A REVIEW ON SOLID DISPERSION

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ABSTRACT:
The rate of dissolution could be a rate-limiting process in the absorption of the drug from the solid dosage form of the relatively insoluble drugs. Hence the increase in the dissolution of the poorly soluble drugs by the solid dispersion method presents a challenge to the researchers. The Solid dispersions has attracted considerable interest as an efficient means of improving the dissolution rate and hence bioavailability of a range of hydrophilic drugs. Solid dispersion technology is a science of dispersing one or more active ingredients in the inert matrix in the solid stage in order to achieve the increased dissolution rate, altered properties of the solid state, sustained release of the drugs, enhanced drug release from suppository & ointment bases, & improved stability & the solubility. The present article reviews on the various types of solid dispersion, its merits and demerits, different method of preparation of solid dispersion, solid dispersion mechanism, the different solid dispersions characterization methods and various types of marketed preparations of solid dispersion.

Key Words: Solid dispersion, Bioavailability, Poorly soluble drugs, Solubility

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INTRODUCTION

The most preferable route of drug administration is the oral route because it is flexible in formulation, easy to administer, & compliance of the patient. Also there are many challenges for the oral route such as poor pharmacological response resulting into inadequate and erratic oral absorption and also limited drug absorption resulting in poor bioavailability.

Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly permeable drugs. The oral bioavailability depends on several factors including, dissolution rate, presystemic metabolism, aqueous solubility, first-pass metabolism, drug permeability and susceptibility to efflux mechanisms. The poor solubility and low permeability are attributed as the most frequent causes of low oral bioavailability.

Solid dispersion technology is a science of dispersing one or more active ingredients in the inert matrix in the solid stage in order to achieve the altered solid state properties, increased dissolution rate, enhanced drug release from suppository & ointment bases, & improved stability & the solubility. In this review the solid dispersion technique of solubilization for the attainment of effective absorption and improved bioavailability are discussed. Solid dispersion is one of the most promising approaches for the solubility enhancement. In the BCS [biopharmaceutical classification system] drugs with low aqueous solubility and high membrane permeability are categorized as the Class II drugs. Hence the solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II
Adv J Pharm Life sci Res, 2015 3;4, 33-45
ISSN 2454 3535 (On-line)
www.ajplronline.org

Advanced Journal of Pharmacie and Life science Research
34

In solid dispersion the drug is dispersed in the matrix generally the hydrophilic matrix & the hydrophobic drug, thereby forming the solid dispersion. When a solid dispersion is exposed to the aqueous media the carrier dissolves & the drug is released as a fine colloidal particles. A resulting enhanced surface area produces higher dissolution rate & bioavailability of the poorly water-soluble drugs

local pharmacy

TYPES OF SOLID DISPERSION [6]

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Solid Dispersion Type</th>
<th>Matrix *</th>
<th>Drug **</th>
<th>Remarks No.</th>
<th>Phases</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eutectics</td>
<td>C</td>
<td>C</td>
<td>The first type of solid dispersion prepared</td>
<td>2</td>
<td>(Chiou and Riegelman, 1971)</td>
</tr>
<tr>
<td>2</td>
<td>Amorphous precipitations in crystalline matrix</td>
<td>C</td>
<td>A</td>
<td>Rarely Encountered</td>
<td>2</td>
<td>(Breitenbach AH, 2002); (Mullins and Macek, 1960)</td>
</tr>
<tr>
<td>3</td>
<td>Solid solutions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>Continuous Solid Solutions</td>
<td>C</td>
<td>M</td>
<td>Miscible at all composition, never prepared</td>
<td>1</td>
<td>(Goldberg et al., 1965)</td>
</tr>
<tr>
<td>ii</td>
<td>Discontinuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>Partially miscible, 2 phases even though drug is molecularly dispersed</td>
<td>2</td>
<td>Sekiguchi K and Obi N (1961)</td>
</tr>
<tr>
<td>iii</td>
<td>Substitutional solid solutions</td>
<td>C</td>
<td>M</td>
<td>Molecular diameter of drug [solute] differs less than 5% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed</td>
<td>1 or 2</td>
<td>(Rastogi and Verma, 1956); (Wilcox et al., 1964)</td>
</tr>
<tr>
<td>iv</td>
<td>Interstitial solid solutions</td>
<td>C</td>
<td>M</td>
<td>Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous.</td>
<td>2</td>
<td>(Chiou and Riegelman, 1971); (Chiou and Riegelman, 1969)</td>
</tr>
<tr>
<td>4</td>
<td>Glass suspension</td>
<td>A</td>
<td>C</td>
<td>Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix</td>
<td>2</td>
<td>Riegelman, 1971); (Sarkari M et al., 2002)</td>
</tr>
<tr>
<td>5</td>
<td>Glass suspension</td>
<td>A</td>
<td>A</td>
<td>Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type</td>
<td>2</td>
<td>Riegelman, 1971); (Sarkari M et al., 2002)</td>
</tr>
<tr>
<td>6</td>
<td>Glass solution</td>
<td>A</td>
<td>M</td>
<td>Requires miscibility OR solid solubility; complex formation or upon fast cooling OR evaporation during preparation, many [recent] examples especially with PVP</td>
<td>1</td>
<td>Simonelli APet al., 1969</td>
</tr>
</tbody>
</table>

* A: matrix in the amorphous state, C: matrix in the crystalline state
** A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix
ADVANTAGES/MERITS OF SOLID DISPERSION \(^{[2, 7-10]}\)

The main advantage of the solid dispersions is that it improves the dissolvability of the poorly water soluble drug in the pharmaceutical composition & results in the rapid dissolution rates thereby improving the drugs bioavailability. The others advantages of solid dispersion are as follows:

A) The rapid disintegration of the oral tablets

The drug is formulated with hydrophilic carrier [For e.g. PEG] as the solid dispersion to increase its dissolution & aqueous solubility. Then a superdisintegrant is used in the formulation of tablet to achieve the rapid disintegration of tablets which are prepared by the wet granulation method[For e.g. superdisintegrant as croscarmellose sodium]. This tablet which is rapidly disintegrating can be used as an alternative to the parenteral therapy that enables patient for self-medication even without the aid of the water.

B) As the formulation vehicle

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

C) The particles with the reduced particle size

The solid dispersions represents the last state on the particle size reduction, & after the carrier dissolution the drug is molecularly dispersed in to the dissolution medium. The solid dispersions apply this principle to the release of drug by creating a mixture of the poorly water soluble drug & the carriers that are highly soluble, and thus the higher surface area is formed, which results in an increased dissolution rate & improved bioavailability.

D) The particles with improved wettability

The enhancement of drug solubility is related to the drugs wettability. Even the carriers without any surface activity such as urea improved the drug wettability it has been observed. The carriers with the surface activity, such as the cholic acid & the bile salts when used, they significantly increase the wettability of the drug. By the direct dissolution or the co-solvent effects a carrier can influence the drug dissolution profile.

E) The particles with higher porosity

The particles in the solid dispersions have been found to have the higher degree of the porosity. The solid dispersions which contains the linear polymers produce larger & more porous particles than those containing the reticular polymers & therefore it results in the higher dissolution rate. The increased porosity of the solid dispersion particles also hastens the release rate of drug.

F) The drugs in amorphous state

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

DISADVANTAGES/DEMERITS OF SOLID DISPERSION \(^{[2, 7-10]}\)

The disadvantages of solid dispersions are mainly related to their instability. Mostly changes occurs in the several systems in crystallinity & the decrease in the dissolution
rate with ageing & the system may be destabilized through the physical treatment such as the pulverization & aging. There is a more deteriorating effect of the moisture & the temperature on the solid dispersions than on the physical mixtures.

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

**APPLICATIONS OF THE SOLID DISPERSION**

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

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

**APPLICATIONS OF SOLID DISPERSION IN PHARMACEUTICAL FIELD**

It would be possible that this solid dispersion technique should be used:
- By the use of poorly soluble or insoluble carriers to formulate sustained release regimen of soluble drugs
- To formulate the fast release primary dose in the sustained released dosage form.
- For the drugs like morphine and progesterone reduce their pre systemic inactivation
- Dispense liquid [up to 10%] or gaseous compounds in the solid dosage form.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- Stabilize the unstable drug.
- The Polymorphs in the given system can be converted into the isomorphous, eutectic or molecular addition compounds, solid solution.
METHOD OF PREPARATION OF SOLID DISPERSIONS:

**Figure No-1: Various methods of preparation of solid dispersion**

**Fusion method** [6,15-19]

The carrier is heated to the temperature just above its melting point & the drug is incorporated in to the matrix. The drug would remain dissolved in the solid state, yielding a solid solution, in the carrier, if the drug has the high solubility. With rigorous stirring the melt is then solidified in the ice bath, then pulverized & finally sieved. A rapid congealing is desirable because it results in the supersaturation of the drug as the consequence of entrapment of the soluble molecule in the solvent matrix by the instantaneous solidification. The first solid dispersions created for the pharmaceutical applications were prepared by the fusion method. The dispersion consisted of the sulfathiazole & urea as the matrix which were melted using the physical mixture at the eutectic composition, which is followed by a cooling step. A eutectic composition was chosen to obtain the simultaneous crystallization of drug & matrix during cooling.

**Advantages of Fusion Method**
- The use of an organic solvent is included by circumventing the enigmas of its removal from the dispersion
- The dissolution for the dispersions obtained by the melting technique are much faster than those prepared using the solvent techniques
- If the drug & carrier are miscible in the molten state technically it will be the easiest method
- It is the most convenient & economical method for the drugs stable at temperature below 100°C

**Disadvantages of Fusion Method**
- At the melting point the thermal degradation or instability may result
- The high melting carrier cannot be used
- The sublimation or the evaporation & the polymeric transformation of the dispersion component may take place
- The decomposition may take place it is often dependent upon the composition, fusion time & the rate of cooling
- The immiscibility between the drug & the carrier results in the irregular crystallization that causes the obvious problems during the formulation
- The solidified melt may be unhandable and tacky

**Solvent method** [20]

The physical mixture of a drug & carrier is dissolved in the common solvent, which is evaporated until the clear, solvent free film is left. This film is further dried to the constant weight. The main advantage of this method is thermal decomposition of the drugs or carriers can be prevented because of the relatively low temperature that is required for the evaporation of organic solvents. Some of the disadvantages are associated with this method are:
- Cost of preparation is high.
- Completely removing liquid solvent is difficult.
- On the chemical stability there are possible adverse effects of the traces of the solvent
- Common volatile solvent selection.
- Reproducing crystal form is difficult.
• Except in the system that shows highly viscous properties the super saturation of the solute in the solid system cannot be attained.

**Melt evaporation method [melting solvent method]** [21,22]

In this method the solid dispersions are prepared by dissolving the drug in the suitable liquid solvent & then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until the film which is clear and which is solvent free is left. This film is further dried to the constant weight. The 5 to 10 percent [w/w] of the compounds of liquid can be incorporated into the polyethylene glycol 6000 without any significant loss of its solid property. The liquid solvent used may also affect the polymorphic form of the drug which precipitates as the solid dispersion. This method has the unique advantages of both the fusion & the solvent evaporation methods. From the practical standpoint, it is only limited to the drugs with the therapeutic dose that is low For e.g. below or less than 50 mg & are particularly useful for the drugs that have the high melting points and for thermolabile drugs also.

**Method of melt extrusion** [23,24]

Hot-stage extrusion consists of the extrusion, at the rotational speed that is high, of the carrier & the drug, for the small period of time that is previously mixed, at the melting temperature. By this method the solid dispersion is composed of the active ingredients & carriers & prepared by the hot-stage extrusion by using the twin-screw extruder that is co-rotating. Simultaneously the drug & carrier mixture is melted, homogenized & then extruded & then shaped as tablets, sheets, granules, sticks or powder, pellets. The intermediates can then be further processed into the conventional tablets. The important advantage of this method is that the drug/carrier mixture is only subjected to the elevated temperature for about one minute, that enables the drugs that are thermolabile somewhat has to processed. About 40% [w/w] is the concentration of the drug in the dispersions. For one minute the Samples are milled by the help of cutting mill & sieved to exclude the particles >355µ.

The reduction in processing the temperature can be achieved by the association of the hot-stage extrusion with the use of the carbon dioxide as the plasticizer which broadens the application of the hot-stage extrusion to the thermally labile compounds. This method also offers many advantages over the traditional pharmaceutical processing techniques including the continuous operation, absence of the solvents, few processing steps, and the short residence time and the low temperature, which prevents the drug-carrier mixture from the thermal degradation more is the possibility of the formation of solid dispersions & improved bioavailability. This method has many disadvantages which are as follows: [a] High shear forces may produce high local temperature in the extruder, hence it may create a problem for the heat sensitive materials, [b] Like the traditional fusion method, miscibility of drug & the carrier matrix can be the problem. Examples of the pharmaceutically approved polymeric materials which are used in this method include vinyl polymers (polyvinylpyrrolidone, PVP-vinyl acetate ], Polyethylene glycol (PEG) and cellulose derivatives, polyethylene oxide [PEO], Eudragit® [acrylates]

**The melt agglomeration process** [25]

This method has been used to prepare the solid dispersion in which the binder acts as the carrier. The solid dispersions are prepared either by heating the binder ,the drug & excipients to the temperature above the melting point of the binder [melt in procedure] or by the spraying of dispersion of the drug in the molten binder on the heated excipients [spray on procedure] by
using the high shear mixer. The effects of binder type, method of the manufacturing & the particle size are critical parameters in the preparation of the solid dispersions by the melt agglomeration. It has also been investigated that the spray on procedure with Polyethylene Glycol-3000, gelucire 50/13 & Poloxamer 188 attributed to the immersion mechanism of the agglomerate formation & growth. Also, the melt in procedure also results in the homogeneous distribution of the drugs in the agglomerate

Super critical fluid (scf) technology\(^{[26-27]}\)

The carbon dioxide are used as an antisolvent for the solute but as a solvent with respect to the organic solvent in the supercritical fluid antisolvent techniques. The different acronyms were used by the various authors to denote the micronization processes which are: Gas antisolvent, Solution enhanced dispersion by supercritical fluids, supercritical antisolvent, Precipitation with a compressed anti solvent fluid, Extraction system of the aerosol solvent,

- The SAS process involves the spraying of the solution composed of a solute & of the organic solvent into the continuous supercritical phase which is flowing concurrently. Use of the supercritical carbon dioxide is favorable as it is much easier to remove from the polymeric materials when the process is completed, even though the small amount of the carbon dioxide remains trapped inside the polymer; it shows no danger to the patient.
- To plasticize & to swell polymers are the ability of the carbon dioxide that can also be exploited & the process can be carried out near room temperature.
- By reducing the melting temperature of the dispersed active agent the supercritical fluids are used to lower the temperature of the melt dispersion process. The reason for this depression is the solubility of the lighter component [dense gas] in the forming phase [heavier component].

Electrospinning\(^{[28-30]}\)

It is the process in which the solid fibers are produced from the polymeric fluid stream solutions or melt delivered through the millimeter-scale nozzle. This method involves the application of the strong electrostatic field over the conductive capillary attaching to the reservoir containing the polymer solution or melt & the conductive collection screen. By increasing the electrostatic field strength up to but not exceeding the critical value, the charge species accumulated on the surface of the pendant drop destabilize the hemispherical shape into the conical shape \(\text{known as Taylor's cone}\). Beyond the critical value, the charged polymer jet is ejected from the apex of the cone \(\text{as the way of relieving the charge built-up on the surface of the pendant drop}\). The ejected charged jet is then carried to the collection screen by the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited, if the viscosity increases, the charged jet is dried. This method has tremendous potential for the preparation of the nanofibres & controlling the release of the biomedicine, as it is simplest method, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

Lyophilization technique\(^{[31]}\)

This technique has been thought of the molecular mixing technique where a drug & carrier are co dissolved in the common solvent, frozen & sublimed to obtain the lyophilized molecular dispersion.
Use of surfactant [21]

The use of a surfactant system in solubilization is very important. The adsorption of surfactant on the solid surface can modify their surface charge, hydrophobicity, & other key properties that govern the interfacial processes such as wetting, solubilization, flocculation/dispersion, floating, detergency & enhanced oil recovery & corrosion inhibition. The surfactants have also been reported to cause the solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, the combined glass transition temperature & glass transition temperature of solid dispersions. Due to these unique properties, surfactants have attracted the attention of the investigators for the preparation of the solid dispersions.

Polymers used in solid dispersions [32-35]

PEG [Polyethylene Glycol]
The term PEG refers to the compounds that are obtained by reacting ethylene glycol with the ethylene oxide. PEGs whose molecular weight is above the 3,00,000 are commonly termed as polyethylene oxides.

Phospholipids:
The complexity of the glycerides advances by the modification of the terminal hydroxyl with the phosphate linked head groups to form the phospholipids. Common phospholipid head groups include ethanolamine, choline, serine, inositol phosphate, inositol & glycerol esters. As like with the triglycerides, numerous species are possible by the various combinations of the different head groups & fatty acyl substitution at the first & the second positions of the glycerol backbone, fluidity differences are evident as the function of the gel to liquid crystalline transition temperatures. The solubility of the phospholipids is intimately linked to the confirmation of the aggregate material rather than the strictly the chemical function of a molecule. Monoacyl phospholipids, which tends to form the micelles, are usually more readily soluble in the aqueous solutions.

PVP [Polyvinyl Pyrrolidone]
It has the molecular weight ranging from 10,000 to 7,00,000. It is soluble in the solvents like water, ethanol, chloroform & the isopropyl alcohol. Polyvinyl Pyrrolidone is not suitable for preparation of solid dispersions prepared by the melt method because of its melt at the very high temperature above 275 °C, where it becomes decomposed.

Cyclodextrins:
These are primarily used to enhance the chemical protection, solubility, taste masking & improved handling by the conversion of the liquids into the solids by the entrapment.

Table 2: List of Solvents Used In Solid Dispersion [12]

<table>
<thead>
<tr>
<th>S.NO</th>
<th>SOLVENT</th>
<th>MELTING POINT (°C)</th>
<th>BOILING POINT (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methanol</td>
<td>-93.9</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>19</td>
<td>189</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol</td>
<td>-117</td>
<td>78.5</td>
</tr>
<tr>
<td>4</td>
<td>1-Propranol</td>
<td>-85</td>
<td>97.4</td>
</tr>
<tr>
<td>5</td>
<td>Chloroform</td>
<td>-63</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>2-Propranol</td>
<td>-127</td>
<td>82.4</td>
</tr>
<tr>
<td>7</td>
<td>Water</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>Acetic Acid</td>
<td>17</td>
<td>118</td>
</tr>
</tbody>
</table>

Selection of solvents [12]
Solvent to be included for the formulation of solid dispersion should have the following criteria:

- Due to less toxicity Ethanol can be used as alternative
- The water based systems are preferred.
- The drug & carrier both must be dissolved.
- The toxic solvents to be avoided due to the risk of the residual levels after the preparation For e.g. Dichloromethane & chloroform.
The surfactants are used to create the carrier drug solutions but as they can reduce the glass transition temperature, so care must be taken in to the consideration.

**Mechanism of solid dispersion**[^2][^36]

There are two sets of observations with regard to the mechanism of drug release from solid dispersions.

**Carrier-controlled Release**

Corrigan [1986] provided the very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself, in this case polyethylene glycol. He found that the dissolution rate of the drug in the polymer & the polymer alone were in fact equivalent, which were leading to the suggestion of carrier-controlled dissolution whereby the dissolution rate of the drug is controlled by the inert carrier. This research was supported by the work of Dubois & Ford [1985] who noted that the dissolution rates of the range of drugs in the single carrier, prepared under the comparable conditions, were identical in most of the cases. In that instance the particles dissolve into the polymer-rich diffusion layer at the sufficiently rapid rate that there is the insufficient time for the particles to be released intact into the medium. Consequently, the drug is molecularly dispersed within this concentrated layer.

**Drug-controlled Release**

Sjokvist & Nystrom [1991] measured a particle size of the griseofulvin particles released from the dispersions & produced strong evidence that the dissolution rate enhancement was the direct function of the size of the particles released. In an attempt to reconcile these contradictions Sjokvist-Saers & Craig [1992 used a homologous series of drugs (paraaminobenzoates) in Polyethylene Glycol-6000 in an attempt to interrelate the solid state structure, drug solubility & dissolution rate. This noted that there was the linear relationship between the intrinsic dissolution rate of a model drugs in the dispersions & the drug solubility, clearly linking the properties of the drug [not the polymer] to the dissolution rate; it may be prove helpful at this stage to refer to such a behavior as drug-controlled dissolution as opposed to the carrier controlled dissolution. Here the dissolution into the polymer diffusion layer is comparatively slow & the drug is released as the solid particles. The dissolution will not be associated with the polymer but will instead be dominated by the properties [size, physical form, etc.] of the drug itself. This may still lead to the considerable improvements in the dissolution compared to the conventional dosage forms due to the higher surface area associated with the particles & the possibility of the improved wetting & the decreased agglomeration.

**Characterization of the solid dispersion system**[^27][^37][^38]

**Table No-3 – Different methods of characterization of solid dispersions**

[^2]: Corrigan [1986]
[^36]: Dubois & Ford [1985]
[^27]: Sjokvist & Nystrom [1991]
[^37]: Sjokvist-Saers & Craig [1992]
Recent advances & future aspects

The solid dispersion has a great potential both for increasing the bioavailability of the drug & developing the controlled release preparations. Hence, to solve bioavailability issues with respect to the poorly water-soluble drugs, the solid dispersion method has grown rapidly. The dosage form can be prepared & developed using a small amount of drugs substances in the early stages of the development process of drug; this system might have an advantage over other commonly used bioavailability enhancement techniques such as micronization of drugs & soft gelatin encapsulation. There are some major research areas where the focus must be given in context to the solid dispersion which are as follows:

a) The Identification of new surface-active carriers & self-emulsifying carriers:
The major focus of the future research will be identification of the new surface-active carriers & self-emulsifying carriers for the solid dispersions. Only the small number of such carriers is available currently for oral use. Some of the carriers that are used for topical application of drug only may be qualified for the oral use by conducting the appropriate toxicological testing.

The Two new surface active carriers was proposed for enhancement of bioavailability
A. Gelucire 44/14: It is the mixture of glycerol and PEG-1500 esters of long chain fatty acid [lauryl monoglycides]. [m.pt - 44°C while HLB value is 14].
B. Vitamin E TPGS NF [D-α-tocopheryl PEG 1000 succinate]

b) Identification of vehicles
The research should also be directed towards the identification of the vehicles or excipients that would retard or prevent the crystallization of the drugs from the supersaturated systems. The attention should also be given to any physiological & pharmacological effects of carriers used. Many of the surface-active & self-emulsifying carriers are lipidic in nature so the potential roles of such carriers on drug absorption, specially on their p-glycoprotein-mediated drug efflux, require careful consideration.

c) Bioavailability enhancement
The solid dispersions have shown a promising future for both for developing controlled-release preparations & increasing the bioavailability of drugs. Very few successful developments of the solid dispersion systems for the preclinical, clinical & commercial use have been feasible in the recent years due to the availability of surface-active carriers & self-emulsifying carriers with relatively low melting points.

d) Extended-release dosage forms
In order to extend the release rate dosage form has been reinvigorated by the availability of surface-active & self-emulsifying carriers & the development of a new capsule filling processes. This is because the formulation of solid dispersion for bioavailability enhancement & extended release of drugs may employ the essentially similar processes, except for the use of the slower dissolving carriers for the later use,
it is to be expected that the research in these two areas will progress simultaneously & be complementary to each other

Xii] marketed products \[24

A list of several marketed products prepared using different solid dispersion techniques is given in the below table

**Table 4: Several marketed and late stage drugs designed for improved solubility by solid dispersion techniques** \[24

<table>
<thead>
<tr>
<th>Product/Substance</th>
<th>Technology used</th>
<th>Company</th>
<th>Dispersion Polymer or Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoptin SRE-240 (Verapamil)</td>
<td>Melt-extrusion</td>
<td>Soliqs</td>
<td>Various</td>
</tr>
<tr>
<td>LCP-Tacro (Tracrolimus)</td>
<td>Melt-granulation</td>
<td>Life Cycle Pharma</td>
<td>HPMC</td>
</tr>
<tr>
<td>Gris-PEG® (Griseofulvin)</td>
<td>Melt process; exact process unknown</td>
<td>Novartis</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td>Kaletra (lopinavir and ritonavir)</td>
<td>Melt-extrusion</td>
<td>Abbott Laboratories</td>
<td>Polyvinylpyrrolidone (PVP/polyvinyl acetate)</td>
</tr>
<tr>
<td>Brilinta (Etravirine)</td>
<td>Spray drying</td>
<td>Tibotec</td>
<td>HPMC</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Melt-extrusion</td>
<td>Soliqs</td>
<td>Various</td>
</tr>
<tr>
<td>Afeditab (Nifedipine)</td>
<td>Melt/absorb on carrier</td>
<td>Élan Corp</td>
<td>Poloxamer or PVP</td>
</tr>
<tr>
<td>Sproramax capsules (Itraconazole)</td>
<td>Spray layering</td>
<td>Janseen pharmaceutica</td>
<td>Hydroxypropylmethylcellulose (HPMC)</td>
</tr>
<tr>
<td>Certican (Everolimus)</td>
<td>Melt or Spray drying</td>
<td>Novartis</td>
<td>HPMC</td>
</tr>
</tbody>
</table>

**CONCLUSION**

There are many techniques for enhancing the solubility. As the enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Solid dispersion is one of the solubility enhancement technique. Because of solubility problem of many drugs the bioavailability of these gets affected and hence solubility enhancement becomes necessary. Dissolution of drug is the rate determining step for oral absorption of drugs which can subsequently affect the in vivo absorption of drug. The method of preparation & the amount of the carrier also plays a vital role in the enhancement of the drug dissolution rate for solid dispersion. The commercial development of this solid dispersion technique requires overcoming the hindrances such as scale up, cost effectiveness & the instability of some of the drugs. More research is required for the better implementation of solid dispersion technology on industrial scale as this is an excellent
technique for the solubility enhancement of the poorly soluble drugs.

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