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A REVIEW ON: SOLID DISPERSIONS USING CARRIERS SUCH AS SUPER-DISINFECTANTS AND SURFACTANTS.

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ABSTRACT

The solubility behavior of the drugs remains one of the most challenging aspects in formulation development & it is key determinant to its oral bioavailability & it is the rate limiting step to absorption of drugs from G.I.T. This results in important products not reaching the market or not achieving their full potential. Solid Dispersion has attracted considerable interest as an efficient means of improving the solubility, dissolution rate & bioavailability of hydrophobic drugs. This strategy has proven to improve the bioavailability by dispersing the class II & IV drug as very fine particles within hydrophilic matrix that results in increased solubility with increased surface area available for dissolution. This article reviews the need for the solubility enhancement of poorly water soluble drugs, historical background, advantages, disadvantages, various categories of solid dispersions, manufacturing methods, superdisintegrants and surfactants polymers characterization of solid dispersions.

KEYWORDS: classifications, carriers, preparations and characterizations, US patents.

INTRODUCTION

Overview of Solid Dispersion

The solubility behavior of the drugs remains one of the most challenging aspect in formulation development & it is key determinant to its oral bioavailability & it is the rate limiting step to absorption of drugs from G.I.T. This results in important products not reaching the market or not achieving their full potential.SD has attracted considerable interest

as an efficient means of improving the dissolution rate & bioavailability of hydrophobic drugs.[1, 2]

Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs.[1, 2]

In addition , in Solid dispersions [2], a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, & excess drug precipitates as fine colloidal particles or oily globules of submicron size. Solid dispersion technique was firstly demonstrated by Sekiguchi and Obi. They proposed the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carries like urea (1961).[2, 3]

Eutectic systems are example of solid dispersion. The solid phases constituting the eutectic each contain only one component & the system may be regarded as an intimate crystalline mixture of one component in the other.[4, 5, 8]

SOLID DISPERSIONS

Solid dispersion is an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly soluble drugs.[6, 7] Solid dispersions are group of solid products consisting of at least two different components, generally, a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Solid dispersion can also be referred as the dispersion of one or more active ingredients in an inert matrix at solid state prepared by the melting, solvent, and melting solvent method.[8, 9]

Mechanism of increased dissolution rate[3, 9]

1. Particles with reduced particle size
2. Drugs in amorphous state
3. Particles with improved wettability
4. Particles with high porosity

Types of Solid Dispersions

On the basis of molecular arrangement, different types of solid dispersions can be distinguished as follows;

1. Solid eutectic mixture
2. Solid solution
3. Glass solution & suspension
4. Amorphous precipitations in crystalline carrier[10]

Solid eutectic mixture[14]

A simple eutectic mixture consists of two components which are completely miscible in liquid State but to a limited extent in solid state. These are prepared by rapid solidification of fused melt of two components. When a mixture of poor water soluble drug and water soluble carrier is dissolved in aqueous medium, the carrier is dissolved rapidly, releasing very fine crystal of drug.[11]

Solid solution[12, 13]

In a solid solution, the two components crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solution is reduced to its molecular size responsible for increase in dissolution rate. On the extent of miscibility of two components, solid solution is classified as continuous and discontinuous. In continuous solid solution, the two components are miscible in the solid state in all proportions. In discontinuous solid solutions, the solubility of each of the components in the other component is limited.[14]

Glass solution and suspension

A glass is a homogenous glassy system in which solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. Characterization of the glassy state is transparency and brittleness below the glass transition temperature.[15, 16]

Amorphous precipitations in crystalline carrier[17]

In the group of dispersion drug is precipitated out in amorphous form while in simple eutectic mixture it is in crystalline form.[18]

Classification of solid dispersion

1. First generation – crystalline carriers
2. Second generation –polymeric carriers
3. Third generation –mixture of surfactants & polymers

First Generation Solid Dispersions[19]

Solid dispersions were first described by Sekiguchi and Obi in 1961 in which they used concept of eutectic mixtures. They mentioned that the formulation of eutectic mixtures improve the rate of drug release and thus increase bioavailability of poorly soluble drug. Thus first generation solid dispersions were prepared using crystalline carriers. Eutectic mixtures are binary systems comprising of poorly water soluble drug and highly water soluble carrier and at eutectic point drug crystallizing out simultaneously only in the specific composition When eutectic mixture is dissolved in aqueous medium, the carrier part will dissolve quickly and drug will be released in the form of fine crystals.[20]

The main disadvantage of first generation Solid dispersion is crystalline nature which leads to less solubility as compare to amorphous form. ; However, they possess good Thermodynamic stability. First generation solid dispersion were generally prepared using crystalline carriers like urea, mannitol.

Second Generation Solid Dispersions

In second generation instead of crystalline carriers, amorphous carriers were used to disperse drugs which are generally polymers. Polymeric carriers can be of fully synthetic origin like providence, polyethylene glycols and polymethacrylates whereas natural product based polymers comprises of cellulosederivatives like hydroxypropylmethylcellulose, ethylcellulose or starch derivatives, like cyclodextrins. Amorphous solid dispersions are further classified as solid solutions, solid suspension or mixture of both as per molecular interaction of drug and carriers. Amorphous carriers: Polyethylene glycol, Povidone, Polyvinylacetate, Polymethacrylates, cellulose derivatives.[21]

Example of amorphous solid dispersion based on marketed drugs include Kaletra® (Ritonavir/Lopinavir); Norvir® (Ritonavir); Viekira Pak™ (Dasabuvir and Ombitasvir and Paritaprevir and Ritonavir); Belsomra® (Suvorexant); Noxafil® (Posaconazole).[22, 23]

Third Generation Solid Dispersions

In the third generation solid dispersion surfactants carrier or mixture of polymer are used as carrier. If carrier has surface active or self-emulsifying properties, the dissolution profile of poorly soluble drug can be improved and hence result in increased bioavailability. Typically used surfactants as solid dispersion carriers are Polaxamer 407, Glacier 44/14 and Compritol 888. [24]

ADVANTAGES OF SOLID DISPERSIONS[24]

Generally, solid dispersion is mainly used;

- To reduced particle size.
- To improve wettability.
- To improve porosity of drug.
- To decrease the crystalline structure of drug in to amorphous form.
- To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
- To mask the taste of the drug substance.
- To prepare rapid disintegration oral tablets.
- To obtain a homogenous distribution of small amount of drugs at solid state.
- To stabilize unstable drugs.
- To dispense liquid or gaseous compounds.
- To formulate a faster release priming dose in a sustained release dosage form.
- To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or
- Insoluble carriers.

DISADVANTAGES OF SOLID DISPERSION SYSTEMS[24]

This technology has been a drawback for the commercialization of solid dispersions.

The disadvantages includes are as follows;

- Laborious and expensive methods of preparation,
- Reproducibility of physicochemical characteristics,
- Difficulty in incorporating into formulation of dosage forms,
- Scale-up of manufacturing process, and
- Stability of the drug and vehicle.

Its method of preparation, various methods have been tried recently to overcome the limitation and make the preparation practically feasible. Some of the suggested approaches to

overcome the aforementioned problems and lead to industrial scale production are discussed here under alternative strategies.

Selection of carrier(s)[24]

The properties of the carrier have a profound influence on the dissolution characteristics of the dispersed drug. A carrier ought to 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. The various carries for solid dispersion are;

Carriers used in Solid Dispersions for Enhancing Dissolution Rate of Drug[25]of carriers

1. Polymers: Polyvinylpyrrolidone, Polyvinylpolypyrrolidone, Polyvinylalcohol, Polyethylene glycols, Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Poly (2-hydroxyethy lmethacrylate), Methacrylic copolymers (Eudragit® S100 sodium salts and Eudragit® L100 sodium salts)
2. Cyclodextrins: β-Cyclodextrins, Hydroxypropyl-β-cyclodextrins
3. Carbohydrates: Lactose, Soluble starch, Sorbitol, Mannitol.
4. Surfactants: Poloxamers (Lutrol® F 127, Lutrol® F 68), Polyglycolized glyceride (Labrasol),Polyoxyethylene sorbitan monoesters (Tweens), Sorbitan esters (Spans), Polyoxyethylene stearates, Poly (beta-benzyl-L-aspartate) -b- poly (ethylene oxide), Poly (caprolactone) -b- poly(ethylene oxide).
5. Hydrotropes: Urea, Nicotinamide, Sodium benzoate, Sodium salicylate, Sodium acetate, Sodium-o-hydroxybenzoate, Sodium p-hydroxy benzoate, Sodium citrate.
6. Polyglycolized glycerides: Gelucire 44/14, Gelucire 50/13, Gelucire 62/05
7. Acids: Citric acid, Succinic acid, Phosphoric acid
8. Miscellaneous: Microcrystalline cellulose, Dicalcium phosphate, Silica gel, Sodium chloride, Skimmed milk Microcrystalline cellulose, Dicalcium phosphate, Silica gel, sodium chloride.

Methods of preparation of solid dispersions[26]

Various methods used for preparation of solid dispersion system. These methods are given bellow.

1 Melting method

2 Solvent method

3 Melting solvent method (melt evaporation)

4 Melt extrusion methods

5 Lyophilization techniques

6 Melt agglomerations Process

7 The use of surfactant

8 Electrospinning

9 Super Critical Fluid (Scf) technology

10 Dropping method

11 Direct capsule filling

12 Gel entrapment techniques

13 Kneading method

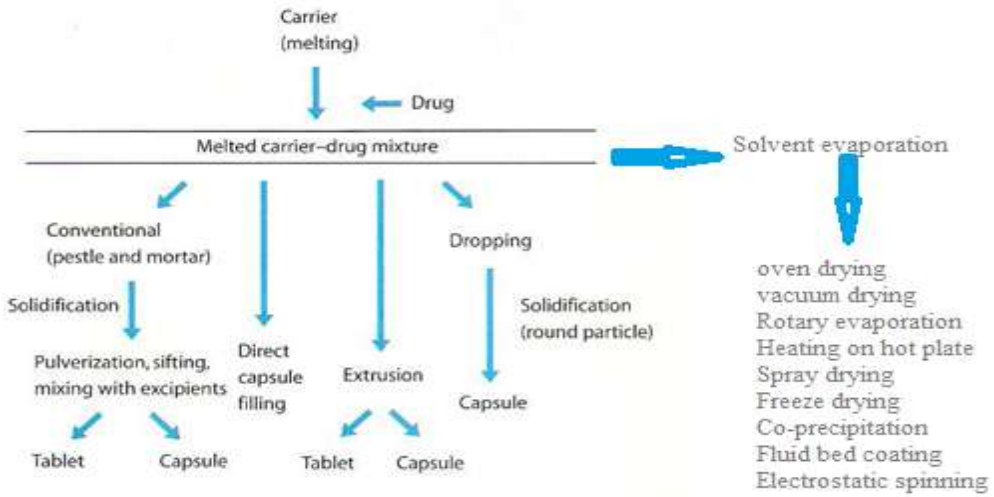

Fig.1 Different processing methods for solid dispersions.[25, 26]

1. Melting method: (Fusion method) In this, preparation of physical mixture of a drug and water-soluble carrier & heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The resultant solid is then crushed, sieved, pulverized & quenched to reduced the particle size or injection molded into dosage forms without undergoing milling. The advantage of this method is that it does not require any solvent.[27, 28]

2. Solvent evaporation method: (Solvent method) In this, the drug & carrier is dissolved in a organic solvent or combination of solvent to get a clear solution. As the solvent is being removed, super saturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue which is then desiccated under vacuum & pulverized. Advantage of this method is that, thermal decomposition of drugs or carriers can be prevented because of relatively low temperature.[27, 28,29]
3. Melt-solvent method: The melting solvent method is the combination of the melting method and the solvent method. In this method, the drugs are dissolved in suitable solvent and mixed with the molten carrier followed by solvent removal and solidification to form solid dispersions. The advantage of this method is that the temperature and the mixing time are lower than melting method, thus protecting the drug from thermal degradation. In addition, the carrier in the molten state is more easily dispersed dissolved in the solvent in comparison with solvent method [29, 30].
4. Melt extrusion method: In this method, the drug and carrier are simultaneously mixed, heated, melted, homogenized and extruded in a form of tablets, rods, pellets, or milled and blended with other excipients for different purposes. The intense mixing and agitation forced by the rotating screw during the process cause disaggregation of drug particles in the molten polymer, resulting in a homogenous dispersion. This process involves the transformation of a solid mass of intertwined particles into a viscous liquid or semisolid mass by heating and intense mixing. The hot melt extruded systems are composed of drugs, one or more meltable polymers and other additives such as plasticizers and pH modifiers.[29, 30, 31]

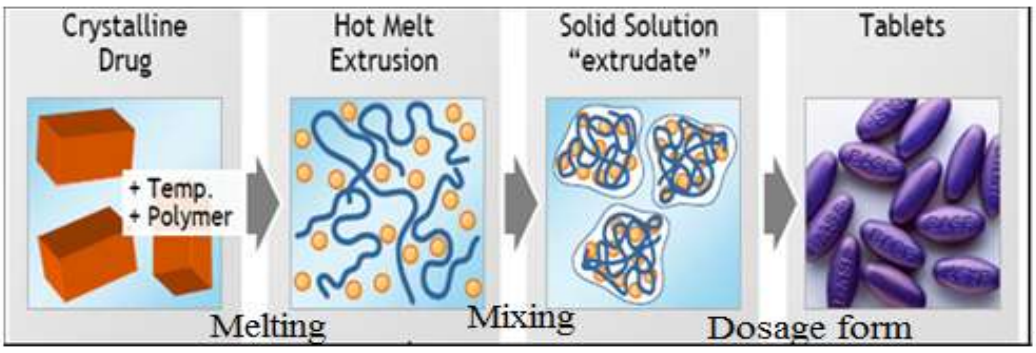

Fig 2: Illustration of melting and mixing of a crystalline API in polymer by hot melt extrusion. [29]

5. Lyophilisation technique: Freeze-drying involves transfer of heat and mass to and from the product under preparation. Lyophillization 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 dispersions.[30,31]

6. Melt agglomeration process : This technique has been used to prepare SD where the binder acts as a carrier. Binder (carrier), drug and excipients are heated to temperature above the melting point of the binder (melt-in procedure) or by spraying a dispersion of drug in molten binder on the heated excipients (spray-on procedure) by using a high shear mixer.[32]
7. The use of surfactant: The utility of the surfactant systems in solubilisation is well known. Surfactant reduces hydrophobicity of drug by reducing interfacial or surface tension because of these unique property surfactants have attracted the attention of investigators for preparation of solid dispersions. Recently a new class of surfactant known as Gelucires are introduced which identify by melting points and HLB values. Gelucire is widely used in the formulation of semi solid dispersions. Gelucire is a saturated Polyglycolized glyceride consisting of mono-, di- and triglycerides and of mono- and di-fatty acid esters of polyethylene glycol (PEG) derived from natural vegetable fatty acids and having amphiphilic character. Gelucires with low HLB can be employed to decrease the dissolution rate of drugs and higher HLB ones for fast release. Gelucire 44/14 and gelucire 50/13 are two examples of this synthetic group where 44 and 50 represent melting point, while 14 and 313 represent HLB values of gelucire respectively . Hemant et al [9] and Sheen et al [10] studied that polysorbate 80, a commonly used surfactant, results in improvement of dissolution and bioavailability of poorly water soluble drug attributed to solubilisation effect of surface active agent. Polysorbate 80 also ensues complete release of drug in metastable finely dispersed state having large surface area.[32,33]
8. Electrostatic spinning: Electrostatic spinning (electrospinning) can be considered a combination of solid dispersion technology and nanotechnology. In this method, a drug–polymer solution is placed into a spinneret connected with a microsyringe pump and a high voltage between 5 and 30 kV is applied to the needle tip to induce a charge on the surface of the solution. A fixed electrical potential is also applied across a fixed distance between the spinneret and the collector. When electrical forces overcome the surface tension of the feeding solution at the air interface, polymer jets are ejected. After coming out, the charged jets go straight for some distance, and then travel a spiral path because of the whipping instability. As the jet accelerates through the electric field, the solvent evaporates rapidly to make fibres at micron or submicron diameter which are collected on

the screen or a spinning mandril. The collected fibres produce a non-woven fabric, which can be used in oral dosage forms by direct incorporation of the materials into a capsule or by further processing such as milling or grinding [33].

9. Super critical fluid (scf) technology: Since the first experiences of Hannay et al in 1879, a number of techniques have been developed and patented in the field of SCF assisted particle design. These methods use SCFs either as solvent: rapid expansion from supercritical solution (RESS) or anti-solvent: gas antisolvent (GAS), supercritical antisolvent (SAS), and solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance. Solution enhanced dispersion by supercritical fluids (SEDS), aerosol solvent extraction system (ASES), supercritical anti-solvent (SAS), gas antisolvent (GAS) and precipitation with a compressed fluid anti-solvent (PCA) are process of micronization. The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently [32, 33].
10. Dropping method: Solid dispersion of a melted drug-carrier mixture is pipette and then dropped onto a cooling plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape. The dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods, and there is no plug formation, mentioned in direct capsule filling method. The disadvantage is that only thermostable drugs can be used and the physical instability of solid dispersions is a further challenge [12].
11. Direct capsule filling: Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier

dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug.[18]

12. Gel entrapment technique: Carrier is dissolved in organic solvent to form a clear and transparent gel. Then drug is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved.[18]
13. Kneading method: Drug and each of surface active carriers were weighed accurately in various ratios (1:1, 1:2) and transferred to china dish sufficient quantity of ethanol was added and the thick slurry was needed for 1hr and then dried at 450c until dryness. The dried mass was pulverized and sieved through sieve num #120.the resulting solid dispersions were stored for 24hrs in desiccators to congeal. The mass obtained was crushed, pulverized. Finally dispersions were stored in air tight containers till further use.[27]

Selection of Solvents: [34]

Solvent to be included for the formulation of solid dispersion should have the following criteria.

1. Both drug and carrier must be dissolved.
2. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane15.
3. Ethanol can be used as alternative as it is less toxic
4. Water based systems are preferred.
5. Surfactants are used to create carrier drug solutions they can reduce glass transition temperature, care must be taken in to consideration.

Solvents commonly used in the preparation of solid dispersions include water, methanol, ethanol, acetic acid, 1-propanol, 2- propanol, chloroform and DMSO.

Superdisintegrants as Carriers: Superdisintegrants are those substances which facilitate the faster disintegration of tablets with smaller quantity due to their high swelling in water. They are insoluble and dispersible in water and exhibit high swelling.

Superdisintegrants are of two types;

1. Natural Super disintegrants: Isapgula, Alginates, Chitin/Chitosan silicon oxide, Lepidium sativum mucilage, *Hibiscus rosa sinensis* Linn-Mucilage, Cucurbita maxima pulp powder, Gellan Gums and Guar Gum.

2. Synthetic Super disintegrants: Modified starch (Sodium starch glycolate, Primojel), Cross linked polyvinyl pyrrolidine (Crosspovidone polyplasdone XL), Modified cellulose, (Crosscarmellose sodium), Ion exchange resin, L-HPC (Low substituted hydroxyl propylcellulose). In recent years super disintegrants are being studied as carriers in solid dispersions for enhancing the dissolution rate of poorly soluble drugs.

Surfactants as Carriers

Surfactants are molecules with distinct polar and nonpolar regions. The polar group can be anionic, cationic, zwitter ionic (amphoteric) or nonionic. Surfactants are used to increase the solubility, dissolution rate and bioavailability of poorly soluble drugs.

The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium.[15]

They can also be used to stabilize drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05-0.10% for most surfactants), micelle formation occurs, entrapping the drugs within the micelles.

This process is known as micellisation and generally results in enhanced solubility of poorly soluble drugs. Commonly used non-ionic surfactants include polysorbate, polyoxy ethylated castor oil, polyoxy ethylated glycerides, lauroyl macroglycerides and mono-and di-fatty acid esters of low molecular weight polyethylene glycols. [16]

CHARACTERIZATION OF SOLID DISPERSIONS[7]

1. Differential Scanning Calorimetry (DSC)
2. Powder X-ray diffraction (PXRD)
3. Fourier Transformed Infrared spectroscopy (FTIR)
4. Dissolution studies
5. Solubility Studies
6. Scanning Electron Microscopy (SEM)
7. Drug content estimation

- Differential Scanning Calorimetry (DSC): Thermal characteristics of the pure materials, the physical mixtures, the solid dispersions of drug with excipients were determined by a

differential scanning calorimeter. The scanning rate was 10 ◦C/min, and the scanning temperature range was between 30 and 350 ◦C. [19, 28, 34]

- Powder X-ray diffraction (PXRD): X-ray powder diffraction patterns were recorded on an X-ray powder diffraction system (PANalytical Spectris Pvt. Ltd, Singapore) using copper target, a voltage of 40 Kv and a current of 30 mA. The scanning was done over 2_ range of 5º to 60º. [20, 29,31]
- Fourier Transformed Infrared spectroscopy (FTIR): The IR spectra were recorded using an FTIR spectrophotometer with diffuse reflectance principle. The samples were scanned over the frequency range 4000–400-1 cm. [21,29]
- Dissolution studies: Dissolution studies were performed using USP apparatus II. Pure drug and all the other products prepared as described earlier were included in this study. Samples of each preparation equivalent to 10 mg of drug were spread over the surface of the dissolution medium (900 ml of phosphate buffer at pH (6.8) maintained at a temperature of 37±0.5 oC, stirring at 50 rpm. The samples were withdrawn at predetermined time intervals, filtered, diluted with methanol and analyzed using a UV-spectrophotometer at 238 nm. Each test was performed in triplicate. [22,32, 35]
- Solubility Studies: Excess amount of the Solid dispersion (10mg) was added to stoppered conical flask containing 20 mL of solvent media and subjected to shaking for nearly 6 hrs. Then the flasks were removed and kept aside for 24 hrs. At a constant temperature to attain equilibrium condition. Suitable aliquots were withdrawn from the filtered solution and analyzed for the drug content after appropriate dilution with a solvent and analyzed for drug content in UV spectroscopic by measuring the absorbance at 273 nm.[23,30] Solubility studies are done for the finding out the solubility behavior shown by the solid dispersion system in different types of solvent system and body fluids.[4]
- Scanning Electron Microscopy (SEM): A scanning electron microscopewas used to examine the particle size and morphology at 20 kV accelerating voltage. The samples were fixed by mutual conductive adhesive tape on aluminium stubs and covered with a 250 A ° film of gold–palladium using a sputter coater. [24,31,32]
- Drug content estimation: The percentage drug content in physical mixtures and solid dispersions was estimated by dissolved 10 mg quantities of physical mixtures and solid dispersions in methanol, mixed thoroughly by shaking and the volume was made-up to the mark with solvent (0.1N HCl). The solution was filtered and the filtrate was diluted suitably with 0.1N HCl (1.2) pH and absorbance was measured at 342 nm using

UV/Visible spectrophotometer.[25,33] The actual drug content was calculated using the following equation.

$$\text{Drug content (\%)} = \frac{\text{Actual amount of Solid dispersion}}{\text{Theoretical amount of Solid dispersion}} \times 100$$

Applications of solid dispersions[6]

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored. It is possible that such a technique be used:

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.
- To stabilise unstable drugs & protect against decomposition by process such as hydrolysis, oxidation, reduction.
- To disperse liquid or gaseous mixture.
- Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds.

A unique method in formulating a liquid drug or chemical in a solid dosage form was recently introduced by Chiou and Smith (40). A liquid drug such as methyl salicylate, vitamin E, clofibrate, benzyl benzoate, and benzonatate was mixed by mechanical stirring with the melted liquid of polyethylene glycol 6000 at a temperature below 70". The mixture was then rapidly cooled, and the resultant "solid" mass was pulverized, encapsulated, and tableted. The method is particularly valuable for drugs with low therapeutic doses because the maximum concentration that can be incorporated into a solid form only ranged between 5 and 10% (w/w). It is believed that other thermoplastic polymers with low melting points can also function as carriers for such purposes.[17]

Table 1: List of US patent issued using spray drying technology[36]

Title of patent	Patent No	publication date/year
Effervescent tablet	US 4,009,292	Feb. 22,1977
Compressible vitamin powder	US 4,892,889	June 9,1990
Nimesulide salt cyclodextrin	US 5,744,165 A	Apr. 28,1998
Method for making porous microparticles by spray drying	US 5,853,698 A	Dec. 29,1998
Lipophilic substance	US 5,891,469 A	Apr. 6, 1999
Diagnostic agents by spray drying	US 6,344,182 B1	Feb. 5, 2002
Method of spray drying pharmaceutical Composition	US 6,565,885 B1	May 20,2003
Homogeneous spray- dried solid amorphous drug dispersions	US 6,763,607 B2	Jul. 20, 2004
Inhalable spray dried protein powders	US 6,838,075 B2	Jan 4, 2005
Alprazolam inclusion complexes	US 7,202,233 B2	Apr. 10,2006
Tricyclic & triazolobenzazepine	US 7,229,985 B2	Jun. 12,2007
Solid amorphous drug dispersions	US 7,780,988 B2	Aug. 24,2010
Drug and concentration enhancing polymers	US 7,887,840 B2	Feb. 15,2011

Table 2: List of commercial formulation prepared using solid dispersion technology[7]

Product	API name	BCS class	Polymer	Manufacturing method	Dosage form
Kaletra®	Lopinavir/ Ritonavir	IV	PVP/VA	Melt Extrusion	Tablet 2005
Norvir®	Ritonavir	IV	Copovidone	Melt extrusion	Tablet 2010
Fenoglide®	Fenofibrate	II	PEG	Melt extrusion	Tablet 2007
Sporanox®	Itraconazole	II	HPMC	Spray drying	Capsule 1992

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