Surface Solid Dispersion – A Review

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ABSTRACT

Preparation of an effective formulation of poorly water-soluble drugs is a key challenge in pharmaceutical technology. Dissolution rate and solubility are rate-limiting steps for increasing the bioavailability of poorly water-soluble drugs. Solid dispersion is an efficient technique for improving dissolution rate and subsequently, the bioavailability of poorly water-soluble drugs. Surface solid dispersion is a novel technique of solid dispersion for dispersing one or more active ingredients on a water insoluble carrier of high surface area in order to achieve increased dissolution rates and bioavailability of insoluble drugs. The various polymers used in this technique are Avicel, Crosspovidone, sodium starch glycolate, pregelatinized starch, Cab-o-sil, Ac-di-sol, KyronT-314, Primojel and potato starch. This article reviews the various methods of preparation and characterization of surface solid dispersion and compiles some of the drugs formulated as surface solid dispersions. Some of the practical aspects to be considered for preparing surface solid dispersion are selection of a suitable carrier and method of preparation of surface solid dispersion.

KEYWORDS: Bioavailability; Carrier; Dissolution rate; Solubility; Solid Dispersion; Wettability.

Introduction

The oral route of drug administration is the most common and preferred mode of delivery due to its convenience and ease of ingestion. Patient compliance and hence drug treatment is more effective with orally administered medications as compared to other routes of administration (Yadav and Yadav, 2010). Drugs with poor aqueous solubility will mainly exhibit dissolution rate: limited absorption, and drugs with poor membrane permeability will exhibit permeation rate: limited absorption (Serajuddin, 1999). The two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents are:

(i) Enhancing the solubility and dissolution rate of poorly water-soluble drugs.
(ii) Enhancing the permeability of less permeable drugs.

Various techniques used to overcome the problems of poor water solubility of drugs include particle size reduction, formation of salts, polymorphs and pseudopolymorphs, complexation, solubilization using hydrotropes, use of surfactants and formation of soluble prodrugs. All these techniques have limitations, except solid dispersions.

In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Solid dispersion technologies are particularly promising in improving the wettability, dissolution, oral absorption and bioavailability of BCS Class II drugs (Leuner and Dressman, 2000). Solid dispersion (SD) can be divided into a single or two phase solid system as explained in Fig 1.

Classification of solid dispersion: Table 1 explains the classification of solid dispersions, based on its molecular arrangement (Dhirendra et al., 2009)
TABLE 1
Classification of Solid dispersions.

<table>
<thead>
<tr>
<th>Solid Dispersion Type</th>
<th>Matrix</th>
<th>Drug</th>
<th>Remarks</th>
<th>No. of phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eutectics</td>
<td>C</td>
<td>C</td>
<td>The first type of solid dispersion prepared</td>
<td>2</td>
</tr>
<tr>
<td>Amorphous precipitations in crystalline matrix</td>
<td>C</td>
<td>A</td>
<td>Rarely encountered</td>
<td>2</td>
</tr>
<tr>
<td>Solid solutions:</td>
<td>C</td>
<td>M</td>
<td>Miscible at all composition, never prepared</td>
<td>1</td>
</tr>
<tr>
<td>Continuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>Partially miscible, existing as two phases even though drug is molecularly dispersed.</td>
<td>2</td>
</tr>
<tr>
<td>Discontinuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>Molecular diameter of drug (solute) is 15% less than the matrix(solvent)diameter. In this case the drug and matrix are substitutional.</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Substitutional solid solutions</td>
<td>C</td>
<td>M</td>
<td>Drug molecular diameter is 59% less than matrix diameter. Usually limited miscibility. eg: Drug in helical interstitial spaces of PEG.</td>
<td>2</td>
</tr>
<tr>
<td>Interstitial solid solutions</td>
<td>C</td>
<td>M</td>
<td>Drug molecular diameter is 15% less than matrix diameter. Usually limited miscibility.</td>
<td>2</td>
</tr>
<tr>
<td>Glass suspension</td>
<td>A</td>
<td>A</td>
<td>Particle size of dispersed phase is dependent on cooling/evaporation rate of many solid dispersions of this type</td>
<td>2</td>
</tr>
<tr>
<td>Glass solution</td>
<td>A</td>
<td>M</td>
<td>Requires miscibility or solid solubility, complex formation occurs on fast cooling or evaporation during preparation with PVP.</td>
<td>1</td>
</tr>
</tbody>
</table>

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.

Basic components of adsorbent based Amorphous Solid Dispersion are shown in Fig 2

This is an amorphous solid suspension as opposed to a true solid solution. Selecting a suitable adsorbent, insoluble carrier is as equally important as the choice of solubilizer to obtain optimum bioavailability (Gupta et al., 2001).

Fig. 2(a). Basic components of adsorbent based Amorphous Solid Dispersion.

TABLE 2
Shows the different methods for applying adsorbent carriers in different solid dispersions.

<table>
<thead>
<tr>
<th>Hot Melt</th>
<th>Solvent adsorption</th>
<th>Emulsion system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly soluble API eg. BAY 12-9566 + Carrier</td>
<td>Poorly soluble API eg. Meloxicam + Carrier</td>
<td>Poorly soluble API eg/ Glyburide + Oil surfactants/ cosurfactants + Carrier</td>
</tr>
<tr>
<td>Polymers or Surfactants or mixture of both</td>
<td>Polymers of Surfactants or mixture of both</td>
<td>SMEDDS/SEDDS</td>
</tr>
<tr>
<td>+ Carrier</td>
<td>Solid dispersions</td>
<td>Tablets or capsule</td>
</tr>
<tr>
<td>Solid dispersions</td>
<td>Tablets or capsules</td>
<td></td>
</tr>
<tr>
<td>Tablets or capsules</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Advantages

- It improves dissolvability of water insoluble drugs in pharmaceutical compositions (Babu and Chowdary, 2008).
- Solid dispersion improves the absorption efficiency of drugs, thereby reducing the dose of drug.
- Solid dispersion tablets can be taken without the aid of water, enabling self-medication (Giri et al., 2008).
- They can be used as an alternate to parenteral therapy for immediate action.
- SD formulations may provide a means to rapidly assess the safety and efficacy profile of the drug substance (Liu et al., 2007).
- SDs improves the onset of action for drugs such as NSAIDs where immediate action is crucial in relieving acute pain and inflammation.
- Bioavailability of anticancer drugs has been improved by incorporating them in solid dispersions.
- They reduce the effect of food on drug absorption thus, making it convenient to take the drug on an empty stomach.

Limitations

The major disadvantages of solid dispersion are related to its instability. Most of the polymers used in solid dispersions can absorb moisture which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state during storage (Goldberg et al., 1996). This may result in decreased solubility and dissolution rate. The problems of solid dispersion include:

1. Physical and chemical stability of drugs and vehicles
2. Method of preparation
3. Reproducibility of its physicochemical properties
4. Formulation of solid dispersion into dosage forms
5. Scale-up of manufacturing processes

Types of Solid Dispersion

Solid dispersion can be classified into three types based on the method of preparation:

1. Binary solid dispersion
   - It consists of drug and a polymeric carrier.
2. Ternary solid dispersion
   - It consists of drug, polymeric carrier and a surfactant. Polysorbate 80 is mostly used as a surfactant in ternary solid dispersions.
   - Binary and ternary solid dispersions have enhanced the dissolution of water insoluble drugs. Dissolution of ternary solid dispersion is faster compared to that of binary solid dispersion (Okonogi and Puttipipatkachorn, 2006) due to the addition of polysorbate 80. Polysorbate 80 improves the wettability of the formulation and solubilises the non-molecularly dispersed or crystalline fraction of drug, eg. Ofloxacin (Dixit and Nagarsenker, 2007).

3. Surface solid dispersion (SSD)
   - Surface solid dispersions are prepared with polymers such as polyvinyl pyrrolidone, polyethylene glycol, polyvinyl pyrrolidone-vinyl acetate copolymer, Sodium starch glycolate, Avicel, Cab-o-sil, and crosspovidone.
   - SSD deposits drugs on the surface of an inert carrier, leading to reduction in particle size of the drug, which can alter the dissolution characteristics of drugs (Docoslis et al., 2007).

Surface Solid Dispersion

It is defined as a technique for dispersing one or more active ingredients on a water insoluble carrier of extremely high surface area to achieve increased bioavailability and dissolution rates of insoluble drugs (Aparna et al., 2011). Surface solid dispersion uses the solvent deposition technique to increase the solubility, dissolution and bioavailability of many insoluble or poorly water soluble drugs. In-vivo results have substantiated the fact that surface solid dispersion improves the release profile of many drugs resulting in rapid onset of bioavailability.

The solvent deposition technique involves deposition of the drug on the surface of the carrier by using volatile solvents (Chowdary and Srinivasa, 2000). Deposition of the drug leads to reduction in its particle size, thereby providing a faster dissolution rate (Cassidy and Rouchotas, 2000). Surface modifications in SSD formulations using hydrophilic carriers can alter the dissolution behaviour of hydrophobic drug materials (Pinnamaneni et al., 2002).

The carriers used in the surface solid dispersions are water insoluble, porous materials which are hydrophilic in nature (Adrian et al., 2005). The common tablet excipients like Avicel, Cab-O-sil, Crosspovidone, etc. have been used as carriers for SSD (Charumanee et al., 2004). Drug release from the carrier material depends on the hydrophilic nature, particle size, porosity and surface area of the carrier. The larger the surface area of the carrier available for adsorption of drug, the better the release rate (Francois and Jones, 1978). Selection of carrier and method of preparation are the critical factors influencing the properties of drug incorporated in the SSD. Fig. 2 shows the advantage of a surface-active carrier over a non-surface-active in improving the dissolution of drug from a capsule formulation (Chatham et al., 1987).

Surface solid dispersion technique has been extensively used to increase the solubility, dissolution and bioavailability of many practically insoluble or poorly water soluble drugs such as piroxicam (Serajuddin et al., 1988), meloxicam, ibuprofen (Corrigan et al., 1985) and ketoprofen.
Fig. 2(b). A schematic representation of the comparative dissolution of a poorly water-soluble drug from surface-active versus non-surface-active vehicles.

**Hydrophilic Carriers used for preparing SSD**

The carriers used in the preparation of SSD are Microcrystalline cellulose, Colloidal silicon dioxide, Sodium starch glycolate, potato starch, pregelatinised starch and crospovidone (Raymond et al., 2009). The physico-chemical properties and pharmaceutical applications of these carriers are explained below:

**Microcrystalline Cellulose**

**Synonyms**

Avicel PH, Celex, cellulose gel, Celphere, Ceolus KG, crystalline Cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose.

**Chemical name:** Cellulose

**Empirical formula:** (C₆H₁₀O₅)ₙ

**Molecular weight:** 220

**Structural formula**

![Structural formula of cellulose](image)

**Functional category**

Adsorbent, suspending agent, tablet and capsule diluents, tablet disintegrant.

**Description**

Microcrystalline cellulose is purified, partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

**Applications in pharmaceutical formulation or technology**

Microcrystalline cellulose is widely used in pharmaceuticals primarily as a binder or diluent in tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. It also has some lubricant and disintegrant properties that make it useful in tableting.

**Stability and storage conditions**

Microcrystalline cellulose is a stable yet hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

**Incompatibilities**

Microcrystalline cellulose is incompatible with strong oxidizing agents.

**Method of manufacture**

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of cellulose, obtained as a pulp from fibrous plant materials. The hydrocellulose obtained is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of broad size distribution.

**Safety**

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is regarded as a relatively nontoxic and non-irritant material. It is not absorbed systemically after oral administration, and thus has little toxicity. Consumption of large quantities of cellulose may have a laxative effect but this is not a problem if it is used as an excipient in pharmaceutical formulations.

**Colloidal Silicon Dioxide**

**Synonyms**

Aerosil,Cab-O-Sil,Cab-O-Sil M-5P, colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed.

**Chemical name:** Silica

**Empirical formula:** SiO₂

**Molecular weight:** 60.08

**Structural formula:** O=Si=O

![Structural formula of silica](image)
**Functional category**
Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer; viscosity-increasing agent.

**Description**
Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white coloured, odourless, tasteless and non-gritty amorphous powder.

**Applications in pharmaceutical formulation or technology**
Colloidal silicon dioxide is used to stabilize emulsions and is used as a thixotropic thickening and suspending agent in gels and semisolid preparations. It is also used as a tablet disintegrant and adsorbent dispersing agent for liquids in powders.

**Stability and storage conditions**
Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. The powder should be stored in a well-closed container.

**Incompatibilities**
It is incompatible with diethylstilbestrol preparations.

**Method of manufacture**
Colloidal silicon dioxide is prepared by vapour hydrolysis of chlorosilanes, such as silicon tetrachloride, at 1800°C using a hydrogen–oxygen flame.

**Safety**
Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and non-irritant excipient. Intraperitoneal and Subcutaneous injection may produce local tissue reactions and/or granulomas; therefore it should not be administered parenterally.

**Sodium Starch Glycolate**

**Synonyms**
Carboxymethyl starch, sodium salt, Explosol, Explotab, Glycolys, Primogel, starch carboxymethyl ether, sodium salt.

**Chemical name:** Sodium carboxymethyl starch

**Molecular weight:** 5x10⁵-1x10⁶

**Structural formula**

**Functional category**
Tablet and capsule disintegrant.

**Description**
Sodium starch glycolate is a white to off-white, odourless, tasteless, free-flowing powder. It consists of oval or spherical granules, 30–100 mm in diameter, with some less-spherical granules ranging from 10–35 mm in diameter.

**Applications in pharmaceutical formulations or technology**
Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is mainly used in tablets prepared by either direct compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration of about 4%. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. It has also been investigated for use as a suspending vehicle.

**Stability and storage conditions**
Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3–5 years if it is stored at moderate temperatures and humidity.

**Incompatibilities**
It is incompatible with ascorbic acid.

**Method of manufacture**
Sodium starch glycolate is a substituted derivative of potato starch. Commercial products are also mostly cross-linked. Starch is carboxymethylated by reacting it with sodium chloroacetate in an alkaline medium followed by neutralization with citric acid or some other acid. Crosslinking may be achieved either by physical methods or chemically by using reagents such as phosphorus oxychloride or sodium trimetaphosphate.

**Safety**
Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and non-irritant material. However, oral ingestion of large quantities may be harmful.

**Potato Starch**

**Synonyms**

**Chemical name:** Starch

**Empirical formula:** (C₆H₁₀O₅)ₙ

**Molecular weight:** 300-1000
**Starch**

*Functional category*

Glidant, tablet and capsule diluents, tablet and capsule disintegrant, tablet binder.

*Description*

Starch occurs as an odourless and tasteless, fine, white-coloured powder comprised of very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

*Applications in pharmaceutical formulation or technology*

Starch is used in oral solid-dosage formulations primarily as a binder, diluent, and disintegrant. Freshly prepared starch paste is used in the concentration of 5–25% w/w in tablet granulations as a binder. It is one of the most common tablet disintegrants used in the concentration of 3–15% w/w. It has been investigated as an excipient in novel drug delivery systems for nasal, oral, periodontal and other site-specific delivery.

*Stability and storage conditions*

Dry, unheated starch is stable only if protected from high humidity. Starch is considered to be inert under normal storage conditions for use as a diluent or disintegrant in solid-dosage forms. Heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties. It should be stored in an airtight container in a cool, dry place.

*Method of manufacture*

Starch is extracted from plant sources through a sequence of processing steps involving coarse milling, repeated water washing, wet sieving and centrifugal separation. The wet starch obtained from these processes is dried and milled before use in pharmaceutical formulations.

*Safety*

Starch is an edible food substance and is generally regarded as an essentially nontoxic and non-irritant material. Oral consumption of massive doses can be harmful due to the formation of starch calculi, which causes bowel obstruction. Starch may also cause granulomatous reactions when applied to the peritoneum or the meninges.

**Pregelatinized Starch**

*Synonyms*

Compressible starch, Instastarch, Lycatab C, Lycatab PGS, Merigel, Pharma-Gel; Prejel; Sepistab ST 200; Spress B820; Starch 1500 G.

*Chemical name:* Pregelatinized starch

*Empirical formula:* \((C_{6}H_{10}O_{5})_{n}\)

*Molecular weight:* 300-1000

*Structural formula*

*Functional category*

Tablet and capsule diluents, tablet and capsule disintegrant, tablet binder.

*Description*

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odourless and has a slight characteristic taste.

*Applications in pharmaceutical formulation or technology*

Pregelatinized starch is a modified starch, being used in oral capsule and tablet formulations as a binder, diluent and disintegrant. Grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression or direct compression processes and wet granulation processes.

*Stability and storage conditions*

Pregelatinized starch is a stable but hygroscopic material which should be stored in a well-closed container in a cool, dry place.

*Method of manufacture*

Food-grade pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62–72.8 °C. Chemical additives that may be included in the slurry are gelatinization aids (salts or bases) and surfactants. They are added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded or drum-dried.
Safety

It is generally regarded as a nontoxic and non-irritant excipient but oral consumption of large amounts of pregelatinized starch may be harmful.

Crospovidone

Synonyms


Chemical name: 1-Ethenyl-2-pyrroldinone homopolymer

Empirical formula: (C₆H₉N₂)ₙ

Molecular weight: >1000000

Structural formula

Functional category: Tablet disintegrant.

Description

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

Applications in pharmaceutical formulation or technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used in 2–5% concentration in tablets prepared by direct-compression or wet and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences the disintegration of analgesic tablets. Larger particles provide faster disintegration than smaller particles. It can also be used as a solubility enhancer to enhance the solubility of poorly soluble drugs.

Stability and storage conditions

Crospovidone is hygroscopic; therefore it must be stored in an airtight container in a cool, dry place.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. It may form molecular adducts on exposure to high water levels.

Method of Manufacture

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidine and acetylene are reacted under pressure. The monomer vinylpyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared by a ‘popcorn polymerization’ process.

Safety

Crospovidone is used in oral pharmaceutical formulations and regarded as a nontoxic and non-irritant material. Short-term animal toxicity studies have shown no adverse effects associated with it.

Method of Preparation of Surface Solid Dispersions

SSD can be prepared by the two common methods of melting and solvent evaporation. These methods are further classified and explained in fig 3.

Fig. 3. Method of preparation of Surface Solid Dispersions.

Various other techniques for preparing SSD are lyophilization (freeze drying), the melt agglomeration process, the extruding method, spray drying technology, use of surfactants, the electrostatic spinning method, and super critical fluid technology.

Fusion Method (Melting method)

The fusion method was first used by Sekiguchi and Obi in 1961 to melt a eutectic mixture of sulfathiazole and urea above its eutectic temperature. In this method, the carrier is heated to a temperature slightly above its melting point and the drug is incorporated into the matrix. The mixture is cooled either slowly to room temperature or rapidly in an ice bath with constant stirring to ensure a homogenous dispersion of drug in the matrix. The end product is pulverized and sieved.

Advantages

1. This method is preferred for drugs and carriers that are miscible with each other in the molten state.
2. It is less time-consuming and easy to perform.
**Disadvantages**

1. Risk of exposure to high temperatures, if the carrier is a high melting solid and the drug is heat sensitive.
2. The solidification temperature affects the crystalline size and hardness of the dispersion.
3. Immiscibility within the phase diagram of drug and carrier may lead to irregular crystallization and instability.
4. Other potential problems include sublimation and polymorphic transformations.

Several modifications introduced to the original process to avoid these limitations are hot stage extrusion, Meltrex®, melt agglomeration and injection molding.

**Meltrex™**

Meltrex™ is a patented solid dispersion manufacturing process. This technique includes the use of a special twin screw extruder and the presence of two independent hoppers in which temperature can vary over a broad temperature range. The residence time of the drug is reduced in the extruder allowing a continuous mass flow and avoiding thermal stress to the drug and excipients.

**Evaporation Method**

Drug and carrier both are dissolved in an organic solvent. The solvent is evaporated after dissolving the drug and the carrier. The solid mass is ground, sieved and dried. Solid dispersions of ofloxacin with polyethylene glycol have been prepared by this method.

A new method of solvent evaporation is the Modified solvent evaporation method. In this method, the drug is dissolved with continuous stirring in an organic solvent at its saturation solubility. The polymer is suspended in a sufficient amount of water (up to the wet mass of the polymer). The drug solution is poured into the polymer suspension and the entire solvent is evaporated and the mass obtained is dried. Various other methods of solvent evaporation are as follows:

- **Kneading method:** The mixture of drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved (e.g. furosemide and crospovidone), and solid dispersion is prepared by this method (Chaulang et al., 2008)

- **Co-Grinding method:** Pure drug powder and the carrier are physically mixed in a blender at the optimum speed. The mixture is then charged into the chamber of a vibration ball mill. The powder mixture is ground and the sample stored in a screw capped glass vial until use. Chlordiazepoxide and mannitol solid dispersion have been prepared by this method.

- **Co-precipitation method (co-evaporates):** Weighed amounts of carrier and drug are dissolved in water and organic solvent, respectively. The aqueous solution of carrier is then poured into the organic solution of drug. The solvents are then heated and evaporated and the dispersion is pulverized, sieved and dried (Nokhodchi et al., 2007).

- **Co-precipitation with supercritical fluid:** Supercritical fluid processing (SCP) is emerging as an alternate to the solvent-evaporation method for preparing co-precipitates of smaller particle size, less residual organic solvent and having 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 due to its low critical temperature thus making it attractive for processing thermo labile pharmaceuticals (Moneghini et al., 2001).

- **Spray drying method:** Weighed amounts of drug and lipid carrier are dissolved in methanol to obtain a clear solution. This solution is then spray dried using a spray dryer. The sample is stored over silica gel in vacuum desiccators (Vanshiv et al., 2009).

- **Gel entrapment technique:** Carriers like HPMC are dissolved in organic solvent to form a clear and transparent gel. Drugs are dissolved in the gel by sonication (e.g. carbamazepine). The organic solvent is evaporated under a vacuum and the solid dispersions obtained are reduced to the optimum size (Bhise and Rajkumar, 2008).

**Fusion-Solvent Method**

The fusion-solvent method is a combination of the above two methods. In this method, the drug to be incorporated into the carrier melt is solubilized in a suitable solvent and then added to the carrier melt with continuous stirring followed by cooling. The carrier used should be capable of retaining a certain proportion of liquid while maintaining its solid state, and the liquid used should be innocuous in nature. This method is useful for drugs that have a high melting point or are thermolabile in nature.

**Disadvantages**

1. This method requires complete evaporation of the solvent because it may cause toxicity.
2. The selected solvent or dissolved drug may not be miscible with the carrier melt.

**Review of Literature**

Charumanee et al. (2004) prepared a surface solid dispersion of Piroxicam by the co-evaporation method using microcrystalline cellulose and potato starch. The extent of surface adsorption was more significant in the piroxicam-microcrystalline cellulose system.

Nagarsenker et al. (2007) reported the in-vitro and in-vivo advantages of celecoxib surface solid dispersion. Celecoxib surface solid dispersions were prepared by the co-evaporation and co-grinding technique using various water-insoluble carriers like Sodium starch glycolate (SSG), Crospovidone, Avicel pH 101, and Pregelatinised starch in different ratios.
Aly et al. (2008) have developed rapidly disintegrating Glipizide tablets through surface solid dispersion. Primojel, Ac-Di-Sol and Kollidon CL were used as super-disintegrants and a methanol: dichloromethane mixture (1:3) as the solvent. Glipizide tablets were prepared by direct compression with various excipients in different ratios using the solvent evaporation method. Glipizide loaded with Kollidon CL showed the best dissolution profile compared to the other excipients and pure drug.

Shastri et al. (2009) have prepared surface solid dispersions of Glimepiride using water-insoluble carriers like crospovidone, croscarmellose sodium, pregelatinized starch, potato-starch and avicel pH101. The optimized dispersion was compressed into tablets with the wet granulation method.

Rao et al. (2010) prepared surface solid dispersions of Simvastatin by co-evaporation method and evaluated for in-vivo performance in albino rats using pharmaco-dynamic markers such as total cholesterol, triglycerides, low-density lipoproteins and very low density lipoproteins.

Lalitha et al. (2011) have developed surface solid dispersions of Nifedipine with different carriers such as Avicel PH 101 in different ratios. The optimized dispersion was then evaluated and formulated into sublingual tablets.

Aparna et al. (2011) have prepared surface solid dispersions of Domperidone using silica adsorbates. The carriers used were Avicel, Cab-o-sil, crospovidone and pregelatinized starch. The surface solid dispersions on Cab-o-sil with a drug to carrier ratio of 1:10 showed the highest dissolution rate.

**Characterization of Surface Solid Dispersions**

Powder X-Ray diffraction can be used for qualitative and semi-quantitative detection of materials with long range order. Sharper diffraction peaks indicate more crystalline material.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Characterisation</th>
<th>Methods</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug-carrier miscibility</td>
<td>Hot stage microscopy (HSM)</td>
<td>Find out the complex formation between drug and carrier.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Differential scanning calorimeter</td>
<td>check the degree of amorphization.</td>
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<tr>
<td></td>
<td></td>
<td>X-ray Diffraction (XRD)</td>
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<tr>
<td></td>
<td></td>
<td>Nuclear magnetic resonance (NMR)</td>
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</tr>
<tr>
<td>2</td>
<td>Drug-carrier interactions</td>
<td>Fourier transform infrared spectroscopy (FTIR)</td>
<td>Study the solid state interaction between drug and carrier and formation of inclusion complex.</td>
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<td>Surface properties</td>
<td>Dynamic vapour sorption</td>
<td>Study the morphology and degree of crystallinity.</td>
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<td>Stability</td>
<td>Humidity studies</td>
<td>Determine the degree of recrystallization.</td>
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<td>Isothermal calorimeter</td>
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<td>Amorphous content</td>
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Differential scanning calorimetry (DSC) is used to determine the interaction between drug and carrier, if any, and detect quantitative endothermic and exothermic phase transformations. It is also used to study the thermal behaviour of materials by melting them.

Infrared spectroscopy IR reveals crystallographic changes of drug and polymer molecules, such as hydrogen bonds which are indicative of complex formation. FTIR spectroscopic imaging is regarded as the more beneficial method because it takes into account the specific absorbance of molecular vibrations in the sample for quality assessment of materials.

Isothermal microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature.

Isothermal titration calorimeter (ITC) helps in measuring the heat absorbed or generated during binding. It involves the addition of one binding component (titrant) into the other binding component (titrate) over time using single or multiple injections. It is a powerful technique with high precision that can quickly and directly explain the complete thermodynamic profiles of interaction in a single experiment (Renu and Sushma, 2010).

Micro–raman spectroscopy is used for characterization of the distribution, polymorphism and stability of drug in its surface solid dispersion.

Scanning electron microscopy (SEM) is done to study the surface morphology. SEM measures the shape and porosity of drugs. It is also used for ultrastructural analysis of pharmaceutical compounds.

TGA is a powerful technique for studying the changes in weight of a sample when heated, cooled, or held at constant temperature. Its main application is to characterize samples with regard to their composition. Moisture content in a solid dispersion can be determined using TGA.
Conclusions

Solubility and dissolution are the most important parameters for the oral bioavailability of poorly soluble drugs. Solid dispersions are extremely useful in improving the dissolution of water insoluble drugs, but their commercial application is limited. Surface solid dispersion technique is successful in improving the dissolution rate and bioavailability of poorly soluble or water insoluble drugs. The nature and amount of carrier used plays an important role in the enhancement of dissolution rate. Surface solid dispersion can be incorporated into conventional dosage forms like tablets or capsules but further studies on scale up and validation of the process are needed for its commercialization.

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