SOLID DISPERSION– STRATEGY TO ENHANCE SOLUBILITY AND DISSOLUTION RATE OF POORLY AQUEOUS SOLUBLE DRUG–AN UPDATED REVIEW

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ARTICLE INFO
Article history
Received 28/11/2013
Available online 02/02/2014

Keywords
Novel approach,
poorly soluble drugs,
Lipophilic,
Dissolution.

ABSTRACT
Now a days majority of drug manufactured by synthetic process, so large volume of drug produce which are highly water in soluble drugs but having no issue on permeability, means BCS class II category drugs. To improve the status of such major problem many approaches have been introduced for the solubility enhancement of such drugs. SD is usually one of the most widely and adopted technology used for this purpose. Poor water solubility is the major drawback for the various types of drugs and various approaches have been introduced so far for the solubility enhancement of such drugs. Solid dispersion is one of unique technique adopted for the formulation of such drugs and various novel methods were used for the preparation of solid dispersion. Solid dispersion techniques have attracted majority because of low cost & due to improving the dissolution rate of highly lipophilic drugs and hence their bioavailability. This article reviews on classification, various preparation methods, advantages and disadvantages of solid dispersion.

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INTRODUCTION
The enhancements of aqueous solubility & oral bioavailability of poorly water-soluble drugs often show poor bioavailability because of low levels of absorption. Drugs that process dissolution rate limited GI absorption generally show increase dissolution and bioavailability as a result of reduction in particle size by using various size reduction method. However, reduction in particle size of drug often or mostly leads to aggregation and agglomeration of particles, which results in poor density. Solid dispersions of poorly aqueous -soluble drugs with hydrophilic carriers have been reduced the incidence of these problems and enhanced dissolution. The development of new strategy for solid dispersions as a practically viable method to enhance bioavailability of poorly aqueous -soluble drugs overcame the limitations of previous approaches such as sing various salt, solubilization by organic solvent co solvent system, and particle size reduction different mills. Most of the literatures were available and reports regarding the studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A very small or fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion [1].

After administering a drug extravascularly, it firstly dissolves in gastric fluid or intestinal fluids before it, and then afterwards permeates in to the membranes of the GI tract to reach blood circulation. Therefore, a drug with low aqueous solubility will typically emerge as poor dissolution rate limited absorption, and a drug which belongs to low lipophilicity, membrane permeability for this category of the drug will typically exhibit less permeation rate limited membrane permeability. Hence, two areas of pharmaceutical research generally that focus on enhancing the oral bioavailability of API include: (i) increasing the solubility and dissolution rate of poorly aqueous soluble drugs and (ii) increasing the membrane permeability of poorly permeable drugs [2].

SOLID DISPERSION
The term SD refers to a group of solid and solute products consisting of at least two different components, mostly a hydrophilic matrix and a water resistant hydrophobic drug material. The matrix may be either crystalline or amorphous[3]. The drug particle can be dispersed molecularly or by weight ratio, in amorphous particles (clusters) or in crystalline particles.

ADVANTAGES OF SOLID DISPERSIONS
There are various reasons for the improvement of solubility of poorly water-soluble drug using solid dispersion technology. The advantages of this technology are as follows:

Drug particles with reduced particle size:
Molecular dispersions, as solute dispersion, represent the last state on particle size reduction, and after inert carrier or matrix material dissolution the drug excipient is molecularly dispersed very easily in the dissolution medium because of the high surface area which results an increased dissolution rate and hence forth further improved the bioavailability of the poorly water soluble drug.

Drug particles with improved wetting:
The solubility enhancement of the drug is mostly related to the drug wettability or density improvement verified in SD.

Particles with higher porosity:
Particles in the dispersions have been found to have a higher degree of porosity and basically the increase in porosity also depends on the properties of the drug carrier. If only the polymers having linear structure are mostly utilized and it produces larger and more porous particle as compared with SDs that prepared with reticular polymers. If the drug particle having porous or void space in nature the particle results higher dissolution rate.

Drugs in amorphous state:
Poorly water-soluble crystalline nature of drugs, in the amorphous state tend to have higher degree of solubility. Drug in its amorphous than crystalline state shows higher drug of release because of no energy is required to break up the crystal lattice during the dissolution process[4].

SDs systems may increase dispersion, dissolution rate and bioavailability of hydrophobic drug when these are exposed to aqueous media, generally the water soluble carrier dissolves, and the drug is released as very fine colloidal particles. Because of reduction in particle size it is always said that increases surface area, which results in improved dispersion, dissolution rates and also the oral absorption rate. Furthermore, because this process is energy independent no energy is required to break up the crystal lattice of a drug during the dissolution process. During entire process drug carriers surrounds and the water solubility with wettability may increased. This approach has been used for a variety of poorly soluble drugs such as nimesulide, ketoprofen, meloxicam, nifedipine, nimodipine, ursodeoxycholic acid, carbamazepine, rofecoxib and me bendazole. Various hydrophilic carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), various gums, sugar, mannitol, sucrose, maltose, urea, hydroxypropylmethyl cellulose phthalate, gelucires all grade, eudragits and chitosan have been investigated for improvement of dissolution rate characteristics and bioavailability of poorly water soluble drugs[5].

APPLICATIONS OF SOLID DISPERSION IN PHARMACEUTICAL FIELD
Apart from absorption and permeability enhancement, the SD technique may have wide pharmaceutical and other industrial applications. It is possible that such a technique can be used for:
1. To obtain a homogenous distribution of a small amount of drug in solute state.
2. To enhance the stability of unstable drug.
3. To dispense or convert liquid or gaseous compounds into a solid dosage.
4. To formulate a rapid release primary dose of the drug in a sustained released dosage form.
5. To formulate SR dosage form of soluble drugs by using poorly soluble or insoluble carriers.
6. To reduce pre-systemic inactivation of drugs like morphine and progesterone.
7. Polymorphs in a given SD system can be converted into isomorphous, solute solution, eutectic or molecular addition compounds [6].

Table 1: Materials used as carrier for solid dispersion[7].

<table>
<thead>
<tr>
<th>S. No</th>
<th>Category</th>
<th>Carriers</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sugars</td>
<td>Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose</td>
<td>Rofecoxib from sorbitol and mannitol</td>
</tr>
<tr>
<td>2</td>
<td>Acids</td>
<td>Citric acid, succinic acid</td>
<td>Felodipine, rofecoxib from citric acid</td>
</tr>
<tr>
<td>3</td>
<td>Polymeric materials</td>
<td>Polyvinyl pyrrolidone(PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan</td>
<td>Temazepam, felodipine, etoricoxib rofecoxib from PEG 4000 &amp; 6000 and troglitazone and rofecoxib from PVP K30</td>
</tr>
<tr>
<td>4</td>
<td>Insoluble or enteric polymer</td>
<td>Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragitL100, eudragit E100, eudragit RL, eudragit RS</td>
<td>Indomethacin from eudragit E100</td>
</tr>
<tr>
<td>5</td>
<td>Surfactants</td>
<td>Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans</td>
<td>Felodipin and rofecoxib from poloxamer 188</td>
</tr>
<tr>
<td>6</td>
<td>Miscellaneous</td>
<td>Pentaerythritol, pentaerythritol tetraacetate, urea, urethane, hydroxy alkyl xanthins</td>
<td>Rofecoxib from urea</td>
</tr>
</tbody>
</table>

The disadvantage OR drawback of SD technology have been a disadvantage for the commercialization of solid dispersions. The general limitations include are as follows:
1. Laborious and some time expensive methods of preparation,
2. Practical yield and reproducibility of physicochemical characteristics of SD,
3. Because of high weight difficulty in incorporating into formulation of dosage forms,
4. Scale-up of manufacturing and dosage design process, and
5. Mostly stability of the drug in SD and in majority of vehicle[8].

**SELECTION OF CARRIER(S)**

The excipient properties of the carrier have a profound influence on the dissolution and percent release of the dispersed drug. A carrier ought to meet the following criteria for being suitable for enhancing the dissolution rate of a poorly water soluble drug by using SD. It should be
1. Hydrophilic in nature with rapid dissolution properties
2. Should not produce toxic effect and should be pharmacologically inert
3. It should be thermo- stable with a low melting point for the melt method
4. It should be soluble in a variety of pharmaceutical solvents
5. Carrier must enhance the aqueous solubility of the drug
6. Should not chemically incompatible with the drug
7. It should form only weak bond with the drug[9].

**First generation carriers**

Example of Crystalline carriers are as: Urea, Sugars, Organic weak acids.

**Second generation carriers:**

Example: Fully synthetic polymers include povidone (PVP), PEG with there all grade and polymethacrylates. Natural polymers based are mainly composed by cellulose and there derivatives, such as HPMC, EC or HPC or starch derivates, like oligosaccharide, cyclodextrins.
Third generation carriers
Example: Surface active self emulsifying carriers: Poloxamer 408,188 etc, Tween 20,40,80, and Gelucire 44/14

Selection of Solvents
Solvent to be included for the formulation of SD should have the following criteria:
1. Both drug and carrier must be dissolved and disperse.
2. Toxic solvents should be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane etc.
3. Ethanol and other alcohol can be used as alternative as it is less toxic.
4. Water based systems are preferred.
5. Surfactants generally used to create carrier for drug solutions but some time as they can reduce Tg temperature, so care must be taken while consideration.

Table 2: An overview of common organic solvents [10].

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Melting point (°C)</th>
<th>Boiling point (°C)</th>
<th>Vapour pressure at 25°C (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0</td>
<td>100</td>
<td>3.16</td>
</tr>
<tr>
<td>Methanol</td>
<td>-93.9</td>
<td>65</td>
<td>16.9</td>
</tr>
<tr>
<td>Ethanol</td>
<td>-117</td>
<td>78.5</td>
<td>5.79</td>
</tr>
<tr>
<td>Chloroform</td>
<td>-63</td>
<td>62</td>
<td>26.1</td>
</tr>
<tr>
<td>DMSO</td>
<td>19</td>
<td>189</td>
<td>0.08</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>17</td>
<td>0.08</td>
<td>1.64</td>
</tr>
</tbody>
</table>

METHODS FOR MANUFACTURING OF SOLID DISPERSIONS
Various manufacturing methods for SD have been reported in most literature. During the manufacturing, production techniques, demixing (partially or complete), and formation of different phases is generally observed. Phase separations like crystallization of the drug particle or formation of amorphous drug clusters or agglomeration are difficult to control and therefore unwanted. It was already recognized and observed in one of the first studies on SD that the phase separation can be extended or avoid and minimized by rapid cooling procedure. Generally, phase separation of the pharmaceutical product can be prevented by maintaining a low molecular mobility in matrix and drug during preparation phase. On the other hand, phase separation is generally prevented by maintaining the driving force in between the carrier and drug particle for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible. The major limitation and disadvantage in the development of SD is the lack of suitable manufacturing techniques or process that could be scaled up to commercial production. Various methods have been tried recently to overcome the limitations and make the preparation more practically feasible while, at the same time, retaining both the physicochemical and bioavailability enhancing properties of SD[11].

PROPERTIES OF SOLID DISPERSION
There are certain exclusive properties of SD and that may be given as follows:

Higher Porosity of Drug Particle:
Particles in SD have been found to have a higher degree of porosity. The generally increase in the porosity depends on the properties of carriers used, for instance, SD containing linear polymers produce most of time larger and more porous particles than those containing reticular polymers and, because of this porosity in the particle, result in a higher dissolution rate and hence bioavailability.

Reduced Drug Particle Size:
It is an general observation that, if the particle size is reduce a high surface area is formed, resulting in an increased more dispersion, more dissolution and improved bioavailability.

Improved Wettability:
A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in SD. It was observed from the literature that even carriers without any surface activity, such as urea improved the drug wettability it will help in improvement of dissolution rate. Carriers with surface activity, such as cholic acid and bile salts, are generally reduces the surface tension of the particle when used, and can significantly increase the wettability properties of drug particle.
Drugs in Amorphous State:
The enhancement of dispersion rate and drug release or dissolution can be improved usually using the drug in its fine amorphous state or reducing the material size only, it is general observation that if material is in fine state no energy is required to break up the crystal lattice during the dissolution process [12].

METHODS OF PREPARATION OF SD
A. Fusion method
The fusion method is sometimes referred to as the melt method or melt dispersion method, which is correct only when the starting materials (or drug material) are crystalline. Hence therefore, the term synonymously used fusion method. The first SD created for pharmaceutical purpose were prepared by the melt method or melt dispersion method [13, 14].

FIG. 1: Solid dispersion of API in polymer matrix

Hot melt extrusion
Melt extrusion is essentially the same as the fusion method except, HME is the process of applying heat and pressure to melt the polymer, that intense mixing of the components is induced by the extruder. When compared to melt method in a proper vessel, the product stability and dissolution are similar but melt extrusion offers better mixing to produce homogeneous solid containing finely API particle, the potential to shape the heated drug-matrix mixture into implants, ophthalmic (product) inserts, or other than parental dosage forms. Just like in the traditional melt method after melting the polymer miscibility of drug and matrix can be a problem. The theoretical approach to understanding the melt extrusion process is therefore, generally presented by flow into four sections
1) Feeding of the extruder.
2) Conveying of mass (mixing and reduction of particle size).
3) Flow through the die.
4) Exit from the die and down-stream processing. Generally, internally the extruder consists of one or two rotating screw which are stationary and cylindrical barrel. The barrel is often manufactured in section, which are bolted or clamped together. Extruder having end-plate die, which is connected to the end of the barrel, to determines the shape of the extruded product [15,16].

Solvent method
The generally first step in the solvent method is preparation of a solution which containing both matrix material and drug. Generally the second step involves the removal of solvent(s) resulting in formation of a SD. Generally mixing at the molecular level is always preferred, because this leads to optimal dissolution properties of the material. Using the solvent method, the most of the time pharmaceutical engineer faces two major challenges. The first and most important challenge is to mix both drug and polymer matrix in one solution, which is very difficult when they differ significantly in density and polarity. To minimize the drug particle size in the SD, the most vital is drug and matrix have to be dispersed in the solvent as fine as possible preferably drug and matrix material are in the dissolved state in one single solution. The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s). Tg is the glass transition temperature and Tm is the melting temperature. If the material is moisture content or some time if extract is used then material is dried by using the vacuum drying process. The solution is dried by the application of vacuum and moderate heating. Now a days, the solvent evaporation is accelerated by using a rotary evaporator for oily and aqueous extract. Afterwards the formed SD is often stored in a vacuum desiccators to remove the residual solvent [17-19].

GENERAL METHODS FOR THE CHARACTERIZATION OF SD
Particle Size:
Scanning electron microscopy (SEM) polarization microscopy method is used to study the microscopic surface morphology of drug and carriers and sometimes the polymorphism of drug. Avery fine, fine, mist or dispersion of drug particles in the carrier matrix may be visualized.

Dissolution Testing:
All the drugs having intrinsic dissolution rate $< 0.1\ \text{mg/cm}^2/\text{min}$ usually exhibit dissolution rate limited absorption is the major consideration. Comparison of dissolution properties or profile of drug, physical mixtures and carrier and SD may help to indicate the mechanism of increase release of drug in the formulation (solubilization / wetting / particle size reduction).
Infrared Spectroscopy:
Mostly Infrared spectroscopy (IR) helpful in determining the solid state characteristics of the drug in the carrier regardless of the state of the carrier. Crystallinity of under 5-10% cannot generally be detected. The IR study is also used to study the interaction occur between drug and polymer by comparing or matching the peaks of spectra. If there is absence of any significant peak change in the IR spectral pattern of drug & polymer its physical mixture indicated by the absence of any interaction between the drug and the polymer.

Differential Scanning Calorimetry:
A frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC). It help to study the changes in the physical state of SD may occur during heating of the material, and the presence of polymer may influence the melting behavior of drug (e.g. melting point depression). Results need to be confirmed by another technique. Crystallinity under 2% cannot generally be detected.

X-Ray Diffraction:
Powder X-ray diffraction pattern can be used qualitatively to detect material with long range of order. Sharper diffraction peaks indicate more crystalline material. Recently developed X-ray equipment is semi quantitative for material analysis. [20-22]

CONCLUSION
Due to the advantageous features of solid dispersions formulation scientists consider it is one of the most potential method of improving, enhancing, dissolution rate and oral bioavailability of the drug. But changes in crystal behavior of drug and/or carrier particles during processing or storage. Such type of condition limits commercialized application of the method. Manufacturing of SD requires a perfect combination of drug to carrier(s). Carrier molecules play the most vital role in enhancing solubility of the resultant or formed dispersion and hence improvement in oral bioavailability. However this technology is also highly potential not only to formulate fast release tablet but also the controlled release dosage forms as the carriers may enhance or delay drug release from the dosage form.

REFERENCE: