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A REVIEW ON SOLID DISPERSION AND IT'S APPLICATION

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ABSTRACT
Poor solubility of drugs is a major challenge in the formulation development. Solid dispersion is introduced as a novel means for enhancement of solubility. Solid dispersion may be defined as a set of solid products comprising of at least two diverse components, usually hydrophilic matrix and hydrophobic drug. Depending on nature of carriers the immediate release solid dispersions and/or controlled release solid dispersions can be formulated. This matrix may be crystalline or amorphous in nature. As per biopharmaceutical classification system class II drugs are with low solubility and high permeability and are the promising candidates for improvement of solubility as well as bioavailability by means of solid dispersion. The carriers used previously were mostly synthetic one. Recent trend towards the use of natural carriers have replaced the use of synthetic carriers. This review is the overview of various synthetic, natural, semisynthetic, modified natural hydrophilic carriers used for formulation of solid dispersions. Since a solid dispersion is basically a drug–polymer two-component system, the drug– polymer interaction is the determining factor in its design and performance. In this review, we summarize our current understanding of solid dispersions both in the solid state and in dissolution, emphasizing the fundamental aspects of this important technology Practical aspects pertaining to preparation of solid dispersions, like the selection of carrier, drugs molecular arrangement in these preparations are discussed in this article. Proposed article highlights the various preparation techniques of solid dispersion, characterization, available recent technologies, marketed preparation, future prospective etc.

KEYWORDS:

INTRODUCTION

The simple and easy way of administration of the drug is through oral route. The oral dosage forms have many benefits compared to other dosage forms like greater stability, accurate dosage, smaller bulk and ease of production. The oral route has been considered as most common and preferred route owing to convenience and easy administration. As a patient's prospect, swallowing a dosage form is a comfortable means of taking medication.[1,2] Solubility is a major challenge for certain drugs to develop a suitable formulation for administration of drugs orally like Griseofulvin, Digoxin, Phenytoin, Sulphathiazole and Chloramphenicol. With the recent advent of high-throughput screening of potential therapeutics, the numerous drug candidates with poor solubility have increased severely and their formulation for oral delivery poses great challenge to formulation scientists in the pharmaceutical industry.[3,4] Major problem encountered during oral delivery of certain active agents is poor bioavailability due to inadequate drug absorption. Therefore, pharmaceutical research is mainly focused on two prime areas: first to improve the oral bioavailability of active agents including solubility enhancement and dissolution rate of poorly water-soluble drugs and secondly to enhance the permeability of poorly permeable drugs. In the Biopharmaceutical Classification System (BCS) (table 1) drugs with high membrane permeability and low aqueous solubility are categorized as Class II drugs. Therefore, solid dispersion (SD) technologies are particularly useful in the improvement of oral absorption as well as the bioavailability of BCS class II drugs.[5]

Table no. General BCS for orally administered drugs.

BCS Class	Solubility	Permeability
BCS 1	High	High
BCS 2	Low	High
BCS 3	High	Low
BCS 4	Low	Low

Solubility

The Solubility is the property of a liquid, solid, or gaseous chemical substance called solute to dissolve in a liquid, solid, or gaseous solvent to obtain a homogeneous solution of the solute in the solvent. The solubility of any substance basically depends on the solvent used in temperature and pressure as shown in (table 2).[6]

Table 2: Solubility parameter.

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practical insoluble	10000 and over

Importance of solubility

Solubility is one of the significant parameters to attain a preferred concentration of drug in systemic circulation for providing a therapeutic response. Oral intake is the most suitable and frequently employed route of drug delivery owing to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms.[7]

Factors affecting solubility

The solubility depends on the physical form of the solid, the nature and composition of the solvent medium as well as temperature and pressure of system.[8,9]

(a) Particle size

It is very much related to solubility and affects surface area to volume. If the particle size is reduced, this ratio gets increased. Greater the surface area greater the interaction with the solvent occurs.[10]

(b) Temperature

Usually, solubility of a solid solute is increased due to increase in temperature.

(c) Pressure

An increase in pressure causes an increase in solubility and vice versa for gaseous solutes while for solid and liquid solutes it has no effect on solubility.[11]

(d) Nature of the solute and solvent

Nature of solute and solvent affect solubility. For example, one gram of lead chloride can be dissolved in 100 grams of water at room temperature; while 200 grams of zinc chloride can be dissolved. This vast difference in solubility is due to the difference in the nature.

(e) Molecular size

Molecular size is also affecting the solubility. The bigger the molecule or greater the molecular weight, the less soluble will be the compound. In the case of organic compounds, the quantity of carbon branching will lead to increase in solubility as more branches reduce the size of the molecule.[12,13]

(f) Polarity

It is known that like dissolve like. Generally polar solute dissolves in polar solvents while non-polar solute dissolves in non-polar solvents. Polar solute compound is having both ends to the molecule positive as well as negative. For polar solvent, the positive end of it attracts negative end of the solute molecule. This type of interaction is known as dipole-dipole interaction.[14]

(g) Polymorphs

The capacity for a substance to crystallize in more than one crystalline form is a 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 enantiotropy. 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 solubility.[15, 16]

Techniques for solubility enhancement

There are various techniques that help in increasing the solubility of drugs are as follows.[1, 17]

I. Chemical modifications

1. Salt formation
2. Co-crystallization
3. Co-solvency
4. Hydrotropy
5. Solubilization
6. Nanotechnology

II. Physical modifications

1. Particle size reduction
2. Modification of the crystal habit
3. Complexation
4. Solubilization by surfactants
5. Drug dispersion in carriers

a. Solid solution
b. Eutectic mixtures
c. Solid dispersion

Solid dispersion

There are various techniques for solubility enhancement. Solid dispersion is one of the best approaches for solubility enhancement. The term SD refers to a set of solid products comprising of at least two diverse components, usually hydrophilic matrix and a hydrophobic drug. The matrix may be crystalline or amorphous, and the drug can be dispersed in either form.[2, 7, 18, 19]

According to Chiou and Riegelman, solid dispersion systems can be defined as 'the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting [fusion], solvent, or melting solvent method'. The drug is hydrophobic in nature whereas matrix is hydrophilic.

Advantages of Solid Dispersion[2,20,21,22]

1. To reduced particle size.
2. To improve wettability.
3. To improve porosity of drug.
4. To decrease the crystalline structure of drug in to amorphous form.
5. To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
6. To mask the taste of the drug substance.
7. To prepare rapid disintegration oral tablets.
8. To obtain a homogenous distribution of small amount of drugs at solid state.
9. To stabilize unstable drugs.
10. To dispense liquid or gaseous compounds.
11. To formulate a faster release priming dose in a sustained release dosage form.
12. To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or
13. Insoluble carriers
14. Improved drug bioavailability and change in water solubility are possible.
15. More efficient than particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine.
16. Increase in dissolution rate and extent of absorption and reduction in pre-systemic metabolism.
17. Transformation of liquid form of drug into solid form.
18. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability.[2, 21]

Disadvantages of Solid Dispersion

Limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations include are as follows.

1. Laborious and expensive methods of preparation,
2. Reproducibility of physicochemical characteristics
3. Difficulty in incorporating into formulation of dosage forms,
4. Scale-up of manufacturing process, and
5. Stability of the drug and vehicle.
6. its method of preparation, Various methods have been tried recently to overcome.
7. the limitation and make the preparation practically feasible. Some of the suggested. approaches to overcome the aforementioned problems and lead to industrial scale production are discussed here under alternative strategies.[23]
8. Changes in crystallinity and a decline in dissolution rate with aging.[24]
9. Moisture and temperature have deteriorating effect on SD than on physical mixtures.
10. Some SD may not lend them to easy handling because of tackiness.
11. Drawback of SD is their poor scale-up for the purposes of manufacturing.[25, 26]

Classification of solid dispersions

Solid dispersions are classified by various ways viz. on the basis of carrier used and on the basis of their solid-state structure.

1. First generation solid dispersion

The solid dispersions which could be prepared by using crystalline carriers are categorized as the first-generation solid dispersions. Examples of used crystalline carriers are urea and sugars. In this type, thermodynamically stable crystalline solid dispersion gets formed which releases the drug slowly. The dissolution rate is faster in case of amorphous solid dispersions (ASDs) as compared to crystalline sold dispersions. The first reported solid dispersion was eutectic mixture or monotectic mixture. In case of eutectic mixture melting point of dispersion is lower than the melting point of carrier and drug the melting point of drug and carrier are constant in case of monotectic mixture. In cooling process of eutectic mixture, the drug and carrier will crystallize simultaneously therefore it is preferred over the monotectic mixture. At the specific composition in eutectic mixture where drug crystallizes out is referred as eutectic point, and the mixture consists of fine crystals of two components. Small particle size will result in increased specific surface area which generally improves rate of dissolution and oral absorption of poorly water-soluble drugs. Moreover, the number of studies having exact eutectic composition in solid dispersion is very limited. Based on the extent of miscibility between the two components or the crystalline structure of solid solution they are of two kinds. One is continuous [or isomorphous, complete, unlimited] solid solutions and the other discontinuous [or restricted, partial, limited, complete] solid solutions. They can also be classified into two groups- substitutional solid solutions in which the solute molecule substitutes the solvent molecule in the crystal lattice of the solid solvent. Whereas, in case of interstitial solid solutions, the solute molecule occupies the interstitial space of the solvent lattice. The disadvantage of first-generation solid dispersion is forming crystalline solid dispersion as they were prepared using crystalline carriers like urea and sugars. Crystalline solid dispersions were more thermodynamically stable which lowers their dissolution rate as compared to amorphous one. Okonogi et.al has studied the effect of urea and mannitol on crystallinity of ofloxacin. The higher solubility and dissolution rate were observed in case of urea based solid dispersions than mannitol based solid dispersions because urea reduced the crystallinity of ofloxacin more than mannitol proved by PXRD and DSC results.[27-31]

2. Second generation solid dispersion

These contain amorphous carriers like PVP, PEG, cellulose derivatives, etc. Second generation solid dispersions were found more effective than first

generation solid dispersions (SD) because of their thermodynamic stability. According to the physical state of drug, ASDs can be classified as amorphous solid suspensions and amorphous solid solutions [glass solutions]. Amorphous solid suspensions consist of two separate phases while amorphous solid solutions contain molecularly homogenous mixture of both the drug and amorphous carriers. Amorphous carriers can be synthetic polymer or natural polymer.8 Amorphous solid suspensions can be formulated in case of drugs with limited carrier solubility or high melting point. In case of second-generation solid dispersions because of forced solubilization of the drug in the carrier the drug is in its supersaturated state. Due to increase in chain length or molecular weights of polymers the aqueous solubility of polymers gets decrease and viscosity get increased. Prevention of recrystallization of drugs in manufacturing, storage and dissolution process can be achieved by using high viscosity polymers. Moreover, the use of high viscosity polymer can delay the dissolution rate of drug in aqueous medium. The major problem regarding second generation solid dispersion is drug precipitation and recrystallization which affect the in vitro or in vivo drug release.[29-31]

3. Third generation solid dispersion

The dissolution profile of drug can be improved using third generation solid dispersions which consists of carriers having surface activity or emulsifying properties. Use of special type of carrier for formulation of solid dispersions will overcome precipitation and recrystallization problems. Use of surfactant or emulsifiers not only improve the dissolution profile of drug but also improves physical and chemical stability of drug in solid dispersion. Examples of these carriers are inulin, Gelucire, poloxamer, etc. The physical and chemical stability of solid dispersion get enhanced by preventing nucleation and agglomeration. The selection of surface-active agent or another polymer is based on dissolution or stability profile of drug, i.e., surfactant is used when faster dissolution is required while polymer with higher Tg may be used when prevention of re-crystallization is needed.[30-32]

4. Fourth generation solid dispersion

These types of dispersions can be referred as controlled release solid dispersions (CRSD). It contains poorly water-soluble drug with a short biological half-life. The carrier used are either water soluble carrier or water insoluble carrier. Solubility enhancement and extended release of drug in controlled manner are the two targets in CRSD. The water-soluble carriers used in CRSD are ethyl cellulose, Eudragit RS, Eudragit RL, HPC, etc. On the basis of physical state and molecular arrangement of active pharmaceutical ingredient (API) and carrier, binary solid dispersions can be divided into six distinct systems as follows: Meng et al have classified solid dispersions into six groups Class C–C, Class C–A, Class A–C, Class A–A, Class M–C, Class M–A based on physical state and molecular arrangement of both API and carrier. Further efforts are needed to shape a clear and semi-synthetic hydrophilic carrier. Initially crystalline carriers like urea, sugars etc. were used in formulation of solid dispersions which have been changed to amorphous carriers including polymers. Therefore, mostly used form of solid dispersions is the ASDs. Use of various polymeric carriers affects dissolution characteristics of dispersed drug. Water soluble carrier results in a fast drug release while poorly soluble or insoluble carrier will retard the drug release from the matrix.[29,30]

Types of Solid Dispersion

Eutectic mixtures

Two compounds which are completely miscible in the liquid state leads to simple eutectic mixture formation but only to a very limited extent in the solid state (fig. 1).[33] This is usually prepared by rapid solidification of fused melt of two components that shows complete liquid miscibility but negligible solid-solid solution.[12,17]

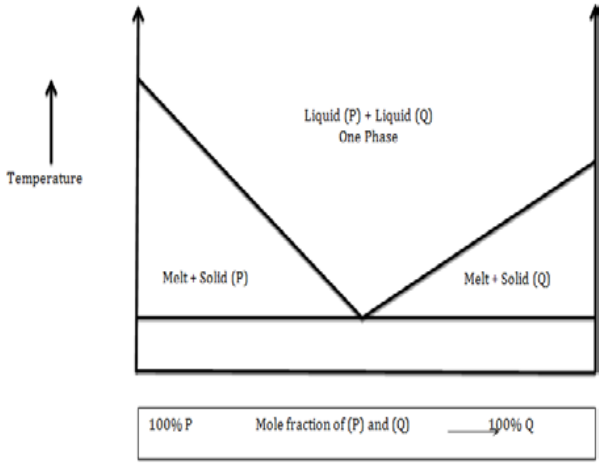

Fig. 1: Simple eutectic mixture phase diagram.

1. Amorphous precipitation in crystalline matrix

This is similar to simple eutectic mixtures but only difference is that drug gets precipitated out in an amorphous form.

2. Solid solutions

When two components crystallize together in a homogeneous single phase considered as solid solution. They are of two types: Substitutional solid solutions, interstitial solutions. Solid solutions can generally attain quicker dissolution rate than the corresponding eutectic mixture.[10, 34]

3. Glass solutions and suspensions

A homogeneous system which consists of solid solute dissolved in a solid solvent is known as glass solutions. Mixed/heterogeneous groups of crystals are formed because both components crystallize simultaneously. A homogeneous system in which the drug molecule is suspended in a glassy carrier is termed as glass suspensions. Glassy state in glass solution and glass

suspension is characterized by transparency and brittleness below the glass transition temperature.[14,19,35]

Methods of preparation

Melting and solvent evaporation methods are the two major processes of preparing SD.

1. Melting method

In this method drug is dissolved in a suitable liquid solvent. Then, the solution is incorporated directly into the melt of polyethylene glycol obtainable below 70 °c, without removing the liquid solvent. It has been shown that without significant loss of its solid property 5-10% (w/w) of the liquid compound could be incorporated into polyethylene glycol 6000.[2,10,36] This method consists of the physical mixture of drug and carrier preparation followed by heating until it gets melted. Finally obtained solid mass is then crushed and sieved. Additionally, supersaturation of drug or solute can be achieved by quenching the melt quickly from a high temperature.[17,37] This method is also known as fusion method. Although numerous compounds either drugs or carriers gets decomposed or evaporate during the process due to elevated temperature. Oxidative degradation of drug or carrier can be avoided possibly by heating the physical mixture in a sealed container or melting it under vacuum or in the presence of inert gas like nitrogen.[25]

2. Solvent evaporation method

The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated as shown in (fig. 2). The thermal breakdown of drugs or carriers can be 4 stopped, since organic solvent evaporation occurs at low temperature.[38] A basic process of preparing SD of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol, chloroform, a mixture of ethanol and dichloromethane. Normally, the resulting films are pulverized and milled.[2, 39]

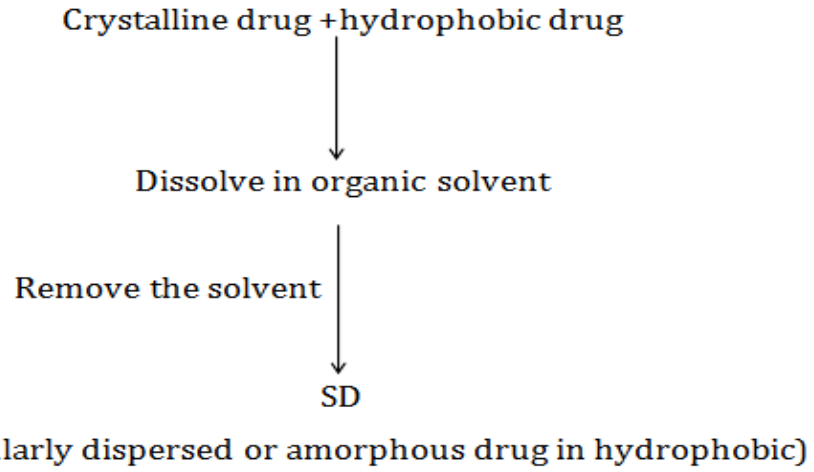

Fig. 2: Preparation of solid dispersion by solvent evaporation method.

3. Melting solvent method (melt evaporation)

Melt evaporation leads to the development of SD by dissolution of drug in an appropriate solvent followed by incorporation of solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The obtained film is dried further till constant weight. The film is further dried to constant weight.[7, 38] This technique possesses unique advantages of fusion as well as solvent evaporation methods.

4. Hot melt extrusion method

In this method extruder is utilized for intense mixing of components. The components of the extruder are barrel, hopper, a kneading screw, heating jacket, and a die.[40] Generally physical mixture of both the carrier and drug is introduced into the hopper then passed through screw and finally it is extruded from the die (fig. 3). The advantage of the method is to get various shapes and designs of the heated drug-matrix mixture into ophthalmic inserts, implants, or oral dosage form.[17,39] Other advantage like the continuous production of SD is possible so that large-scale production can easily be achieved. The product produced by this method can easily be handled because any shape can be adopted.[41] Like other methods, miscibility of drug and matrix also creates a problem. Thermolabile compounds can be degraded due to the production of heat generated by the extruder.[5,7]

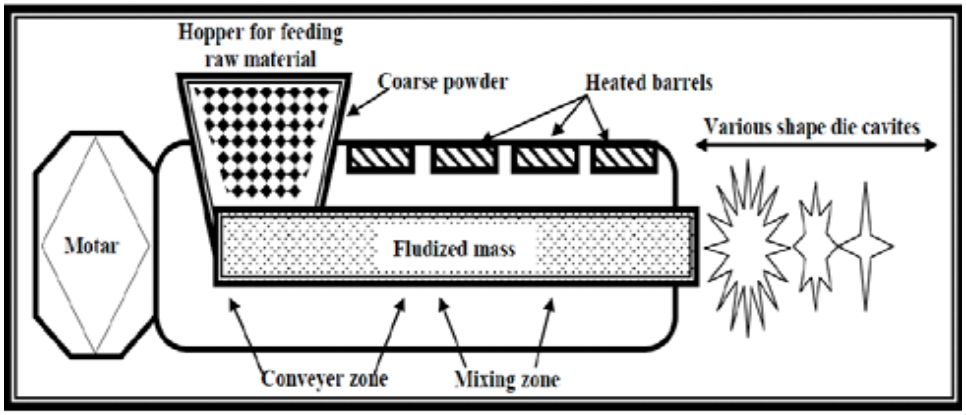

Fig. 3: Hot melt extruder.

5. Fusion method

This is sometimes used interchangeably as the melt method that is appropriate only when the crystalline substances are used as the starting materials. Hence, generally fusion term is chosen. The first SD was developed by this method for pharmaceutical applications. This was a mixture of sulfathiazole and urea which fused and later cooled to get the final dispersion. The eutectic composition was chosen in order to attain to attain concurrent crystallization of drug and matrix during cooling.[33,42,43]

6. Supercritical fluid methods

These methods are generally applied with carbon dioxide, which is used either as a solvent for drug and matrix or as an anti-solvent. While supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through nozzle, into an expansion vessel with lower pressure, and particles are immediately formed (fig. 4). The mixture causes rapid cooling. In this technique it does not involve the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is rapid expansion of supercritical solution.[25,44,45]

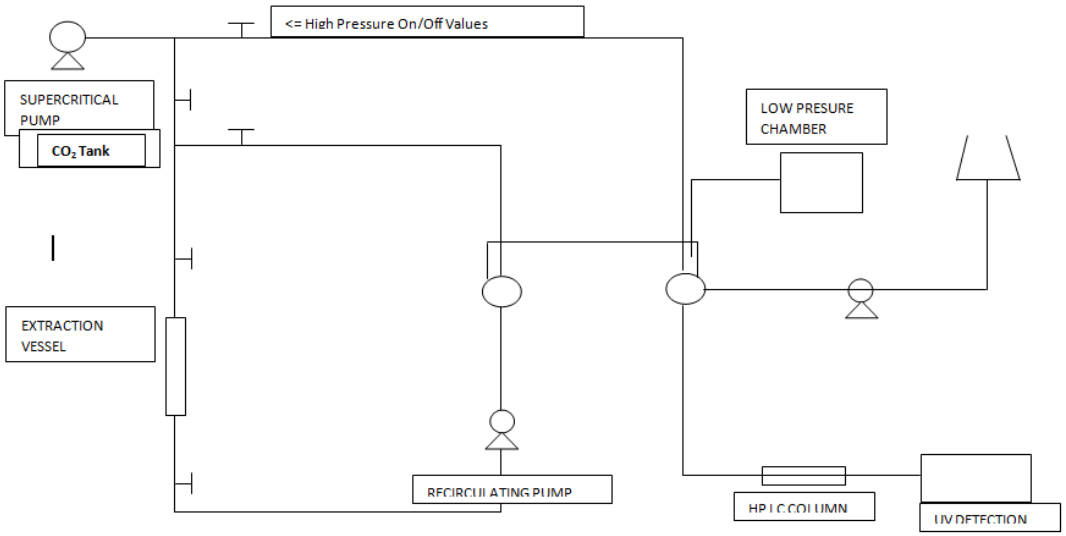

Fig. 4: Schematic diagram for supercritical fluid technology[9]

7. Spray drying

This method was developed in 1920 in which the manufacture of milk powder was one of the first applications of spray drying. Presently, this technique is having great utility in pharmaceutical industry owing to rapid drying and specific characteristics such as particle size and shape of the final product. In this method atomization of suspensions or solutions into fine droplets is done and drying of particles that may lead to the formation of solid particles.[14] This process permits production of fine, dust free powder.[33,46]

8. Freeze-drying

This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized.[1] The main advantage of this technique is that the drug exposed to minimum thermal stress and low

risk of phase separation. Freeze drying technique is poorly explored for making SD.[47,48]

9. Lyophilization technique

In this technique the drug and carrier are dissolved in a common solvent, frozen and sublimed to attain a lyophilized molecular dispersion.[49,50]

Possible mechanism of SD

The enhancement in dissolution rate because of SD formation, relative to pure drug, varies from as high as 400-fold to less than two-fold. The increase in dissolution rate can be attributed to myriad factors and it is very difficult to show the experimentally importance of one factor in comparison to other. SD improves the dissolution rate of poorly water-soluble drugs by following mechanisms.[17, 51]

- Reduction in particle size.
- Improvement in wettability and dispersibility.
- Change in crystalline form of drug to amorphous form.
- Reduction in aggregation and agglomeration of drug particles.

Mechanisms of incorporation of drug into polymer

Carriers used in solid dispersions are polymers. When drug and polymer are in intimate contact then drug occupy void spaces between polymeric chain and makes polymer chain relatively flexible. For example, in case of hot melt extrusion process, polymer is allowed to heat up to some extent that the heat given is responsible for loosening of polymer chain and incorporation of drug molecule into it. While in spray drying method, the solvent used in process is responsible for weak cohesive inter and intra molecular interactions of polymer chain and resulting in formation of solvent polymer interactions. After this, drug molecules dissolved in solvent are incorporated into the loosened polymer chains.

Antiplasticization effect is observed when the mechanical properties of substance changes into stiff and brittle when another substance is added. In another way it can be explained as, compound with low Tg of resulting mixture would fall somewhere in between the Tg's of both compounds. In this case drug undergoes antiplasticization. Whereas polymer undergoes plasticization as its Tg decreases.[52]

Drug release mechanism from solid dispersion

Dissolution performance of solid dispersion after its oral administration in the form of tablet, capsules, etc. will give proper idea about ultimate success. One of the successful approaches for enhancement of solubility of poorly soluble drug is conversion of crystalline form of drug to an amorphous from. For successful solid dispersion formulation major keys are supersaturation state maintenance and amorphous form stabilization. The problem regarding solid dispersions is precipitation of supersaturated drug which will ultimately affect its bioavailability. Increases stability and solubility of drug in medium is observed due to particle size reduction and reduced agglomeration. In supersaturating drug delivery system such as solid dispersion spring like effect is observed due to enhancement of dissolution rate of drug. At the stage of supersaturation decrease in dissolution rate is observed due to drug precipitation. Furthermore, in such system parachute like effect is observed on dissolution profile of drugs when precipitation inhibitors are added. Drug controlled release and carrier-controlled release are two types of mechanisms involved in drug release from immediate release solid dispersions. While in case of CRSD diffusion and erosion drug release mechanisms are observed depending on characteristics of polymer and the miscibility of the drug and carrier. If the carrier is soluble in the dissolution medium, then the release of ASD is dissolution-controlled mechanism while in case of insoluble carrier diffusion-controlled mechanism is observed.[52-55]

Characterization of SD

The physical nature of SD can be characterized by various methods. Single method is not sufficient to furnish the complete information rather a combination of two or more techniques is needed.[56,57]

1. Thermal analysis
2. X-ray diffraction method
3. Spectroscopic method
4. Modulated temperature differential scanning calorimetric
5. Environmental scanning electron microscopy
6. Dissolution testing
7. Dissolution rate method
8. Microscopic method
9. Thermodynamic method[4]

Thermal analysis techniques

The thermal analysis comprises a group of techniques in which a physical property of a substance is measured as a function of temperature while the substance is subjected to a controlled temperature programmed.[58] In differential thermal analysis (DTA), the temperature difference existing between a sample and an inert reference material is measured.

X-ray crystallography

This method can be used to determine the arrangement of atoms within a crystal. In this method X-ray beam hit a crystal and diffracts into many directions. A crystallographer can produce a three-dimensional picture of the density of electrons within the crystal from the angles and intensities of these diffracted beams. The mean positions of the atoms in the crystal can be determined from this electron density.[59]

Spectroscopy

It is the study of the interaction between radiation and matter as a function of wavelength (λ). Conventionally, spectroscopy referred to as the use of visible light dispersed according to its wavelength, e. g. by a prism.

Later on, the concept was further extended to comprise the measurement of a quantity as a function of either wavelength or frequency.

Environmental scanning electron microscopy

The morphology of the spray-dried ternary SD 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.[61,62]

Applications of Solid Dispersion in pharmaceutical field

Apart from absorption enhancement, the SD could have numerous other pharmaceutical applications, which need to be explored.[57] Currently, they have been applied successfully.

1. to develop dispersible tablets.
2. mouth dissolving tablets.
3. enhancement of dissolution rate.
4. mucoadhesive drug delivery.
5. dry powder for reconstitution.
6. controlled drug delivery.

CONCLUSION

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Successful development of SD system for preclinical, clinical and commercial use has been feasible in recent years due to the availability of surface-active carriers and self-emulsifying carriers. These significantly help to improve the bioavailability and bioequivalence. Finally, it is asserted that if the manufacturing of SD are properly controlled and validated then it can be suitably propelled on commercial scale and various cost-effective dosage form can be launched.

Future prospects

The most frequent concerns with SD have been the ability to scale-up the manufacturing method, the physical stability of the dispersion, and the amount of carrier needed to facilitate the required increase in the release rate. When a high carrier/drug ratio must be used, the amount of dispersion required to administer the usual dose of the drug may be too high to produce a tablet or capsule that can be easily swallowed. The higher the unit dose of the drug, the more likely this problem is to occur. Another aspect that must be considered is the correlation between *in vitro* and *in vivo* results. Dispersions with a rapid *in vitro* release rate may fail to improve the oral bioavailability if the *in vitro* test conditions do not adequately simulate the gastrointestinal conditions, or if there is some specific interaction between the carrier and a component of the GI. Several products containing SD are already on the market and the number is expected to increase dramatically in the next years.

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