WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 11, 818-836 Review Article ISSN 2278 – 4357

A TECHNIQUE TO ENHANCE THE BIOAVAILABILITY AND SOLUBILITY FOR POORLY WATER SOLUBLE DRUGS BY USING: SOLID DISPERSION

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Article Received on
08 Sept. 2018,

Revised on 28 Sept. 2018,
Accepted on 18 October 2018

DOI: 10.20959/wjpps201811-12663

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ABSTRACT

Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The focus of this review article on advantages, disadvantages and the method of preparation, and characterization of the solid dispersion. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The various techniques are available for enhancement of solubility. Solid dispersion is one of the most promising approaches for solubility enhancement. Currently only 8% of new drug candidates have both high solubility and permeability. More than 60% of potential drug products suffer from poor water solubility.

KEYWORDS: Solubility, Solid Dispersions, Carrier, Bioavailability Hydrophilic, Fusion method.

1-INTRODUCTION

Oral drug delivery is the most popular, simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. More than 90% of drugs 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.[1] When an active agent given orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the gi tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will.

Typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas focus on improving the oral bioavailability of active agents include (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs.

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. There are various techniques such as, particle size reduction, micronization, physical modifications, nano suspension, modification of crystal habit such as, polymorphs, pseudo polymorphs, complexation, solubilization, salt formation, and use of cyclodextrins which can enhance the solubility & dissolution rate of insoluble drug but this techniques having some practical limitations, solid dispersion technique overcome this practical limitations.[2] In the biopharmaceutical classification system (bcs) drugs with low aqueous solubility and high membrane permeability are categorized as class ii drugs therefore, solid dispersion technologies are particularly promising forimproving the oral absorption and bioavailability of bcs class ii drugs. In case of solid dispersion drug disperse in the matrix generally a hydrophilic matrix and a hydrophobic drug, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs.[2] modified ***noyes-whitney equation*** gives some idea how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.[2]

$$\frac{dC}{dt} = \frac{AD(Cs - C)}{h}$$

Where,

Dc/dt is the rate of dissolution,

A is the surface area available for dissolution,

D is the diffusion coefficient of the compound,

Cs is the solubility of the compound in the dissolution medium,

C is the concentration of drug in the medium at time t,

H is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

Surface area directly proportional to rate of dissolution, it is increased by decreasing the particle size of drug or by optimizing wetting characteristics. Particle size reduction, salt formation, complexation and solubilization of drug in solvent(s) also useful to increase dissolution, however, there are limitations for this techniques.[3] In 1961, *sekiguchi and obi* reported the formation of eutectic mixture of sulfathiazole with urea and demonstrated that the drug existed in microcrystalline state.[4,10] On the contrary, another study reported that the drug need not exist in a microcrystalline state; a certain fraction of the drug may be molecularly dispersed in the matrix, forming solid solution. When a solid dispersion is dispersed in aqueous medium, the carrier solubilised and released the drug as fine colloidal particles, leading to the enhancement of dissolution rate and bioavailability of poorly water-soluble drugs which could be attributed to enhanced surface area.[4]

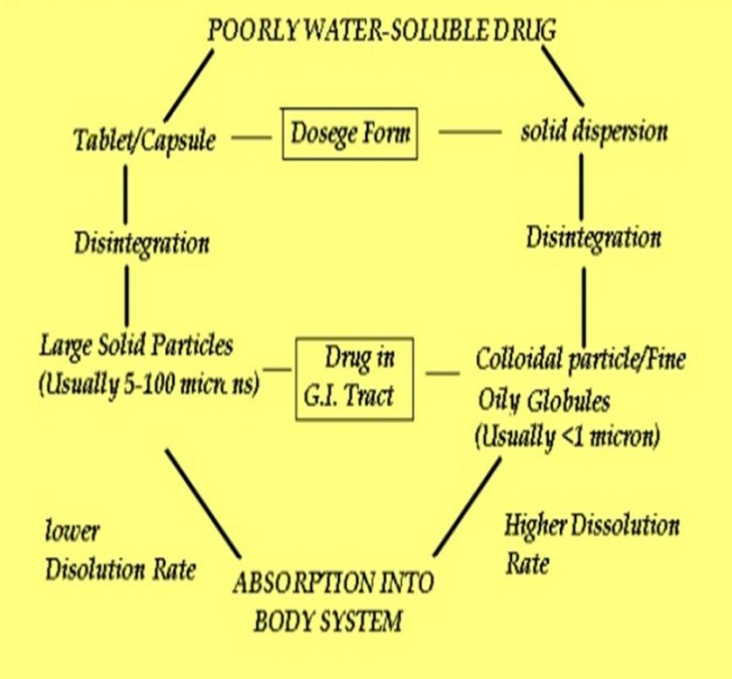
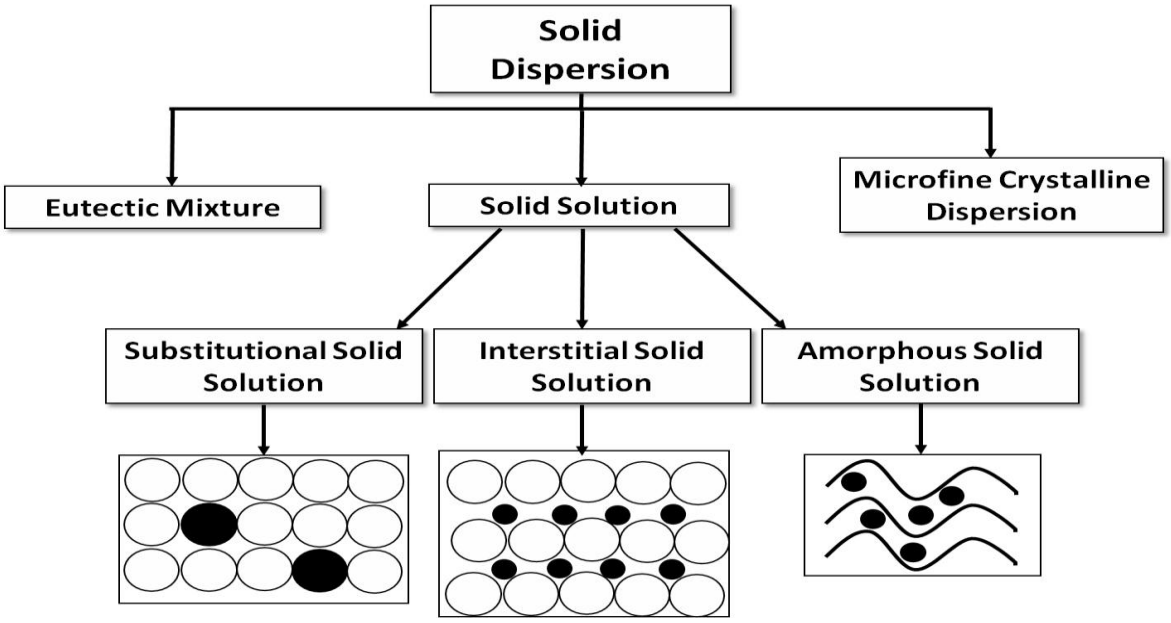


Fig. 1: A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

2-Classification of solid dispersion

Since the 1960s, many solid dispersion formulations have been developed. Currently there are six major types of solid dispersions together with various subtypes. These solid dispersion types are summarized in, based on their number of phases and solid-state properties.[5]



2,1. Eutectic mixtures

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution.

2,2. Amorphous precipitation in crystalline matrix

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

2,3. Solid solution

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. The molecular dimensions and the dissolution rate is determined by the dissolution rate of the carrier. Classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).

2.4. Continuous solid solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the

bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical world till date.

2,5. Discontinuous solid solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Due to practical considerations it has been suggested by goldberg et al. That the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.

2,6. Substitutional solid solutions

Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules. Classical solid solutions have crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the intrsticies between the solvent molecules.

2,7. Interstitial solid solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter.

2,8. Glass solution and 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. Lattice energy is much lower in glass solution and suspension.

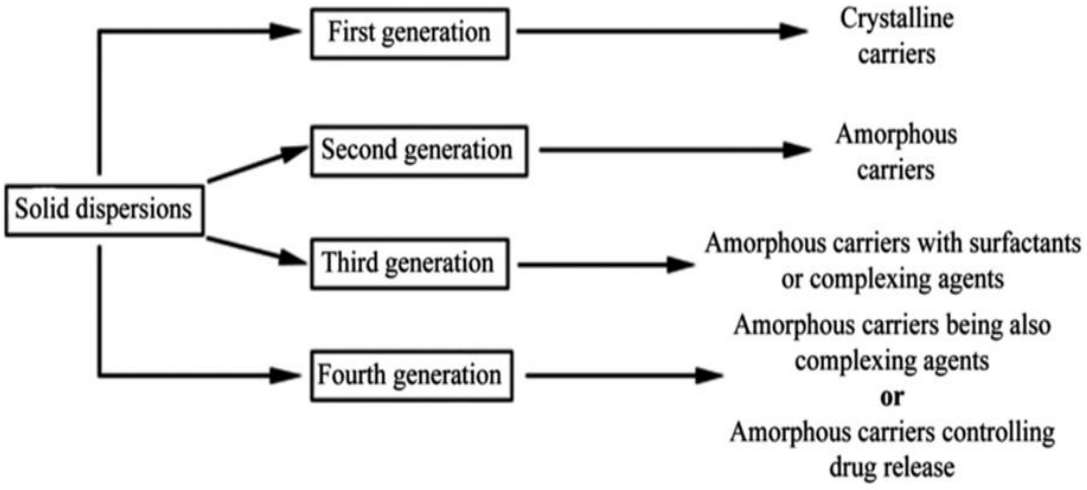


Figure 2: Classification of Solid Dispersions Based on Nature of Carrier.[6]

3. Methods of solid dispersion preparation

Melting and solvent evaporation methods are the two major processes of preparing solid dispersions.[6]

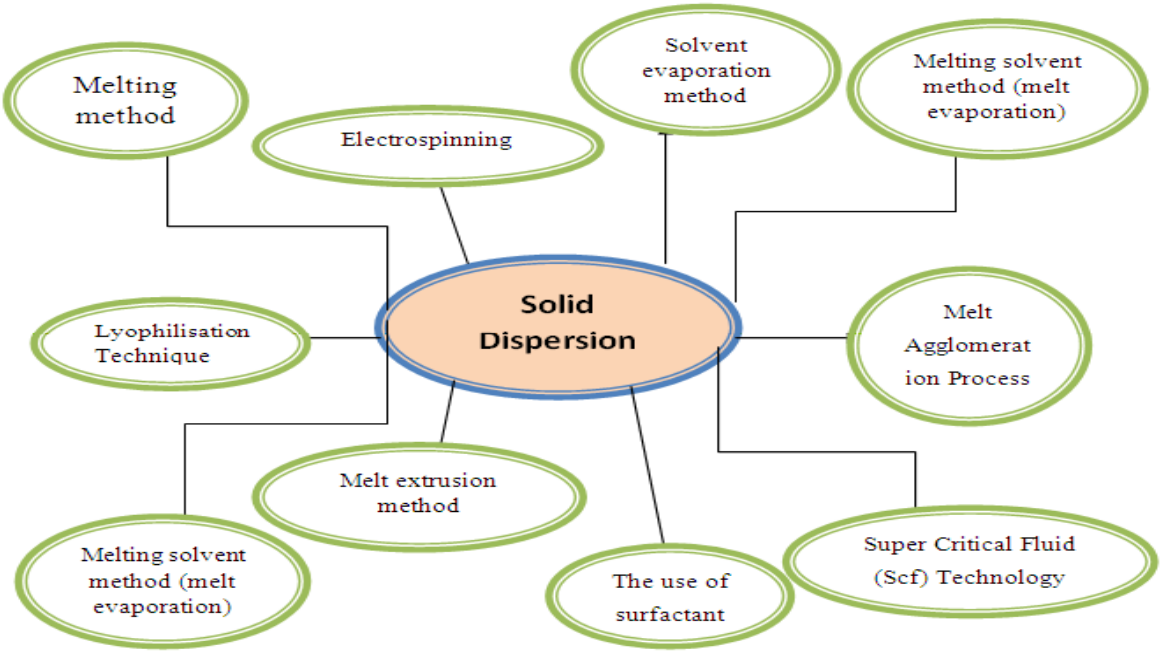


Fig. 3: Methods of preparation of solid dispersion.

3.1. Melting method

Sekiguchi et al. Were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. In the melting process, the molecular mobility of carrier is high enough to change the drug's incorporation. The use of high temperatures, and the fact that several drugs can be degraded by the melting process, can be a limitation of this method.[3]

3.1.1. Hot stage extrusion

Hot stage extrusion has in recent years gained wide acceptance as a method of choice for the preparation of solid dispersions. The hot stage extrusion process is highly dependent on the physicochemical properties of the compounds and their miscibility in the Molten state. Hot-stage extrusion consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. Extrusion then collected after cooling at room temperature and milled. Moreover, it was observed that solid dispersions of itraconazole/intec sp1 prepared by hot-stage extrusion presented itraconazole

in a fully glassy state, whereas it was only partially glassy in solid dispersions prepared by spray drying.[3]

3.1.2. Melt agglomeration

Melt agglomeration allows the preparation of solid dispersions in conventional high shear mixers. It is made by adding the molten carrier containing the drug to the heated excepients. It is prepare by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier. It is also possible to produce stable solid dispersions by melt agglomeration in a rotary processor.

3.2. Solvent evaporation method

The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature. A basic process of preparing solid dispersions of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol, chloroform, mixture of ethanol and dichloromethane. Normally, the resulting films are pulverized and milled.[7]

3.2.1. Spray-drying

Spray-drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Van drooge et al. Prepared an alternative solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized.

3.2.2. 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. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices, the technique is poorly exploited for the preparation of solid dispersions. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid

dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified.[6]

3.2.3. Supercritical fluid method

Supercritical fluid methods are mostly applied with carbon dioxide (co2), 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 co2. 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.

3.2.4. Co-precipitation method

Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. In this method non- solvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the non- solvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The solution was first dried under vacuum at room temperature and kept inside incubator (370c) for 12 hrs. Finally it was passed through sieves.

3.2.5. Dropping method

This technique may overcome some of the difficulties inherent in the other method And developed by ulrich et al. To facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions a solid dispersion of a melted drug carrier mixture is pipetted and then dropped onto aplate, where it solidifies into round particles.[3] the size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. The dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. This method also avoids the pulverization, sifting and compressibility difficulties.[3]

4-Suitable carriers for solid dispersion

Many water soluble excipients are employed as carriers for solid dispersions. Following is the criteria that should be considered during selection of such carriers: higher water solubility,

which improve wettability and enhance dissolution; high glass transition point leading to improved stability; minimal water uptake (reduces tg); soluble in common solvent with drug (solvent evaporation); relatively low melting point (melting process); capable of forming a solid solution with the drug-similar solubility parameters.[8]

4.1-Selection of carriers

The properties of the carrier have a profound influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following prerequisites for increasing the dissolution rate of a drug.[9]

**** freely water soluble with rapid dissolution properties.***

****nontoxic and pharmacologically inert.***

****heat stable with a low melting point for the melt method.***

****soluble in a variety of solvents.***

****preferably enhancing the aqueous solubility of the drug.***

****chemically compatible with the drug.***

****forming only weakly bounded complex with the drug.***

Chemical name.	***Example.***
Acids	*Citric acid, tartaric acid, succnic acid.*
Sugars	*Dextrose, sorbitol, sucrose, maltose, galactose, xylitol.*
Polymer material	*Material polyvinyl pyrrolidone, peg 4000, peg 6000, sodium alginate, carboxy methylcellulose, guar gum, xantham gum, methylcellulose.*
Surfactant	*Polyoxyethylene stearate, polaxamer, deoxycholic acid, tweens and spans, gelucire 44/14, vitamin e, tpgs nf.*
Miscellaneous	*Pentaerythritol, urea, urethane, hydroxy alkyl xanthene.*

4.2-Carriers used in solid dispersions[9]

Poloxamers

The poloxamers are a group of surface active compounds widely used in the pharmaceutical industry. Poloxamers are described as block polymers of the type aba, consisting of a central, hydrophobic block of polypropylene oxide, which is edged by two hydrophilic blocks of polyethylene oxide. The polymers are derived from the sequential polymerization of propylene oxide and ethylene oxide. Due to the possibility to combine blocks of different molecular weights, the properties of the resulting polymers vary in a wide range. Generally, these are waxy, white granules of free-flowing nature and are practically odorless and tasteless. Aqueous solutions of pluronic in presence of acids, alkalis, and metal ions are very stable. The poloxamers are readily soluble in aqueous, polar and non-polar organic solvents

and due to this fact they have established themselves as a preferred molecule in the formulation techniques.

Polymers

Polymers like polyethylene glycol (pegs), hydroxypropyl methylcellulose (hpmc), hydroxypropyl cellulose (hpc), polyvinylpyrrollidone (pvp) etc. When used in optimum concentration will leads to increase in dissolution rate due to reduction in particle size, solubilization effect of the carriers, increase wettability, increase dispersibility, formation of hydrogen bonds between drug and carrier. When polymers are used in higher proportion these can decrease dissolution rate due to leaching out of the carrier during dissolution which might form a concentration layer of solution around the drug particles so the migration of the released drug particles to the bulk of the dissolution medium slows down.

Polyethylene glycol (peg)

The term polyethylene glycols refer to compounds that are obtained by reacting ethylene glycol with ethylene oxide. Peg's are polymers of ethylene oxide, with a molecular weight (mw) falling in the range 200-3,00,000. For the manufacture of solid dispersions and solutions, pegs with molecular weights of 1500 - 20000 are usually employed. As the mw increases, so does the viscosity of the peg. At the mw of up to 600 pegs are fluid, in the range 800-1500 they have a consistency vaseline like, from 2000 to 6000 they are waxy and those with mw of 20,000 and above form hard, brittle crystals at room temperature. Their solubility in water is good, but decreases with mw. One of the advantages of pegs is that they also have good solubility in many organic solvents. The melting point of pegs lies under 65˚c in every case these relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Additional features of the pegs include their ability to solubilize some compounds and also to improve compounds wettability

Polyvinyl pyrrolidone (pvp)

Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (pvp) of molecular weight ranging from 2,500 to 3, 00,000. These can be classified according to the k value, which is calculated using fikentschers equation. provides an overview of the relationship between the k values and the approximate molecular weight of pvp. K value is dependent not only on its mw but also on the moisture content.

Crospovidone

This polymer also belongs to polyvinyl group which swells when dispersed in water. Although crospovidone does not dissolve in water, it can also be used as a carrier to improve drug release rate in solid dispersions. For example, solid dispersion of furosemide with crospovidone led to an increase in the dissolution rate by a factor of 5.8 in comparison to either the drug powder or physical mixture of furosemide with crospovidone. The mechanism of increase in the release rate of furosemide was due to the presence of the drug in the amorphous form in the developed dispersion, which was proved by x-ray diffraction studies.[10]

Cellulose derivatives, hpmc

Celluloses are naturally occurring polysaccharides, which can be further derivatized to form different carriers. The molecular weight of hpmc lies between 10 000 to 15 00 000 and are completely soluble in water. They are mixed ethers of cellulose where 16-30% of hydroxyl groups are methylated and about 4-32% are derivatized with hydroxypropyl groups hpmc when used for the preparation of solid dispersion of albendazole enhanced the release rate and bioavailability. It was further determined that hpmc was able to hinder the crystallization of albendazole, and further improvement in release characteristics could be achieved by using hpmc and hpmcp in combination. Other drugs which exhibit faster release from solid dispersion in hpmc include poorly soluble weak acids nilvadipine and benidipine.

Hydroxypropylcellulose[6]

Hydroxypropylcellulose solubilise in water (up till 408°), ethanol, methanol and chloroform. The average molecular weight of the hydroxypropylcellulose ranges from 37 000 (type ssl) to 11 50 000 (type h). Extensive research has been done to determine the effect of chain length hydroxypropylcellulose and also the concentration of hydroxypropylcellulose on the release of solid dispersion of flurbiprofen. The release rate was enhanced as the amount of hydroxypropylcellulose was increased.

Carboxymethylethylcellulose (cmec)

Cmec belongs to the cellulose ethers, but it is resistant to dissolution under gastric or acidic conditions. It dissolves at ph above 5, with lowest dissolution ph being dependent on the grade of the cmec. Amorphous solid dispersions of nifedipine and spironolactone Showed massive enhancement in the dissolution rate of the drug at ph value.[6]

Polyacrylates and polymethacrylates

Both polyacrylates and polymethacrylates are glassy substances which are formed by polymerization of acrylic and methacrylic acid. In pharmaceuticals, they are commonly utilized as coatings to modify the release of drug from the dosage form. Commonly the trade name eudragit refers to them. Among all eudragits, eudragit e is frequently used to improve the release rate as it is soluble in all buffer at ph up to 5 and swells when ph is increased, while eudragit l can be used when it is desirable to evade release in the stomach. Eudragit l has been effectively used to increase the dissolution of griseofulvin and spironolactone at a ph value of 6.8.

Urea

Urea is the end product of human protein metabolism, it has a light diuretic effect and is regarded as non- toxic. Its solubility in water is good and it also exhibits fine solubility in several common organic solvents. In a bioavailability study of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea. In case of ursodeoxycholic acid, it was found that the release rate from urea solid dispersions prepared by the hot melt method was more rapid as compared to other carriers, which were studied, like peg 6000].

Sugar, polyols and their polymers

Even though sugars and associated compounds are highly water soluble and have less toxicity issues, yet they are less suitable than other carriers for the preparation of solid dispersions. The sugars have high melting point, therefore restricting the applicability of hot melt method for preparation of solid dispersion. Similarly, due to its poor solubility in most organic solvents, it is difficult to form co-evaporates. In spite of these drawbacks, various attempts have been made to prepare solid dispersions with sugars and their derivatives. Mannitol, is one such example, it has a melting point of 165-168° and decomposes only above 250° and has been employed in some cases to prepare dispersions by hot melt method[6]

- ***Example first generation carriers:*** Crystalline carriers: urea, sugars, organic acids.
- ***Second generation carriers example*****:** fully synthetic polymers include povidone (pvp), polyethyleneglycols (peg) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (hpmc), ethylcellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins.

- ***Third generation carriers example:*** surface active self emulsifying carriers: poloxamer 408, tween80, and gelucire 44/14.[11]

5- Advantages of solid dispersion technology

The major advantage of solid dispersions is that they improve the solubility of poorly water soluble drugs in pharmaceutical dosage forms which results in rapid dissolution rates and improved bioavailability of drugs. Moreover, the approach also offers others advantages including.

1. Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. The ultimate result is improved bioavailability.[12]
2. Wettability is improved during solid dispersion production. Improved wettability results in increased solubility. Here the carriers play the major role to improve the wettability of the particles.[12]
3. Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties.[12]
4. In solid dispersions drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles.
5. The carrier used in the solid dispersion plays a major role in improving the wettability of the particles. Improved wettability results in increased solubility thus improving the bioavailability.[10]
6. In solid dispersion drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting the drug in amorphous form and increases the solubility of the particles.[10]
7. Particles with higher porosity.[13]
8. Drugs in amorphous state.[13]

6-Disadvantages of solid dispersion technology

Serajuddin (1999) identified some problems limiting the commercial application of solid dispersion which involved.[12]

(a) Its method of preparation,

(b) Reproducibility of its physicochemical properties,

(c) Its formulation into dosage forms,

(d) The scale up of manufacturing processes, and

(e) The physical and chemical stability of drug and vehicle. Solid dispersions are not broadly used in commercial products due to mainly the problem of crystallization of the components from amorphous state during

(f) Most of the polymers used in solid dispersions can absorb moisture, which may results in phase separation, crystal growth or conversion from the amorphous state to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may results in decreased solubility and dissolution rate.[14]

(g) Poor scale-up for the purposes of manufacturing.[14]

(h) Stability problems: younis18 reported the dissolution rate lowering of solid dispersions on aging owing to recrystallization of the amorphous drug in system and/or polymorphic transitions that are frequently associated with the aged solid dispersions.[14]

7- Characterization of the solid dispersion system

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 into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion.[15]

7,1-Drug -carrier miscibility

A. Hot stage microscopy.

B. Differential scanning calorimetry.

C. Powder x-ray diffraction.

D. Nmr 1h spin lattice relaxation time.

7,2-Drug carrier interactions

A. Ft- IR spectroscopy.

B. Raman spectroscopy.

C. Solid state NMR.

7,3-Physical structure

A. Scanning electron microscopy.

B. Surface area analysis.

C. Surface properties.

D. Dynamic vapor sorption.

E. Inverse gas chromatography.

F. Atomic force microscopy.

7,4-amorphous content

A. Polarized light optical microscopy.

B. Hot stage microscopy.

C. Humidity stage microscopy.

D. DSC (mtdsc).

E. ITC.

F. Powder x-ray diffraction.

7,5-Stability

A. Humidity studies.

B. Isothermal calorimetry.

B- Dsc (tg, temperature recrystallization)

C. Dynamic vapor sorption.

D. Saturated solubility studies.

7,6-Dissolution enhancement[15]

A-Dissolution.

B-Intrinsic dissolution.

C-Dynamic solubility.

D-Dissolution in bio-relevant media.

8- Future prospects

Solid dispersions for poorly soluble drug will flaunt due to recent advancements in the technology with respect to method of preparation, scale-up, and development of newer methods for better predictability of solid state structure. Future research on solid dispersions should adopt new techniques to study the solubility and molecular state of the drug and its interaction with the polymer to remove the difficulty in design of new carriers that can prevent crystallization of drug. The effects of storage conditions on the properties of drug, carrier used, drug release profile and bioavailability of drug need to be addressed more extensively. Moreover, it is a possible assertion that substitution of a hydrophobic carrier for

a hydrophilic carrier may result in a well-controlled solid dispersion process. The method could be easily adopted to attain the sustained release of drug or to alter solid state properties. It is imperative that the solid dispersion technique offers vast potential for future research and subsequent growth which may result in development of novel applications for oral drug delivery.

9-Some eg. of poor water soluble drugs, Category & Solubility profile[11]

S.n.	*Drugs*	*Category*	*solubility profile*
1	Ibuprofen.	Anti-inflammatory analgesic.	Ibuprofen is only very slightly soluble in water. Less than 1 mg of ibuprofen dissolves in 1 ml water (< 1 mg/ml). However, it is much more soluble in alcohol/water mixture.
2	Furosemide.	Diuretics.	Soluble in acetone, sparingly soluble ethanol (95%), slightly soluble in ether
3	Gliclazide.	Anti-diabetic.	Spairingly soluble in dichloromethane, slightly soluble in ethanol 95%
4	Felodipine.	Felodipine.	Spairingly soluble in dichloromethane, slightly soluble in ethanol 95%

10-Some examples of Solid dispersions in Market

***sporanox® (itraconazole).**

***intelence® (etravirine).**

***prograf® (tacrolimus).**

***crestor® (rosuvastatin).**

***gris-peg® (griseofulvin).**

***cesamet® (nabilone).**

11-Pharmaceutical applications of solid dispersion

The pharmaceutical applications of solid dispersions technique are:

***To enhance the absorption of drug.**

***To obtain a homogeneous distribution of a small amount of drug in solid state.**

***To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.**

***To dispense liquid or gaseous compounds.**

***To formulate a fast release priming dose in a sustained release dosage form.**

***To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.**

To reduce side effects (a) the binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex, (b) the damage to the stomach mucous membranes by certain non-steroidal anti- inflammatory drugs can be reduced by administration as an inclusion compound.

To mask unpleasant taste and smell. The very unpleasant taste of anti-depressant famoxetine hindered by the development of oral liquid formulations. The bitter taste was greatly suppressed when the solid complex of famoxetine was formulated as aqueous suspension.

12-Challenges in Development of Solid Dispersion

Solid dispersion has a great potential for increasing the bioavailability of drug as well as developing controlled release formulations. Despite of long research on solid dispersions, its commercial application is very limited. Much better solubility enhancement of the drug can be obtained with solid dispersion technology, but unfortunately, there are only few products made by this technology that have been marketed so far[Some of them are mentioned in table. Commercial application of the solid dispersion is limited due to: method of preparation: laborious and expensive; reproducibility of physiochemical properties; formulation into dosage forms; scale-up of manufacturing processes; physical and chemical stability of drug and vehicle. In spite of numerous advantages of solid dispersion, the above mentioned reasons limit its use in commercial dosage forms. The conventional methods for preparation of solid dispersions pose many problems, which limit its use. Processing variables of the melt method influence the physicochemical properties and stability of solid dispersions. Organic solvents used during preparation should be completely removed, which is a difficult process. Dosage form development.

CONCLUSION

Solid dispersion technology has been considered one of the well-established techniques in formulation of poorly-soluble drug. The poor solubility of new chemical entities decreases the 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 scientis. So for enhancing the solubility many techniques have been used, solid dispersion being one of them. Various techniques described in this review are successfully used for the preparation of solid dispersions in the bench and lab scale and can be used as industrial scale also. Due to the advantageous features of solid dispersions formulation scientists consider it

as one of the most potential method of improving oral bioavailability. Carrier molecules play the most important role in enhancing solubility of the resultant dispersion and hence improvement in oral bioavailability. Whatever this technology is also highly potential to formulate controlled release dosage forms as the carriers may enhance or delay drug release.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

REFERENCES

1. Singh et al. "a review on solid dispersion". "international journal of pharmacy & life sciences", sep., 2011; 2(9): issn: 0976-7126.
2. Dixit et al. "a review: solid dispersion". "world journal of pharmacy and pharmaceutical science". 2014; 3(9): Issn- 2278 – 4357.
3. Pati m.rahul et al. "solid dispersion: strategy to enhance solubility" international journal of pharmaceutical sciences review and research, may – june 2011; 8(2): 0976 – 044x.
4. Singh g. Et al. "enhancement of the solubility of poorly water soluble drugs through solid dispersion: a comprehensive review. "indian journal of pharmaceutical sciences", sci., 2017; 79(5): 674-687.
5. Sultan sakina et al. "review article: solid dispersion currently practiced in pharmaceutical field". International journal of advancements in research & technology, march-2016; 5(3): 2278-7763.
6. Singh, et al.: "solubility enhancement by solid dispersion". indian journal of pharmaceutical sciences. Sci., 2017; 79(5): 674-687.
7. Dhirendra k. Et al. "solid dispersions: a review". Pak. J. Pharm. Sci., april 2009; 22(2): 234-246.
8. Singh n, sarangi m. "solid dispersion - a novel approach for enhancement of bioavailability of poorly soluble drugs in oral drug delivery system". Glob j pharmaceu sci., 2017; 3(2): 555608.doi:
9. Yadav bindu et al. "applications of solid dispersions", journal of chemical and pharmaceutical research, 2015; 7(2): 965-978.
10. Kumar b; "solid dispersion- a review"; pharmatutor, 2017; 5(2): 24-29. Issn: 2394-6679 | e-issn: 2347-7881.
11. Dixit et al. "a review: solid dispersion". World journal of pharmacy and pharmaceutical sciences, 2014; 3(9): Issn 2278 – 4357.

12. Saffoon nadia et al, "enhancement of oral bioavailability and solid dispersion: a review". Journal of applied pharmaceutical science, 2011; 01(07): 13-20, issn: 2231-3354.
13. Sultan sakina and safiuddin. ahm. "review article: solid dispersion currently practiced in pharmaceutical field" international journal of advancements in research & technology, march-2016; 5(3): 2278-7763.
14. Younis a. Mahmoud, "solid dispersion technology, a contemporary overview on a well established technique", universal journal of pharmaceutical research, 2017; 2(3): 2456-8058.
15. Ramesh v., "enhancement of solubility for poorly water soluble drugs by using solid dsipersion technology", international journal of pharmaceutical research and bio-science, 2016; 5(2): 47-74, issn: 2277-8713.
16. K. Arun prasad, "preparation and evaluation of solid dispersion". International journal of pharmaceutical sciences review and research, july – august 2010; 3(1): article 027.