.

In another way carriers can also be classified as

1] Polymers- These include polyvinyl alchol, poly vinyl poly pyrrolidone, polypyrrolidone, polyethylene glycols, hydroxyl propyl cellulose, hydroxyl propyl methylcellulose, methacrylic copolymers S100 sodium salts etc.

2] Cyclodextrins- These includes

Beta-cyclodextrins, hydroxypropyl-beta-cyclodextrins.

3] Carbohydrates- These includes

Lactose, sorbitol, mannitol, glucose, maltose, soluble starch, cyclylodextrin, galactose, xylitol, galctomannan etc.

4] Surfactants- These includes

Tweens, spans, polyoxyethylene stearates, poly (caprolactone)-b-poly (ethylene oxide) etc.

5] Superdisintegrants- These includes

Sodium starch glycolate, croscarmellose sodium, cross-linked polyvinyl pyrrolidone, cross-linked algin, gellen gum, xanthan gum, calcium silicate etc.

6] Dendrimers-These includes

Citric acid, succinic acid, phosphoric acid, starburst, polyamidoamine etc.

7] Hydrotropes- These includes

Sodium acetate, sodium citrate, sodium-o-hydroxyl benzoate, sodium-phydroxyl benzoate etc.

8] Polyglycolized glyceride acids: These includes
Gelucire44/14, gelucire 50/13, gelucire62/05 etc.

9] Miscellaneous: This includes Dicalcium phosphate, silica gel, sodium chloride, skimmed milk, microcrystalline cellulose etc.

2.7. Characterization of solid dispersions[12]

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions. However, most effort has been put in to differentiate between amorphous and crystalline material. Various methods include Thermal analysis, DSC, Powder X-ray diffraction method, Spectroscopic methods (FTIR, NMR, Raman spectroscopy), microscopic method (Hot-stage microscopy) and *in-vitro* dissolution studies.

Mechanisms suggested being responsible for the improved aqueous solubility/ Dissolution properties of Solid dispersions includes[13]

A) Reduction of the particle size of the incorporated drug, In solid dispersions, the particle size of the drugs was reduced, and the wettability and the dispersibility of the drugs were enhanced; therefore, drug dissolution was improved markedly.
B) Partial transformation of crystalline drug to the amorphous state.
C) Formation of solid solution.
D) Formation of complexes.
E) Reduction of aggregation and agglomeration.
F) Improved wetting of the drug and solubilization of drug by the carrier at the diffusion layer.

2.8. Applications of solid dispersions[14]

1. The Solid dispersion systems were shown to provide the bio available oral dosage forms for the anti-cancer drugs, which could be substituted for the standard injections to improve the patient compliance & comfort.

2. Solid dispersion also act as the functional carriers that offer the added benefit of the targeting the release of the highly soluble forms of the poorly water soluble drugs for absorption to an optimum site.
3. The solid dispersion systems were also found to reduce the food effects on the drug absorption, thus by increasing the convenience of the drug therapy as it is the need for some drugs to be taken with food was eliminated.
4. The solid dispersion formulations were demonstrated to accelerate the onset of action for the drugs such as NSAIDS [nonsteroidal anti-inflammatory drugs] where immediate action is crucial in relieving acute pain and inflammation.
5. The improved absorption efficiency was demonstrated for the solid dispersion systems that allows for the reduction in the content of the active agent per dose thus it decreases the cost associated with these drug therapies
6. The dry powder formulation consisting of the solid dispersion [For e.g. Cyclosporine A] for use as inhalation is prepared in improving the immunosuppressive therapy in the lung transplant patients. Many problems can be avoided which includes use of local anesthesia & irritating solvents.
7. The dosage form based on Solid dispersion allows for greater drug loading per dose & improved stability over the soft gelatin capsule formulation which thereby improves the convenience of drug therapy by reducing the dosing regimen & eliminating the need for the refrigerated storage.

The above benefits demonstrate the current contributions & future potential of the solid dispersion systems towards the improving drug therapies for the variety of the important medical conditions whose treatment involves poorly water soluble drug.

Table 1.1: Commercially available solid dispersions[15]

Commercial products	**Dispersant**	**Manufacturer company, Country**
Afeditab (Nifedipine*)	Polaxamer or Polyvinyl Pyrrollidone (PVP)	Elan corp, Ireland
Cesamet (Nabilone*)	Polyvinylpyrrolidone(PVP)	Valeant Pharmaceuticals, Canada
Cesamet(Nabilone*)	Povidone	Lilly, USA
Certican (Everolimus*)	Hydroxypropylmethylcellulose (HPMC)	Novartis,S witzerland
Fenoglide (Fenofibrate*)	Polyethyleneglycol(PEG)	Life Cycle Pharma, Canada
Gris-PEG (Griseofulvin*)	Polyvinylpyrrolidone	VIP Pharma, Denmark
Gris-PEG (Griseofulvin*)	Polyethyleneglycol	Novartis, Switzerland
Intelence (Etravirine*)	Hypromellose	Tibotec, Yardly,PA

	/Microcrystallinecellulose	
IsoptinSRE-240 (Verapamil*)	Various	Soliqs, Germany
Ibuprofen*	Various	Soliqs, Germany
Kaletra(Lopinavir* Ritonavir*)	Polyvinylpyrrolidone/Polyvinylacetate	Abbott Laboratories, USA
LCP-Tacro (Tacrolimus*)	HPMC	Life Cycle Pharma, Denmarck
Rezulin (Troglitazone*)	PVP	Pfizer, USA
Sporanox (Itraconazole*)	HPMC	Janssen Pharmaceuticals, Belgium
Torcetrapib*	HPMC acetate succinate	Pfizer, USA

Table 1.2 Data of solid dispersions of various drugs formed with different polymers along with different techniques used in formulation.

Name of Drug	Technique used	Carriers used
Tolvaptan[16]	Solvent evaporation	Kolliphor Soluplus
Entacapone[17]	Spray drying	Gelucire, campitrol
Spiranolactone[18]	Fusion	PEG 4000
Efavirenz[19]	Hot-melt extrusion	Eudragit EPO/Plasdone S-630
Ticagrelor[20]	Solvent evaporation	Kolliphor
Telmisartan[21]	Physical mixture	PEG 6000, Eudragit L 100,PVP K30
Glimepiride[22]	Solvent evaporation	PVP K30
Aceclofenac[23]	Solvent evaporation	PVP
Paracetamol[24]	fusion	PEG 4000,6000
Aceclofenac[25]	Solvent evaporation	PVP
Mesalamine[26]	Kneading	SLS,Urea
Carvediol[27]	Fusion, Solvent evaporation	PEG 6000, HPMC, Polaxamer-407
Ketoconazole[28]	Fusion	PEG 6000
Mefenamic acid[29]	Melt method	PEG 3350
Mefanamic acid[30]	Solvent evaporation	PVP
Esomeprazole zinc[31]	Solvent method	PEG 4000
Lovastatin[32]	Solvent evaporation	SLS, Tween 80, Oleic acid, PVP
Acyclovir[33]	Spray drying	PEG,PVP
Lovastatin, Simvastatin[34]	Spray drying	PVP,PEG
Isaradipine[35]	Solvent evaporation	PVP
Aceclofenac[36]	Melting	Gelucire 44/14, Polaxamer 407
Indomethacin[37]	Common solvent	HPMC, HPC-SL, HEC
Ibuproxam[38]	Co-evaporation/Co-grinding	PVP, PEG, Urea
Nimesulide[39]	Solvent evaporation, Co-grinding	PEG 400, PVP K30, SLS, Tween 80
Meloxicam[40]	Physical mixing Solvent evaporation	PEG 600
Glyburide[41]	Co- fusion or Co-evaporation	PEG
Rofecoxib[42]	Solvent evaporation	PVP K30
Ritonavir[43]	Spray drying	PVP, Vinyl acetate
Metoclopramide HCL[44]	Solvent evaporation	Eudragit
Ibuprofen[45]	Melting	PEG 20000
Chlordiazepoxide[46]	Solvent, Co-grinding	PVP, Mannitol, Eudragit E
Albendazole[47]	Melting, Solvent, Kneading	PEG 6000, Urea
Gliclazide[48]	Co-grinding	PVP K30
Carbamazepine[49]	Co-grinding	MCC

Sulfamethoxazole[50] Nifedipine	Lyophilization/ spray drying	PEG 6000
Spiranolactone[51]	Electrospinning Melt extrusion	Poly vinyl caprolactam-Polyvinyl acetate-PEG(Soluplus)
Carvediol[52]	Electrospinning	Eudragit E
Meloxicam[53]	Dropping	PEG 4000
Atrovastatin calcium[54]	Dropping	PEG 4000, 6000
Azithromycin[55]	Solvent evaporation	Kolliphor P237, 338, 407
Olanzapine[56]	Solvent evaporation	PEG
Pioglitazone[57]	Spray drying	PVP K17, K30, HPMC E3

CONCLUSION

The growing number of new chemical entities/drug candidates, which are mostly poorly soluble in nature leads to decreased oral bioavailability of these drugs as dissolution being the rate-limiting step. Hence enhancing of solubility and bioavailability is the major challenge faced by formulation scientist. So for enhancing the solubility many techniques have been used, solid dispersion being one of them. Solid dispersion has been used since past few decades for the enhancement of solubility. Hence solid dispersion technique has become one of the promising approach for improving the release rate and oral bioavailability of hydrophobic drugs. The preparation method and amount of the carrier also play a vital role in the enhancement of drug dissolution rate. Many of the carriers that can be used in solid dispersion technique are already extensively used in the pharmaceutical industry as excipients, no toxicity studies are required. The release rate and oral bioavailability of poorly water soluble drugs can be enhanced by carefully selecting the carrier which helps to delay or slow down the release pattern of a drug by formulating it into solid dispersion. Most of the solid dispersion work is in lab-scale set ups; therefore the manufacturing process requires enough knowledge to scale up to the commercial scale.

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