Solid dispersions

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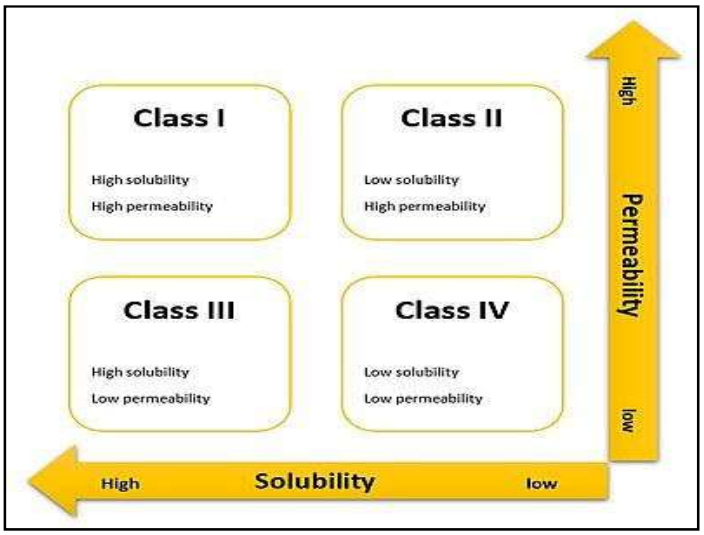
Introduction

The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited, gastrointestinal absorption generally show improved dissolution and bioavailability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which results in poor wettability.

Poor aqueous solubility of the drug frequently results in poor dissolution which is the prime determinant of the rate and extent of absorption of the drug. The drugs having low aqueous solubility often elicit poor therapeutic response and limited bioavailability. An improvement in aqueous solubility/dissolution can overcome this problem. For this variety of strategies have been developed such as Micronization, Nanosuspension, Complexation, Self micro emulsifying drug delivery systems, solid dispersions etc.

The Biopharmaceutics Classification System is used by the FDA is a scientific method in which drugs are classified according to the solubility in water related to their dose at three different pH and intestinal permeability. The BCS system divides the drug substances into following four classes:



Solid dispersion (SD)

is one of such methods that improve solubility ,it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method, Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine colloidal particles, because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water soluble drugs were expected to be high.

The promising results of solid dispersion in solubility and dissolution rate enhancement of poorly soluble drugs can be attributed due to:-

• Amorphous structure was replaced by crystalline structure to improve local solubility and wettability of the poorly soluble drug in the solid dispersion matrix .

• The ability of carrier functional groups to form interactions with the drug to the increase in glass transition temperature (Tg) of the solid dispersion mixture

• Inhibited drug precipitation from super saturated solution to resulting metastable drug polymorphous

Advantages of solid dispersion

Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.

Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as colic acid and bile salts. When used, can significantly increase the wettability property of the drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

Drugs in amorphous state

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

For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

Particles with higher porosity

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

Disadvantages of solid dispersions

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization.

Moreover, 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 or from a metastable crystalline form to a more stable structure during storage and this may result in decreased solubility and dissolution rate . Therefore, exploitation of the full potential of amorphous solids requires their

stabilization in solid state, as well as during *in vivo* performance. Another drawback of solid dispersions is their poor scale-up for the purposes of manufacturing.

How to avoid drug recrystallization?

As amorphous systems, they are thermodynamically unstable and have the tendency to change to a more stable state under recrystallization. Molecular mobility is a key factor governing the stability of amorphous phases, because even at very high viscosity, below the glass transition temperature (Tg), there is enough mobility for an amorphous system to crystallize over pharmaceutically relevant time scales. Furthermore, it was postulated that crystallization above Tg would be governed by the configurational entropy, because this was a measure of the probability of molecules being in the appropriate conformation, and by the mobility

Molecular mobility of the amorphous system depends, not only on its composition, but also on the manufacturing process as stated by Bhugra et al.. Solid dispersions exhibiting high conformational entropy and lower molecular mobility are more physically stable. Polymers improve the physical stability of amorphous drugs in solid dispersions by increasing the Tg of the miscible mixture, thereby reducing the molecular mobility at regular storage temperatures, or by interacting specifically with functional groups of the drugs.

For a polymer to be effective in preventing crystallization, it has to be molecularly miscible with the drug. For complete miscibility, interactions between the two components are required. It is recognized that the majority of drugs contain hydrogen bonding sites, consequently, several studies have shown the formation of ion–dipole interactions and intermolecular hydrogen bonding between drugs and polymers, and the disruption of the hydrogen bonding pattern characteristic to the drug crystalline structure. These lead to a higher miscibility and physical stability of the solid dispersions.

The strategies to stabilize the solid dispersions against recrystallization strongly depend on the drug properties and a combination of different approaches appears to be the best strategy to overcome this drawback. Third generation solid dispersions intend to connect several strategies to overcome the drug recrystallization, which has been the major barrier to the solid dispersions marketing success.

Drug properties

For a drug to be successfully formulated via solid dispersion, it should possess certain ideal properties to ensure stability, efficacy, and manufacturability. Here are the most important properties:

1. Poor Aqueous Solubility

Solid dispersion is primarily used for drugs that have low solubility in water (BCS Class II or IV drugs), to enhance dissolution and bioavailability.

2. High Permeability

Drugs used in solid dispersion should have good permeability (i.e., easily pass through biological membranes) to ensure that enhancing solubility leads to improved absorption and bioavailability.

3. Thermal Stability

The drug must have thermal stability to withstand the heating processes commonly involved in solid dispersion techniques (such as hot-melt extrusion or solvent evaporation).

4. Compatibility with Carriers

The drug should be chemically and physically compatible with carriers (like polymers) used in the solid dispersion matrix. It should not react or degrade when in contact with the carrier.

5. Adequate Glass Transition Temperature (Tg)

For drugs that are intended to be in an amorphous form in solid dispersions, they should have a relatively high glass transition temperature (Tg) to prevent recrystallization over time, which could affect stability and solubility.

6. Non-hygroscopic Nature

It’s ideal for drugs and carriers to have a low hygroscopicity to avoid absorption of moisture, which could lead to degradation or recrystallization of the drug.

7. Stability in Amorphous Form

The drug should remain stable in its amorphous form after processing, as many solid dispersion techniques rely on keeping the drug in this form to enhance solubility. Recrystallization can reduce the benefits of solid dispersion.

8. Molecular Interactions

There should be potential for molecular interactions (e.g., hydrogen bonding) between the drug and the carrier. These interactions can help maintain the amorphous state and prevent drug recrystallization.

9. Particle Size and Surface Area

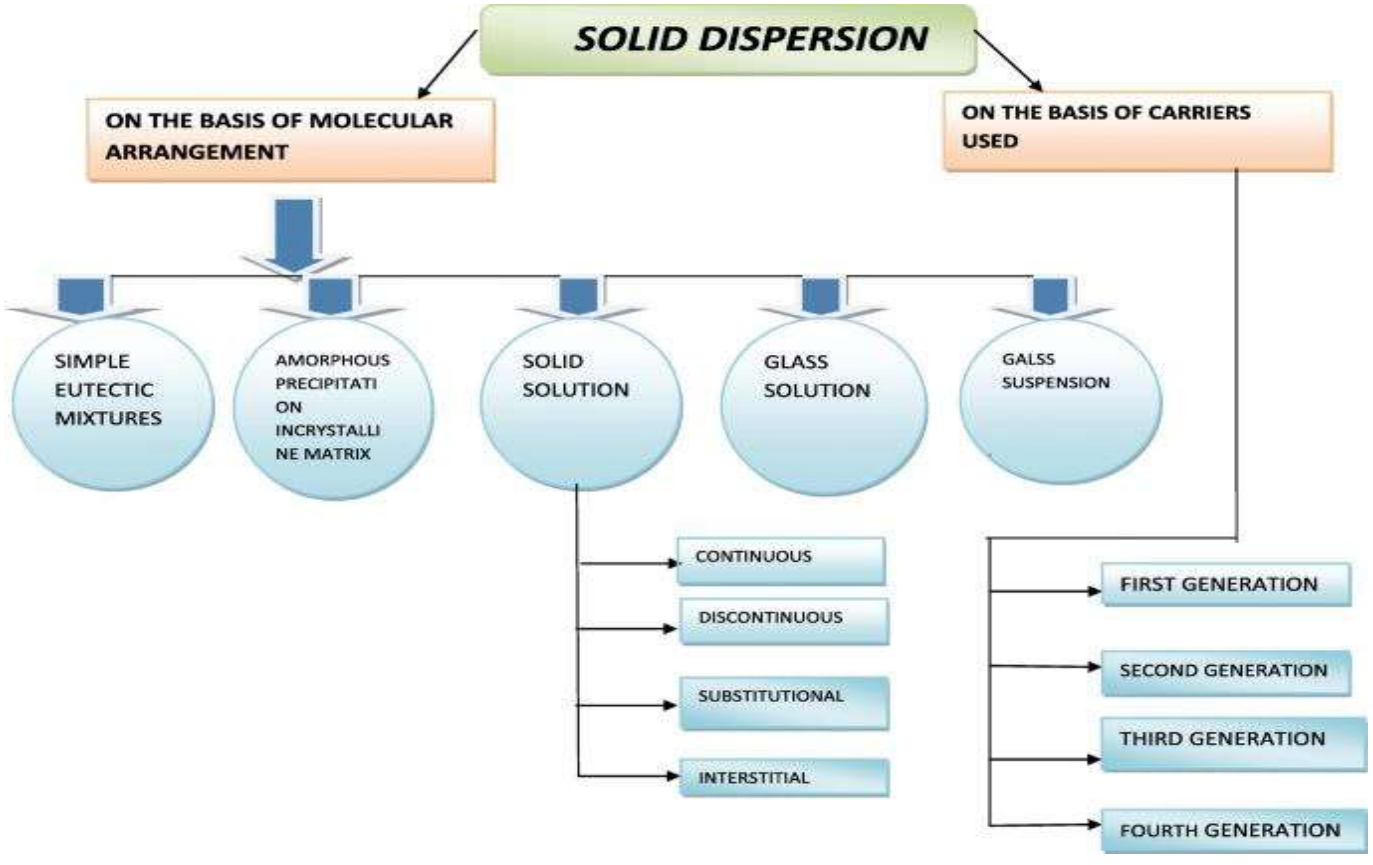
The drug should have an appropriate particle size and surface area to maximize the surface interaction with the dissolution medium, enhancing the dissolution rate.

Selection of carrier

The properties of the carrier have an influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following prerequisites for being suitable for increasing the dissolution rate of a drug. It should be:-

- Freely water soluble with rapid dissolution properties.
- Nontoxic and pharmacologically inert.
- Heat stable with a low melting point for the melt method.
- Soluble in a variety of solvents.
- Preferably enhancing the aqueous solubility of the drug.
- Chemically compatible with the drug.
- Forming only weakly bounded complex with the drug.

Chemical Class	Examples
Acids	Citric acid, Tartaric acid, Succinic acid.
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Xylitol, Galactose
Polymer material	Polyvinyl pyrolidone,PEG4000,PEG 6000,Sodium alginate, carboxyl methyl cellulose, Guar gum, Xanthan gum, Methyl cellulose
Surfactants	Polyoxyethylene stearate, polaxamer, Deoxycholic acid, Tweens and spans, Gelusire 44/14,Vitamin E TPGS NF
Miscellaneous	Urea, urethane, pentaerythrotrial, Hydroxyalkyl xanthenes



On the base of carrier use

First generation

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

They noted that the formulation of eutectic mixtures improves the rate of drug release and consequently, the bioavailability of poorly water soluble drugs.

Second generation

Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. This have advantages over crystalline that the drug maintained in the crystalline state, might not be as effective as the amorphous cause that crystalline is more thermodynamically stable.

Polymeric carriers have been the most successful for solid dispersions, because they are able to originate amorphous solid dispersions. These polymers include synthetic polymers such as povidone (PVP), polyethylene glycols (PEG) and polymethacrylate as well as natural product based polymers such as hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose, and hydroxyl propoylcellulose or starch derivates like cyclodextrins.

Third generation

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization.

The use of surfactants such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer-407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.

Fourth generation

The SDs belonging to the fourth-generation were developed as controlled release dispersion due to a need to improve the performance of drugs that are poorly soluble in water with a short biological half-life and/or a narrow therapeutic margin. The fourth-generation SDs improve the solubility of the poorly water-soluble drug while delaying the release of the drug in the dissolution medium due to the use of water insoluble or swellable polymers .These dispersions allow an adequate amount of drug to be administered over a prolonged period of time and offer advantages such as better patient compliance due to a decrease in dosing frequency, lesser development of side effects and prolonged therapeutic effect for poorly water soluble drugs. The mechanisms by which the drug can be released in fourth-generation SDs are diffusion and erosion. To prepare fourth-generation SDs, polymers such as ethyl cellulose, HPC, RL, poly (ethylene oxide), carboxyvinylpolymer (Carbopol) and Soluplus can be used

On the base of molecular arrangement

Eutectic Mixtures

Eutectic mixture was first described as solid dispersions, is formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility.

When a drug (A) and a carrier (B) are co-melted at their eutectic composition defined by point ‘e’, the melting point of the mixture is lower than the melting point of either drug or carrier alone. At the eutectic composition (e), both drug and carrier exist in the finely divided state, which results in higher surface area and enhanced dissolution rate of the drug.

To form the eutectic mixture a drug is required to dissolve in molten polymer at temperature equal to its melting point or, the opposite, the polymer must dissolve in molten drug substance. Usually however, the drug substance has higher melting point than macromolecular compound

Solid solutions

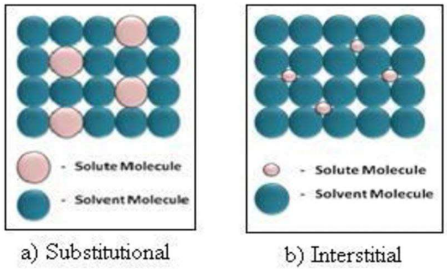
Similarly to liquid solutions, solid solutions form a single phase system, regardless of the number of their components. However, such a system is not formed unless both solid components mix together simultaneously and particle size of a drug product in solid solutions is reduced to an absolute minimum, Solid solutions should be used when mutual solubility of both components exceeds 5%.

These solid solutions may be either of amorphous or crystalline type. In amorphous solid solutions as the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. Amorphous solid solutions have improved physical stability of amorphous drugs by inhibiting drug crystallisation by minimising molecular mobility.

Crystalline solid solution may result when a crystalline drug is trapped within a crystalline polymeric carrier. Poorly soluble drugs have been incorporated in carrier molecules using crystal inclusion and crystal doping techniques, although the usage of such technologies has not yet gained widespread application in pharmaceutical product development.

According to extent of miscibility of the two components, solid solutions are continuous or discontinuous type. In continuous solid solutions, the two components are miscible in the solid state in all proportions. The components that are immiscible at intermediate composition, but miscible at extremes of composition are referred to as discontinuous solid solutions.

According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional and interstitial. In the substitutional solid solution, the solute molecule substitutes for the solvent molecule in the crystal lattice. In this case, the molecular size of the two components should not differ by more than 15%. An interstitial solid solution is obtained when the solute (guest) molecule occupies the interstitial space in the solvent (host) lattice. Therefore, the volume of the solute molecule(s) should be less than 20% of the solvent molecule(s). Examples include solid solutions of digoxin, prednisolone acetate and hydrocortisone acetate in the matrix of PEG 6000



a) Substitutional b) Interstitial

Glassy solid solutions and glass suspensions

Glassy solid solution is a multi-ingredient, glassy system, which consists of one phase only. At the molecular level it is homogeneous and uniform. The car- rier in this system occurs in an amorphous state, while the dissolved molecules are molecularly dispersed; this solution formation occurs upon rapid cooling/ evaporation of solvent.

Sugars, i.e. dextrose, fructose, galactose, trehalose, inulin and polymers i.e. polyvinylpyrrolidone (PvP), copolimer of polyvinylpyrrolidone and polyvinyl acetate (PvP- PvA), hydroxypropyl methylcellulose (HPMC) often are used as carriers for preparation of this form.

Glass suspension is a two-phase system consisting of a carrier in amorphous state with the incorporated drug substance in crystalline form. Method to obtain glass suspensions consists in crystallization of the drug substance in amorphous carrier, while particle size of dispersed phase is dependent on the rate of cooling/ evaporation of solvent

Amorphous precipitation in solid carriers

Based on molecular structure two types of amorphous precipitations were distinguished. In the former, drug sub- stance is dispersed in form of amorphous agglomerates in amorphous carriers. The latter comprises a carrier in crystalline form and the drug substance in amorphous form. The solid dispersion sub-types listed consist of two phases and are characterized by lack of homogeneity at the molecular level. While studying these systems by DSC meth- od glass transition Tg is observed for both components: drug substance and the carrier

Method of preparation

1. Melting method

The melting or fusion method is the preparation of a physical mixture of a drug and a water-soluble carrier and heating it directly until it melts. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverised and sieved. pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate.

Super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixture.

However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperatures. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

2. Solvent method

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents

However, some disadvantages are associated with this method such as

1) The higher cost of preparation.

2) The difficulty in completely removing liquid solvent.

3) The possible adverse effect of traces of the solvent on the chemical stability

4) The selection of a common volatile solvent.

5) The difficulty of reproducing crystal form.

6) In addition, a super saturation of the solute in the solid system cannot be attained except in a System showing highly viscous properties.

3. Melting solvent method (melt evaporation)

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property.

It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. This method is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

4. Melt extrusion method

Solid dispersion by this method is composed of an active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w).

Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry. Melt extrusion suitable for large scale production and The product is easier to handle and can be adapted to the next processing step without grinding. High energy inputs require shear forces and temperature and degradation of drugs and excipients because of the design of screw assemblies and extruder dies, could be the disadvantage of this method

5. Lyophilization technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative method to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

Advantage- Risk of phase separation is minimized

Disadvantage- very expensive. The technique is not suitable for all the products.

6. Spray-drying method

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using the spray dryer.

Advantages

- Ability to work with temperature sensitive APIs.
- Tremendous formulation flexibility from the wide variety of solvents, polymers and adjuvants that can be employed.
- Enhancement in performance that can be obtained by mixing the API and polymer at the molecular level in the solution and then freezing this morphology in place through rapid solvent removal.

Disadvantage

- Added costs associated with the use and consumption of the organic solvents.
- Requirement of unit operation for residual solvent removal.

7. Melt agglomeration process

This technique has been used to prepare Solid Dispersion where the binder acts as a carrier. SDs are prepared either by heating the binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer. A rotary processor has been shown to be an alternative equipment for melt agglomeration because of easier control of the temperature and because higher binder content can be incorporated in the agglomerates.

8. Electro spinning method

The electro spinning technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology. In this procedure, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30kV. When electrical forces prevail over the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are produced.

As the solvent evaporates, the formed fibers can be collected on a screen to give a non woven fabric, or they can be collected on a spinning mandrel This technique has tremendous potential for the preparation of nanofibers and controlling the release of biomedicine, as it is simplest and the cheapest this technique can be utilized for the preparation of solid dispersions in future.

9. Supercritical fluid technology

This technique consists of dissolving the drug and the inert carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel .

This SCF technology provides a novel alternative method of preparation of small particles with higher surface area, free flowing property, and a very low content of residual organic solvent and this technology also avoids most of the drawbacks of the traditional methods.

Factors influencing drug release

Nature of carriers

Drug release from solid dispersion is dependent upon the nature of the carrier, whether hydrophilic or hydrophobic. Thus, incorporation of poorly water soluble drug into inert and slightly water soluble carrier leads to retardation of drug release from matrix. However, incorporation of poorly water soluble drug into water-soluble carrier(s) leads to acceleration of drug release.

Drug carrier ratio

The dissolution rate of a drug increases with increase in the proportion of drug carrier. However, this is true only up to a certain limit beyond which the dissolution rate decreases. As much as 38-fold increase in the dissolution rate of piroxicam was reported when used as solid dispersion using drug: PVP in the ratio of 1:4. With further increase in PVP concentration, the dissolution rate decreased, attributable to the leaching of carrier during dissolution. This leached out carrier could form a concentrated layer of solution around the drug particle, resulting in lowering of the release rate.

Method of preparation

Solid dispersions prepared by melting generally showed faster dissolution rates than those prepared by solvent method. Solid dispersions of griseofulvin-PEG 6000 prepared by solvent method have been reported to yield dissolution rates much slower than the ones obtained using melting method. For example solid dispersion of diazepam-PEG 6000, prepared by melt method with 1:10 and 1:5 w/w ratio, showed faster dissolution rates. This rapid release was attributed to very fine state of subdivision of the drug particles, and solubilizing plus wetting effect of the carrier.

Cooling conditions

In melt technique, drug is incorporated in a molten carrier, and subsequently cooled, forming the dispersion. The method of cooling, whether slow or flash, affects the rate of dissolution. While preparing tolbutamide–PEG 6000 (1:2) dispersion, the melt has cooled by two processes. First process involved flash cooling by placing melt on aluminum and subsequently in a bath of dry ice and acetone. Second process involved slow cooling in oil bath under ambient conditions. More than 15% of drug release was observed in case of flash cooled dispersion as that of slow cooled dispersion due to the difference in particle size, as flash cooled crystallinity.