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Review Article

SOLID DISPERSION: A NOVEL APPROACH FOR POORLY WATER SOLUBLE DRUGS

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ABSTRACT

Objective: Out of newly discovered drugs more than 40% pharmacologically active molecule having poor solubility. This is one of the serious challenges in the pharmaceutical industry and commercialization of the drug.

Methods: With the introduction of new manufacturing technologies such as solid dispersion pH modification, SEED, salt formation, co crystallization.

Results: it should be possible to overcome problems. Potential of solid dispersion technology has been well established for hydrophobic agents because of ease of optimization, simplicity and easy scale up.

Conclusion: This article begins with an overview of the historical background and definition and importance of solubility and solid dispersion. The remainder of the article is devoted to the production, the different carriers and the methods used for the characterization of solid dispersions.

Keywords: Dispersion, Carrier, Solubility, Characterization.

INTRODUCTION

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 [1, 2]. The BCS system divides the drug substances into following four classes:

I] High solubility High permeability

II] Low solubility High permeability

III] High solubility Low permeability

IV] Low solubility Low permeability

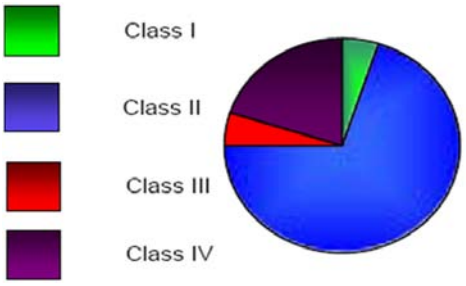

Fig. 1: The frequency of pharmaceutical drugs found in each BCS class

Solubilization of poorly aqueous soluble drug is challenging task for formulation experts. 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, Nanonization Nanosuspension, Complexation, Self micro emulsifying drug delivery systems, solid dispersions etc. Now a day there is increasing interest in the development of amorphous materials, particularly for low solubility drugs as amorphous materials. Along with having higher energy, the amorphous state of a material will have the higher solubility than its crystalline state. The low solubility of many crystalline drug materials can affect on bioavailability of the drug, as well as creates problems for manufacturing and development of the material. Insoluble drug materials are difficult to work with and the effect *in vivo* may be limited by dissolution as well. Developing the amorphous form of a drug has the potential to offer solubility and bioavailability advantages over the development of a crystalline form, provided the stability liability can be overcome [3, 4]

The potential of solid dispersion technology in improvement of bioavailability and therapeutic activity of hydrophobic agents has been well established due to simplicity of preparation, ease of optimization and reproducibility.

Solid dispersion concept firstly introduced by Sekiguchi. The term solid dispersion refers dispersion of one or more active ingredients in an inert carrier at solid state. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles [5].

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 [6].
- 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 [7].

Principals involved in enhancement of solubility by solid dispersions

1. Majority of solid crystallite formed are extremely small, even in solid solution leads to molecular dispersion.

2. The carrier material as dissolves may have solubility effect on the drug.

3. Absence of aggregation and agglomeration.

4. Excellent wettability and dispersibility.

5. Increase in rate of dissolution by formation of metastable, amorphous form.

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 cholic 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.

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.

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.

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 [8,9]. 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. This may result in decreased solubility and dissolution rate [10]. 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.

Strategies to avoid drug recrystallization

Recrystallization is the major disadvantage of solid dispersions. 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 [11], 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 [12,13]. 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, because this was related to the number of collisions per unit time [14]. Several experiments have been conducted to understand the stabilization of solid dispersions. Recent studies observed very small reorientation motions in solid dispersions showing a detailed heterogeneity of solid dispersions and detecting the sub-glass transition beta-relaxation as well as alpha-relaxation [15], which may lead to nucleation and crystal growth. Molecular mobility of the amorphous system depends, not only on its composition, but also on the manufacturing process as stated by Bhugra *et al.* [16]. 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. Specific drug polymer interactions were observed by Teberekidis *et al.*, showing that interaction energies, electron density, and vibrational data revealed a stronger hydrogen bond of felodipine with PVP than with PEG, which was in agreement with the dissolution rates of the corresponding solid dispersions.

Other studies have shown stabilization in systems where hydrogen-bonding interactions are not possible, because of the chemistry of the system. Vippagunta [17] *et al.* concluded that fenofibrate does not exhibit specific interactions with PEG, independent of the number of hydrogen bonds donating groups presented. The same conclusion was achieved by Weuts et al. in the preparation of solid dispersions of loperamide with PVP K30 and PVP VA64, in which, hydrogen bonds were no absolute condition to avoid crystallization. Konno *et al.* determined the ability of three different polymers, PVP, HPMC and hydroxyl propyl methylcellulose acetate succinate to stabilize amorphous felodipine, against crystallization.

The three polymers inhibited crystallization of amorphous felodipine by reducing the nucleation rate. It was speculated that these polymers affect nucleation kinetics by increasing their kinetic barrier to nucleation, proportional to the polymer concentration and independent of the polymer physiochemical properties.

The strategies to stabilize the solid dispersions against recrystali zation 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.

Classification of solid dispersion

Solid dispersions are classified by various ways viz. on the basis of the carrier used and on the basis of their solid state structure as shown in fig. **2** and table 1 respectively

A] On the basis of carrier used [18]

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 thermo-dynamically more stable and did not release the drug as quickly as amorphous ones.

Second generation

Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers such as povidone (PVP), polyethylene glycols (PEG) and polymethacrylate as well as natural product based polymers such as hydroxyl propyl methyl cellulose (H PMC), ethyl cellulose, and hydroxyl propoyl cellulose or starch derivates like cyclodextrins.

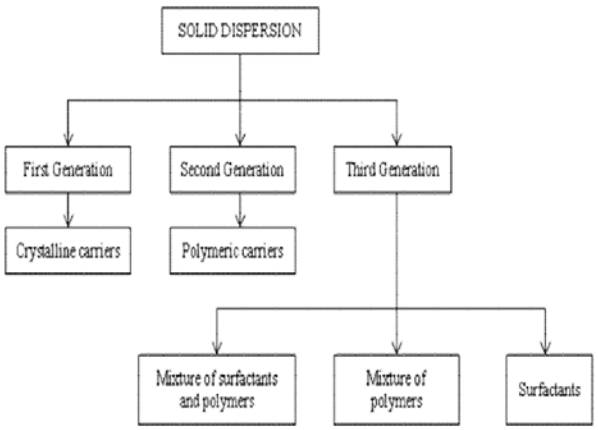

Fig. 2: Classification of solid dispersion on the basis of carrier used

Third generation

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self emulsifying properties. Therefore, third generation solid dispersions appeared. The use of surfactant such as inulin, inutec SP1, the competitor 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.

B] On the basis of solid state structure [19]

1. Drug and polymer exhibiting immiscibility in fluid state

If a drug and polymer are immiscible in their fluid state, it is expected that they would not exhibit miscibility on solidification of the fluid mixture. Such systems may be regarded as similar to their corresponding physical mixtures and any enhancement in dissolution performance may be owing to modification in morphology of drug and/or polymer due to physical transformation (i.e., solid to liquid state and back), intimate drug–polymer mixing, and/or enhanced surface area. Formation of crystalline or amorphous solid dispersions can be biased by the rate of solidification of the mixture and the rate of crystallization of the drug and/or polymer.

2. Drug and polymer exhibiting miscibility in fluid state

If the drug and polymer are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, thereby influencing the structure of solid dispersion.

Eutectic Mixtures

Eutectic mixture was first described as solid dispersions in 1961 by Sekiguchi & Obi. Eutectic mixtures are 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', as shown schematically in fig. 3, 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. This was first reported for sulfathiazole-urea [20, 21]. Other examples of eutectic mixture include acetominophen-urea and the dispersion of griseofulvin and tolbutamide in polyethylene glycol (PEG)-2000.

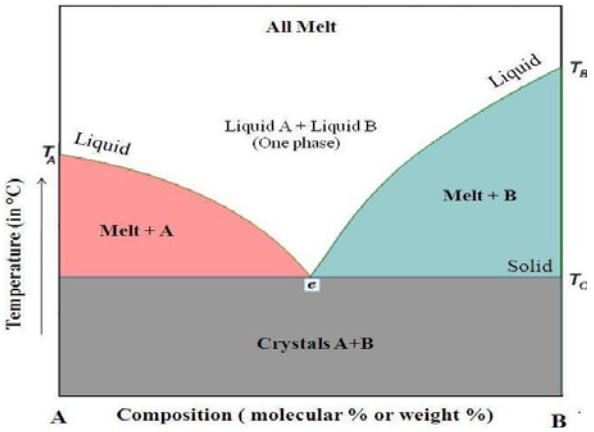

Fig. 3: Phase diagram of a eutectic mixture

Crystalline solid dispersion

A crystalline solid dispersion (or suspension) is formed when the rate at which drug crystallizes from drug–polymer miscible mixture is greater than the rate at which drug–polymer fluid mixture solidifies [19].

Amorphous solid dispersion

If the drug–polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then drug is kinetically trapped in its amorphous or a "solidified-liquid" state. These types of dispersions have the risk of potential for conversion to a more stable and less soluble crystalline form [19].

Solid solution

Solid solution is a solid dispersion that is miscible in its fluid as well as solid state. 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 crystallization by minimizing molecular mobility [22]. 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 as shown in fig. 4. 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. For this to occur, the solute molecule diameter should be less than 0.59 than that of solvent molecule. Therefore, the volume of the solute molecule(s) should be less than 20% of the solvent molecule(s). Examples include solid solutions of digitoxin, methyl estosterone, predinsolone acetate and hydrocortisone acetate in the matrix of PEG 6000. They all exhibit faster rate of dissolution.

The reason for the improvement in dissolution rate is that the drug has no crystal structure in solid solution. Therefore, the energy normally required to break up the crystalline structure of the drug before it can dissolved is not a limitation to the release of the drug from a solid solution.

A further way in which a solid solution could enhance dissolution is through improvement of the wettability of the drug. Even carriers that are not surface active, e. g. urea and citric acid, can improve wetting characteristics. If carriers with surface activity such as cholic acid, bile salts, lecithine, are used the improvement in wetting can be much greater.

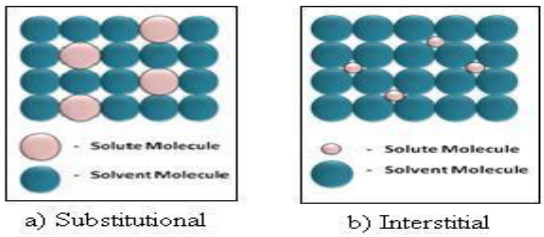

Fig. 4: Schematic representation of substitutional and interstitial solid solutions

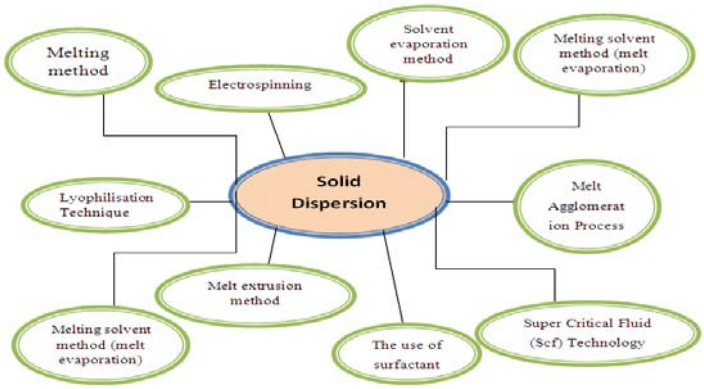

Fig. 5: Preparative methods of solid dispersion

Methods of preparation of solid dispersions [23]

Melting method

Drug and carrier are mixed using mortar and pestle. To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components. It is then cooled to acquire a congealed mass. It is crushed and sieved.

Advantages

- It is more convenient and economical method for drugs stable at temperature below 100 °C
- Technically it is an easier method if the drug and carrier are miscible in the molten state [5]
- It precludes the use an organic solvent thereby circumventing the enigmas of its removal from the dispersion
- Dissolution for dispersions obtained by melting technique are much faster than those prepared using solvent techniques.

Drawbacks

- High melting carrier cannot be used
- Thermal degradation or instability may result at the melting point.
- Decomposition may take place, often dependent upon composition, fusion time and rate of Cooling.
- Evaporation or sublimation and polymeric transformation of the dispersion component may take place.
- Solidified melt may be tacky and unhandable
- Immiscibility between drug and carrier results in irregular crystallization that causes obvious problems during formulation.

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.

Advantages

- Possibility of continuous production makes it suitable for large scale production.
- The product is easier to handle because at the outlet of the extruder, the shape can be adapted to the next processing step without grinding.

Drawbacks

- High energy inputs require shear forces and temperature.
- Design of screw assemblies and extruder dies, has significant impact on degradation of drugs and excipients.

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 alternative equipment for melt agglomeration because of easier control of the temperature and because higher binder content can be incorporated in the agglomerates.

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.

Advantages

- Risk of phase separation is minimized as soon as the solution is vitrified.
- Offers the potential to customize the size of the particle to make them suitable for further processing.

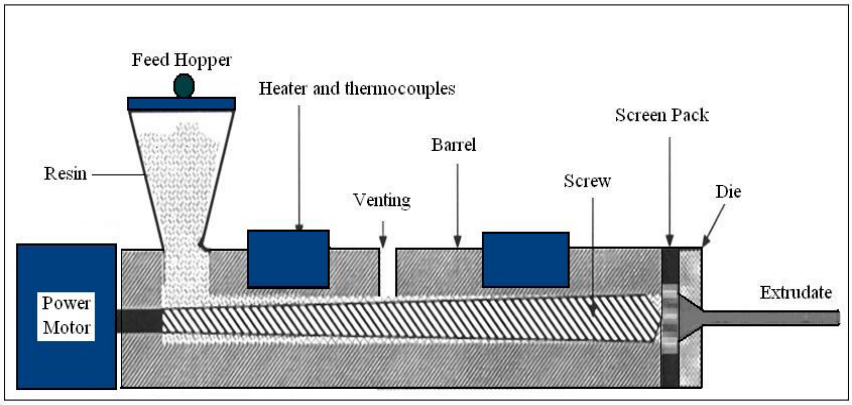

Fig. 6: Schematic showing components of a single screw melt extruder

Drawbacks

- The tablets are very fragile.
- The manufacturing process is very expensive.
- The technique is not suitable for all the products.

Solvent evaporation method

This technique involves dissolving the drug and the carrier in a suitable organic solvent or a combination of solvents to get a clear solution. As the solvent is being removed, supersaturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The solvent is then evaporated directly on a water bath or hot plate or using a rota-vapour. The resulting solid dispersion is stored in the desiccator under vaccum and pulverized to obtain the desired size fraction. The important prerequisite for the manufacturing of solid dispersion using the solvent method is that both drug and the carriers are sufficiently soluble in the solvent.

Advantages

- High melting carries can also be utilized.
- Thermal decomposition of drug and carriers associated with the fusion method can be avoided.

Drawbacks

- Larger volumes or organic solvent have to be used which makes the process slightly expensive.
- Removal of the solvent is difficult.
- Residual solvent can have the possible adverse effect.
- Difficulty of reproducing crystal forms.
- Supersaturation of the solute cannot be attained unless the system goes through a highly viscous phase.
- Selection of common solvent is difficult.

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.

Drawbacks

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

Electro spinning method

The electro spinning technology used in the polymer industry combi nes 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[27]. 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 nano fibres 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.

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 [28]. 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.

At the critical point, densities of liquid and gas are equal and there is no phase boundary, as shown in fig. 5. Above the critical point that is, in the supercritical region, the fluid possesses the penetrating power typical of a gas and the solvent power typical of a liquid.

Advantages

- Dissolving power of the SCF is controlled by pressure and/or temperature.
- SCF is easily recoverable from the extract due to its volatility.
- Non-toxic solvents leave no harmful residue.
- High boiling components are extracted at relatively low temperatures.
- Thermally labile compounds can be extracted with minimal damage as low temperatures can be employed by the extraction.
- Non-inflammable and inexpensive technique.

Drawbacks

- Elevated pressure required.

- Compression of solvent requires elaborate recycling measures to reduce energy costs.
- High capital investment for equipment.

Kneading technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for the particular time. The kneaded mixture is then dried and passed through the sieve if necessary.

Co-Grinding

In this method, accurately weighed drug powder and the carrier are mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill for grinding. Strong grinding force gives to solid increases in the activation energy on the surface and in the distortion of the crystal lattice together with communition.

Selection of carrier [24]

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.

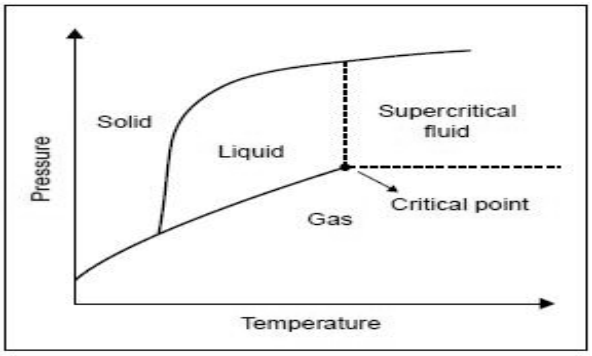

Fig. 7: Supercritical region of a hypothetical compound (Indicated by the dotted lines)

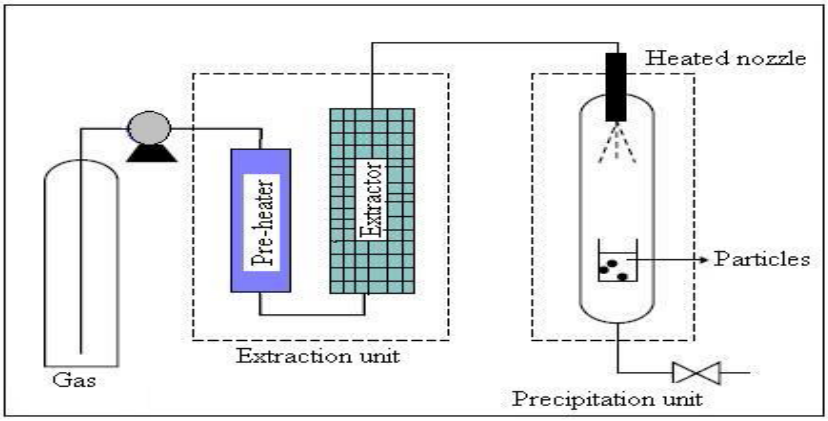

Fig. 6: Schematic of the RESS apparatus used in supercritical fluid technology

Table 1: Carriers used in the preparation of solid dispersion

Chemical Class	Examples
Acids	Citric acid, Tartaric acid, Succsinic acid.
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Xylitol, Galactose
Polymer material	Polyvinyl pyrolidone,PEG4000,PEG 6000,Sodium alginate, carboxy 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

Factors influencing drug release [23]

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. Accordingly, for the solid dispersion to be effective in enhancing the solubility, an appropriate drug-carrier proportion is desired. It would certainly be more advantageous if carrier is used in minimal amounts. Coprecipitates of flurbiprofen; phospholipids, for instance, when used in the ratio of 20:1, yields 9-fold greater dissolution rate of flurbiprofen. Albeit the proportion of carrier is far less as compared to that of drug, yet it is quite effective in dissolution enhancement. This is because phospholipids spontaneously form liposome bilayer structures in an aqueous media that entrap solutes either in an aqueous phase or bilayer, thereby hastening the dissolution process. Similarly, In case of glipizide the rate of dissolution was increased when the ratio of polymer is increase, about 5-fold greater dissolution rate of glipizide with poloxamer 188 in the ratio of 1:10.

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. However, the corresponding solid dispersion prepared by coprecipitation showed slower dissolution owing probably to greater size of diazepam particles.

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.

Synergistic effect of two carriers used

This has been exemplified in ibuprofen solid dispersions using PEG, talc and PEG-talc as dispersions carriers. It was reported that in 9.1% drug loading, ibuprofen dissolved at the end of 120 min was about 66% 73% and 93% from Ibuprofentalc, ibuprofen-PEG and PEG-talc dispersions respectively. Workers attributed this synergism to the partial replacement of PEG with talc. This would cause improved wettability of ibuprofen and hence enhanced solubility of the drug by overlapping the diffusion layers between PEG and ibuprofen.

Influence of carrier chain length/molecular weight

The carrier chain length or its molecular weight may play a significant role in drug release from solid dispersions. Chain length of PEGs or Molecular weight (MW) 4000-6000 are the most frequently used for the manufacture of solid dispersion, because in this MW range the water solubility is still very high, but hygroscopic is not a problem and the melting points are already over 50oC. Usually PEGs with MW weights of 1500-20000 are used. If PEG with too low MW is used, this can lead to product with a sticky consistency that is difficult to formulate in to pharmaceutically acceptable product. Similarly, the chain length of PVP has very significant influence on dissolution rate of the dispersion as the aqueous solubility of the PVPs become poorer with increasing chain length and a further disadvantage of high MW PVPs is their much higher viscosity at a given concentration.

Characterization of solid dispersion

Detection of crystallinity in solid dispersions:

The amount of amorphous material is never measured directly but mostly derived from the amount of crystalline material in the sample.

Powder X-ray Diffraction

It can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material.

Infrared spectroscopy

It can be used detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. FTIR is useful to accurately detect crystallanities ranging from 1 to 99% in pure material.

Water vapour sorption

It can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous sample.

Isothermal microcalorimetry

It measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg).

Dissolution calorimetry

It measures the energy of dissolution, which is dependent on the crystallinity of the sample. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

Macroscopic techniques

Those measure mechanical properties that are different for amorphous and crystalline material can be indicative for degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity and viscosity and thus affected by the degree of crystallinity

Thermal analysis [34]

Thermo-microscopic methods

This is a visual method of analysis using a polarized microscope with a hot stage to determine the thaw and melting points of solids. The technique has been used to support DTA or DSC measurement. It gives information about the phase diagram of binary systems.

Differential Scanning Calorimetry (DSC)

In DSC, both the sample and reference materials are subjected to linear heating, but both are maintained at the same temperature. Here change in temperature is not recorded, but the heat flow into the system is recorded which is required to maintain isothermal conditions. The method is useful to study the behavior of crystallization and melting and deriving phase diagrams of solid dispersions.

Differential thermal analysis (DTA)

This is an effective thermal method for studying the phase equilibria of pure substance or solid mixture. Differential heat changes that accompany physical and chemical changes are recorded as a function of temperature as the substance is heated at uniform rate. In addition to thawing and melting, polymorphic transition, evaporation, sublimation, desolvation and other types of changes such as decomposition of the sample can be detected. The method has been used routinely to identify different types of solid dispersion.

Detection of molecular structure in amorphous solid dispersions [33]

The properties of solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix.

Confocal raman spectroscopy

It is used to measure the homogeneity of the solid mixture drug and polymer. It was described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the pixel size of 2 μm3, uncertainty remains about the presence of nano-sized amorphous drug particles.

Temperature modulated differential scanning calorimetry (TMDSC)

It can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC. Therefore this technique can be used to assess the amount of molecularly dispersed drug, and from that the fraction of drug that is dispersed as separate molecules is calculated.

Applications

1. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.

2. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.

3. To reduce side effect of certain drugs.

4. Masking of unpleasant taste and smell of drugs.

5. Improvement of drug release from ointment creams and gels.

6. To avoid undesirable incompatibilities.

7. To obtain a homogeneous distribution of a small amount of drug in solid state.

8. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.

9. To formulate a fast release primary dose in a sustained released dosage form.

10. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

11. To reduce pre systemic inactivation of drugs like morphine and progesterone.

CONFLICT OF INTERESTS

Declared None

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