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Paramount Role of Solid Dispersion in Enhancement of Solubility

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ABSTRACT: One of the favorable strategy to improve the solubility and hence bioavailability of poorly water soluble drugs is the formulation of solid dispersion. It refers to dispersion of an active ingredient in a carrier at solid state which is prepared by solvent evaporation method, melting method, melt solvent method, kneading method, co-grinding method, co-precipitation method, modified solvent evaporation method, spray drying, gel entrapment technique, and co-precipitation with supercritical fluid. On the basis of the carrier used in solid dispersion it is classified as first, second and third generation solid dispersions. As per biopharmaceutical classification system class II drugs are with low solubility and high permeability and are the promising candidates for improvement of bioavailability by solid dispersion. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier, molecular arrangement of drugs in solid dispersions are discussed in this article.

KEYWORDS: Solid Dispersion; Solubility; Bioavailability; Hydroxypropylmethylcellulose (HPMC); Polyvinylpyrrolidone (PVP); Polyethylene Glycol (PEG); Biopharmaceutical Classification System (BCS).

INTRODUCTION

Improving oral bioavailability of the drugs which are given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore increase in dissolution of poorly soluble drugs by solid dispersion technique can overcome the problem of poor solubility. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their solubility by reducing drug particle size, improving wettability and forming amorphous particles. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier and a hydrophobic drug. [1] This article reviews historical background of solid dispersion technology with its classification, various preparation techniques, advantages and applications. This review also discusses the various drugs for which this technique has been used.

Definition

Solid dispersion is an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly soluble drugs as shown in figure 1 [4]. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix

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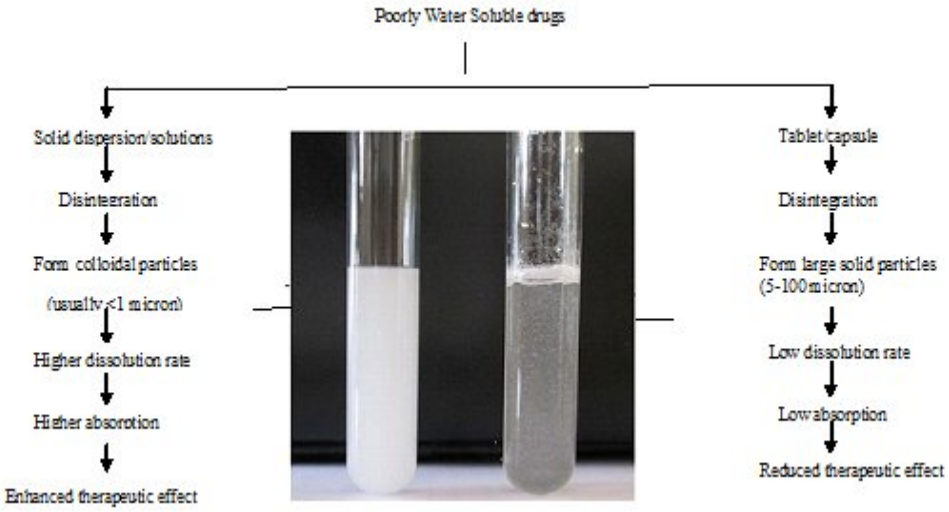

Figure 1 Schematic representation of enhanced bioavailability of the drug by formulation of solid dispersion compared with conventional tablet/capsule. [4]

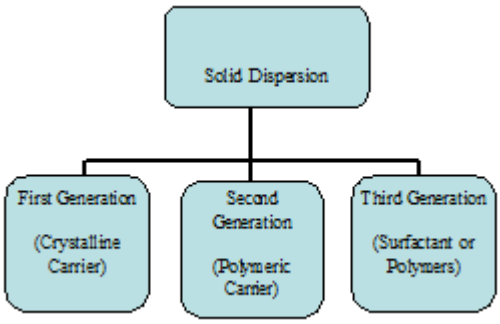

Figure 2 Classification of solid dispersion.

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. [2]

Ideal Drug Candidates for Solid Dispersion

In the Biopharmaceutical Classification System (BCS) class II drugs are those with low aqueous solubility and high membrane permeability and therefore solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. According to the BCS, drug substances can be classified as belonging to one of four classes as shown in table 1. It is obvious that for class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption then their ability to permeate through the membrane. Therefore, the formulation work for class II compounds should focus on the enhancement of aqueous solubility or dissolution rate. [3]

CLASSIFICATION OF SOLID DISPERSION

Classifications of solid dispersion on the basis of carrier used is described as following and shown in figure 2.

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Table 1: BCS calssification system

Class	Solubility	Permeability	Example of drugs
Class I	High solubility	High permeability	Benzapril, Loxoprofen, Sumatriptan etc.
Class II	High solubility	High permeability	Valsartan, Nimesulide, Loratadine, Aceclofenac, Glimepiride etc.
Class III	High solubility	How permeability	Gabapentine, Topiramate, Atropine etc.
Class IV	Low solubility	Low permeability	Hydrochlorthiazide, Furosemide, Meloxicam etc.

Table 2: List of carriers used in solid dispersion

Carriers	Examples
Sugars	Dextrose, sucrose, lactose, sorbitol, maltose, mannitol, galactose
Acids	Citric acids, succinic acids
Polymeric Material	Povidone, polyethylene glycol, hydroxyl propyl methyl cellulose, methyl cellulose, hydroxyl ethyl, cellulose, pectin
Insoluble or enteric polymers	Hydroxy propyl methyl cellulose phthalate, Eudrgit RS
Surfactants	Polyoxyethylene stearate, Renex, Poloxamer 188, Texofor AIP, Deoxycholioc acid, Tweens, Spans
Miscellaneous	Urea, Hydroxyalkylxanthins, Urethans

A. First generation

First generation solid dispersions are prepared using crystalline carriers such as urea and sugar, which were the first carriers to be employed in solid dispersion. They have the disadvantage of forming crystalline solid dispersion, which are thermodynamically more stable and did not release the drug as quickly as amorphous ones. [3]

B. Second generation

Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers such as povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates as well as natural product based polymers such ashydroxylpropylmethyl-cellulose (HPMC), ethyl cellulose, and hydroxypropoylcellulose or starch derivates like cyclodextrins. [3]

C. Third generation

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self emulsifying properties. Therefore, third generation solid dispersions appeared. The use of surfactant such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer 407 as carriers are shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.[3]

CRITERIA FOR SELECTION OF CARRIERS USED IN SOLID DISPERSION

The selection of the carrier has the influence on the dissolution characteristics of the dispersed drug. A water soluble carrier results in a faster release of the drug from the matrix. Classification of carriers is shown in table 2. An insoluble carrier leads to slower release of a drug from the matrix. The carriers to be used should have the following characteristics: [4]

- Readily soluble in water and in gastrointestinal fluids
- Physiologically inert
- Melting point not much higher than that of drug
- Thermal stability at melting temperature
- Low vapor pressure
- High molecular weight
- Non toxic

Sugars

Although sugars and related compounds are highly water soluble but few sugars have toxicity issues, they are less suitable than other carriers for the manufacture of solid

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dispersions. Lactose is useful as a carrier for the production of solid dispersions of drugs prepared by melting and rapid cooling showed marked increase in dissolution rate. Chitosan has also been used as a carrier in solid dispersions. Mannitol can be employed in some cases to prepare dispersions by the hot melt method. [4]

Table 3: Review on carrier used for manufacturing solid dispersion

Carrier Used	Name of Drugs	Technique Used
Mannitol	**Aceclofenac**[11]	Melt solvent method
	Glibenclamide[12]	Solvent evaporation method
	Roxithromycin[13]	Physical mixtures, Melt solvent, Melting
	Atorvastatin[14]	Solvent evaporation method
	Aceclofenac[15]	Solvent evaporation, Physical mixing, Fusion
	Chlordiazepoxide[16]	Solvent evaporation method
	Aceclofenac[17]	Solvent evaporation method
	Allopurinol[18]	Melting and solvent evaporation
Cross povidone	**Amlodipine besylate**[19]	Solvent evaporation method
	Glimepiride[20]	Surface solid dispersion
	Furosemide[21]	Kneading
PEG 4000	**Atorvastatin**[14]	Solvent evaporation method
	Indomethacin[22]	Solvent evaporation method
	Nifedipine[23]	Solvent evaporation and Melting fusion
	Etoricoxib[24]	Solvent evaporation method
	Indomethacin[25]	Hot melt extrusion
	Allopurinol[18]	Melting and solvent evaporation
	Simvastatin[26]	Fusion
PEG 6000	**Glibenclamide**[12]	Solvent evaporation method
	Piroxicam[27]	Hot melt method, Solvent evaporation
	Ofloxacin[28]	Fusion and Solvent evaporation
	Clonazepam[29]	Melt granulation
	Glimepiride[30]	Modified solvent fusion
	Aceclofenac[15]	Solvent evaporation, Physical mixing, Fusion
	Acyclovir[31]	Solvent evaporation
	Gliclazide[32]	Fusion
	Fenofibrate[33]	Fusion solvent
	Indomethacin[22]	Solvent evaporation, Co-evaporation
	Terbinafine hydrochloride[34]	Solvent evaporation, Co-evaporation
	Gliclazide[35]	Fusion
	Allopurinol[18]	Melting and solvent evaporation
	Simvastatin[26]	Fusion
PEG 8000	**Gliclazide**[36]	Fusion solvent
Polyvinypyrrolidine (PVP-K30)	**Glibenclamide**[12]	Solvent evaporation method
	Irbesartan[37]	Solvent evaporation method
	Celecoxib[38]	Physical mixtures, kneading method and solvent evaporation method
	Candesartan cilexetil[39]	Kneading method
	Mefenamic acid[40]	Solvent evaporation method
	Atorvastatin[14]	Solvent evaporation method
	Nifedipine[41]	Solvent evaporation method
	Aceclofenac[15]	Solvent evaporation, Physical mixing, Fusion
	Furosemide[21]	Kneading technique
	Paracetamol[42]	Kneading technique
	Fluvastatin[43]	Melt mixing, Solvent evaporation
	Acyclovir[44]	Solvent evaporation method
	Terbinafine hydrochloride[45]	Solvent evaporation, Co-evaporation

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	Chlordiazepoxide[46]	Solvent evaporation method
	Bicalutamide[47]	Fusion method
	Allopurinol[18]	Melting and solvent evaporation
	Evodiamine[48]	Solvent evaporation
Polyvinypyrrolidine (PVP-K25)	**Glimepiride**[30]	Modified solvent fusion
Polyvinypyrrolidine (PVP-K90)	**Allopurinol**[18]	Melting and solvent evaporation
Poloxamer	**Gliclazide**[49]	Lyophilization
	Lovastatin[50]	Hot melt, Solvent evaporation
	Glibenclamide[51]	Lyophilization
	Fenofibrate[52]	Fusion solvent
	Glimepiride[53]	Solvent evaporation method
Eudragit	**Verapamil HCl**[54]	Solvent evaporation method
	Nimodipine[55]	Hot melt granulation
	Fluvastatin[56]	Melt mixing, Solvent evaporation
	Itraconazole[57]	Melt/cool
	Indomethacin[22]	Solvent evaporation, Co-evaporation
	Nimodipine[58]	Solvent evaporation method
	Chlordiazepoxide[59]	Solvent evaporation method
	Diclofenac sodium[60]	Spray drying
	Promethazine HCl[61]	Spray drying, freeze drying
Hydroxypropylmethylcellulose (HPMC)	**Verapamil HCl**[51]	Solvent evaporation method
	Irbesartan[62]	Spray drying
	Diclofenac sodium[63]	Spray drying
	Aceclofenac[64]	Solvent evaporation method
Urea	**Glibenclamide**[16]	Solvent evaporation method
	Ibuprofen[65]	Melt dispersion and Solvent evaporation
	Aceclofenac[17]	Solvent evaporation, Physical mixing, Fusion
	Allopurinol[18]	Melting and solvent evaporation
Lactose	**Fluvastatin**[66]	Melt mixing, Solvent evaporation
	Aceclofenac[17]	Solvent evaporation method
	Indomethacin[22]	Solvent evaporation, Co-evaporation
Sorbitol	**Glibenclamide**[12]	Solvent evaporation method
	Indomethacin[22]	Solvent evaporation, Co-evaporation
	Chlordiazepoxide[67]	Solvent evaporation method
Cyclodextrin	**Ibuprofen**[65]	Co-evaporation
	Ketoconazole[68]	Solvent evaporation method
Gelucire-50/13	**Valasartan**[69]	Hot melt granulation
	Indomethacin[25]	Hot melt extrusion
Citric acid	**Glibenclamide**[12]	Solvent evaporation method
Chitosan	**Fluvastatin**[66]	Melt mixing, Solvent evaporation
Ethyl vinyl acetate, Ethyl acetate	**Nimodipine**[58]	Solvent evaporation method
Carbopol 940	**Aceclofenac**[70]	Solvent evaporation method

Acid

Organic acids such as citric acid, succinic acid and their derivatives with varying functional groups can be used as carriers of solid dispersions. They help improve drug's bioavailability by accelerating the drug's release rate. There are several researches which have identified that drug release rate can be increased twenty times if these organic acids are used. [5]

Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is orthorhombic. Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical

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formulations and food products, primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablet. Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations. [5]

Polymeric Material

Polyethylene glycols (PEGs) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200 ± 3,00,000. Their solubility in water is generally good, but decreases with MW. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents. The melting point of the PEGs of interest lies under 65°C in every case (e.g. the m.p. of PEG 1000 is 30-40°C, the m.p. of PEG 4000 is 50-58°C and the m.p. of PEG 20,000 is 60-63°C) . These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. PEGs of 4000-6000 MW are the most frequently used for the manufacture of solid dispersions, because in this MW range the water solubility is very high. If a PEG with too low MW is used, it can lead to a product with a sticky consistency which is difficult to formulate into a pharmaceutically acceptable product. [6]

Poly vinyl pyrrolidone - Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3,000,000. These can be classified according to the K value. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed drug from the solid dispersion. The aqueous solubility of the PVPs becomes poorer and viscosity lowers with increasing chain length. [6]

Cellulose derivative - Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by β-1, 4-glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl- (MC), hydroxypropyl (HPC), hydroxypropylmethyl (HPMC) and many other semi-synthetic types of cellulose. A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP).

Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an a-(1–4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The hydroxyl groups may also be acetylated. Pectin gelation characteristics can be divided into two types as high-methoxy and low-methoxy gelation. Gelation of high- methoxy pectin usually occurs at pH < 3.5. Low-methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solids content. Amidation may interfere with gelation, causing the process to be delayed. However, gels from amidated pectins have the ability to re-heal after shearing. [5]

Emulsifiers

The release behavior of many drugs can also be improved through the use of emulsifying agents. Two mechanisms are possible such as improvement of wetting characteristics and solubilization of the drug. Owing to their potential toxicity problems, such as damage to mucosal surfaces, they are used in combination with another carrier. Surfactants are suitable carriers for low dose and very low water soluble drugs. Poloxamers are nonionic triblock copolymers. Because of their amphiphilic structure, the polymers have surfactant properties that make them useful in industrial applications. The recently used surface-active carrier is Gelucire® 44/14 and other grades of Gelucire®. Bile salts and their derivatives are natural surfactants; they enhance the wetting and solubility

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of many lipophilic substances, leading to an increase in dissolution rate. [5]

Insoluble or enteric polymers

Polyacrylates and polymethacrylates are glassy substances that are produced by polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. They are mostly used in coatings to modify the release of the drug from the dosage form. Commonly they are referred by the trade name Eudragit. Polyacrylate is a chemical class of acrylate polymers derived from the polymerization of acrylic acid esters and salts. Each acrylate monomer contains a vinyl group, a pair of double-bonded carbon atoms attached to the carbon of a carboxyl group. Due to the high reactivity of carbon double bonds, acrylates polymerize readily and are used in a variety of plastics, adhesives and chemical binder applications. These polyacrylates are transparent thermoplastic polymers that are physiologically harmless and readily soluble in organic solvents and are characterized by low resistance to oil and gasoline. Polyacrylates are produced by polymerization of esters of acrylic and methacrylic acids (acrylates and methacrylates, respectively). [6]

Surfactants

The polyoxyethylene stearates are a series of polyethoxylated derivatives of stearic acid. Polyoxyethylene stearates are nonionic surfactants produced by polyethoxylation of stearic acid. Two systems of nomenclature are used for these materials. The number '8' in the names 'poloxyl 8 stearate' or 'polyoxyethylene 8 stearate' refers to the approximate polymer length in oxyethylene units. The same material may also be designated 'polyoxyethylene glycol 400 stearate' or 'macrogol stearate 400' in which case, the number '400' refers to the average molecular weight of the polymer chain. Polyoxyethylene stearates are generally used as emulsifiers in oil-in-water- type creams and lotions. Their hydrophilicity or lipophilicity depends on the number of ethylene oxide units present: the larger the number, the greater the hydrophilic properties. Polyoxyl 40 stearate has been used as an emulsifying agent in intravenous infusions. [5]

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide. Poloxamers are nonionic polyoxyethylene polyoxypropylene copolymers used primarily in pharmaceutical formulations as emulsifying or solubilizing agents. The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. [5]

All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Their physical and surface-active properties vary over a wide range and a number of different types are commercially available. Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups. Poloxamers may also be used as wetting agents in ointments, suppository bases, gels etc. and also used as tablet binders and coatings. [5]

Tweens (Polyethoxylated sorbitan esters) are ethoxylated spans. These are hydrophilic in nature and are soluble or dispersible in water and dilute solutions of electrolytes. The solubility of tweens in aqueous solutions increases with degree of ethoxylation. For a fixed degree of ethoxylation, aqueous solubility decreases as the number of aster grouping increases. [5]

Spans (sorbitan esters) are a series of mixtures of partial esters of sorbitol and its mono and di anhydrides with fatty acids. Sorbitan diesters are a series of mixtures of partial esters of sorbitol and its monoanhydride with fatty acids. These are nonionic surfactants and are produced by dehydration of sorbitol. [5]

Miscellaneous

Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 in 1 and it also exhibits good solubility in many common organic solvents. In one of the

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first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea. [7]

Urethanes it is a class of synthetic elastomers, which is used for a variety of medicinal implants, particularly for long terms implant. Polyurethane is a polymer composed of a chain of organic units joined by carbamate (urethane) links. While most polyurethanes are thermosetting polymers that do not melt when heated, thermoplastic polyurethanes are also available. Polyurethane polymers are formed by reacting an isocyanate with a polyol. Both the isocyanates and polyols used to make polyurethanes contain on average two or more functional groups per molecule. Polyurethane products often are simply called "urethanes", but should not be confused with ethyl carbamate, which is also called urethane. Polyurethanes neither contain nor are produced from ethyl carbamate. [7]

METHODS OF PREPARATION OF SOLID DISPERSION

1. Solvent Evaporation Method: Drug and carrier both are dissolved in an organic solvent. After complete dissolution, the solvent is evaporated. The solid mass is ground, sieved and dried. [8]

2. Modified Solvent Evaporation Method: Drug is dissolved in organic solvent at its saturation solubility with continued 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. [8]

3. Melting Method: Accurately weighed drug and carrier are mixed using glass mortar and pestle. The mixture is heated at or above the melting point of all the components to achieve a homogenous dispersion. It is then cooled to obtain a congealed mass. It is pulverized and sieved. [8]

4. Melt-Solvent Method: Accurately weighed drug is dissolved in organic solvent and the solution is incorporated into the melt of mannitol by pouring into it. It is then suddenly cooled. The mass is kept in desiccator for complete drying. The solidified mass is crushed, pulverized and passed through sieve. [8]

5. Kneading Method: A mixture of accurately weighed drug and carrier is wetted with solvent, kneaded thoroughly for some time in a glass mortar, the paste formed is dried and sieved. [8]

6. Co-grinding Method: Accurately weighed pure drug powder and the carrier are physically mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill. A certain number of steel balls are added. The powder mixture is ground. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. [8]

7. Co-Precipitation Method (Co-Evaporates): Accurately weighed carrier is dissolved in water and drug in organic solvent. After complete dissolution, the aqueous solution of carrier is then poured into the organic solution of the drug. The solvents are then heated and evaporated. The dispersion is pulverized with pestle and mortar, sieved and dried. [8]

8. Co-Precipitation with Supercritical Fluid: Conventional methods for the preparation of solid dispersions include either the fusion or solvent processes, with supercritical fluid processing (SCP) emerging as an alternative solvent-evaporation method for formulating co precipitates of smaller particle size, lower residual organic solvent and better flowability. A supercritical fluid exists as a single fluid phase above its critical temperature and pressure. Carbon dioxide is currently the most commonly used supercritical fluid because of its low critical temperature of carbon dioxide makes it attractive for processing heat labile pharmaceuticals. In the context of manufacturability, rate of cooling and solvent removal is stringently controlled, resulting in acceptable batch to batch variation. [8]

9. Spray Drying Method: Accurately weighed amount of drug with lipid carrier are dissolved in methanol to obtain a clear solution. This solution is then spray dried using a

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laboratory scale dryer. The sample is stored over silica gel in a vacuum desiccator. [8]

10. Dropping Solution Method: The dropping method facilitates the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. 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. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape. [8]

11. 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. [8]

12. Lyophilization Technique: 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. [8]

13. Gel Entrapment Technique: Carrier 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 glass mortar and sieved. [9]

ADVANTAGES OF SOLID DISPERSION

1. Particles with Reduced Particle Size and Increased Dissolution Rate: 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. Due to this a high surface area is formed resulting in an increased dissolution rate and improved bioavailability. [10]

2. Particles with Improved Wettability: A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. 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 can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects. [10]

3. Particles with Higher Porosity: Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity depends on the carrier properties, for instance solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and so result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile. [10]

4. Drugs in Amorphous State: Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. [10]

APPLICATION OF SOLID DISPERSION [10]

Solid dispersion systems can provide numerous additional benefits; some of them are as following:

- In improving immunosuppressive therapy in lung transplant patients, dry powder formulation consisting of a solid dispersion for inhalation is prepared. It can avoid

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many problems like use of local anaesthesia and irritating solvents.

- Solid dispersion formulations were demonstrated to accelerate the onset of action for drugs such as nonsteroidal anti-inflammatory drugs (NSAIDS) where immediacy of action is crucial in relieving acute pain and inflammation.
- Solid dispersion systems were shown to provide bio available oral dosage forms for anti-cancer drugs, which could be substituted for standard injections to improve patient comfort and compliance.
- Solid dispersion systems were also found to reduce food effect on drug absorption, thus increasing the convenience of drug therapy as the need for some drugs to be taken with food was eliminated.
- Solid dispersion- based dosage form allowed for greater drug loading per dose and improved stability over a soft gelatin capsule formulation which thereby improved the convenience of drug therapy by reducing the dosing regime and eliminating the need for refrigerated storage.
- Improved absorption efficiency demonstrated for solid dispersion systems allows for a reduction in the content of active agent per dose, thus decreasing the cost associated with these drug therapies.

It also act as a functional carriers that offer the added benefit of targeting the release of highly soluble forms of poorly water soluble drugs to an optimum site for absorption.

CONCLUSION

Based on the various polymers which play a paramount role in manufacturing of solid dispersion, a review of the drugs for which this technology has been used is reviewed in table 3. Hence solid dispersion technique can overcome the hurdle faced by BCS class II drugs by enhancing solubility and hence bioavailability.

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