IOSR Journal Of Pharmacy www.iosrphr.org
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 8, Issue 7 Version. II (July 2018), PP. 28-38

Different Methods Used In Solid Dispersion

Prosun Kanti Ghosh, Hemanta Kumar Sharma*, Nayanmoni Boruah
Department of Pharmaceutical Sciences, Dibrugarh University
Dibrugarh Assam, India -786004
Corresponding Author: Prosun Kanti Ghosh

Abstract: Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs[2]. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling. Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

Date of Submission: 29-06-2018 Date of acceptance: 17-07-2018

I. INTRODUCTION

Oral drug delivery is the most popular, simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosage forms have many advantages over other types of oral dosage forms. 1, 2. The rate and extent of dissolution of the active ingredient in the g.i.t. from any solid oral dosage form determines rate and extent of absorption of drug. 3. In solid dispersion method drug is dispersed in inert water soluble carrier at solid state. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. 4. Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvents(s), and particle size reduction have also utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques.5

According to biopharmaceutical classification system drugs are divided into four classes depending on in-vitro solubility and in-vivo permeability data.The class II drugs shows poor solubility and high permeability.6. Therefore class II drugs have the low ability to dissolve and it is a more important limitation to their overall rate and extent of absorption and also their ability to permeate through the membrane. The dissolution rate of a poorly water soluble drug in a solid dispersion is increased by i) increasing the surface area from which dissolution of the drug can take place as a result of a reduction in drug particle size up to the molecular level and the impediment of aggregation, ii) improving wet ability hence decreasing the thickness of the diffusion layer by appropriate selection of carrier system, iii) enhancing the solubility of the drug by the formation of a supersaturated solution. 7, 8,9 Thus the solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rate and consequently the bioavailability of poorly water soluble drugs.

II. DEFINITION

The concept of solid dispersion was firstly introduced by Sekiguchi and Obi10, 2. Solid dispersion is defined as "a dispersion of one or more active ingredients in an inert carrier or matrix of solid state prepared by melting (fusion), solvent or melting solvent method". • Solid dispersion also termed as co-precipitates and melts. • Dispersions obtained through the fusion process are often called melts. • Dispersions obtained through the solvent method are referred as a co-evaporates or co-precipitates, e.g. Cisapride- PVP solid dispersion, Piroxicam-PVP solid dispersion.3

III. ADVANTAGE OF SOLID DISPERSION

- To reduce particle size.
- To improve wettability.
- To improve porosity of drug.
- To decrease the crystalline structure of drug into 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 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. 11

IV. DISADVANTAGES OF SOLIDDISPERSION

- Moisture & temperature have most deteriorating effect on solid dispersion than physical mixture.
- Sometimes difficult to handle because of tackiness.
- Reproducibility of its physicochemical properties.
- Its formulation into dosage forms.

V. TYPES OF SOLID DISPERSION

TABLE no-1: **TYPES OF SOLID DISPERSION**

Solid dispersion type		Matrix *	Drug **	Remarks	No. phases	Ref. to lit.
I	Eutectics	C	C	The first type of solid dispersion Prepared.	2	(Chiou & Reigelman, 1971)
II	Amorphous precipitation in crystalline matrix	C	A	Rarely encountered.	2	(Breitebench AH, 2002); (Mullins and Macek, 1960)
III	Solid solutions	C				
	Continuous solid solutions	C	M	Miscible at all composition, never Prepared.	1	(Goldberg et al.,1956)
	Discontinuous solid solutions	C	M	Partially miscible, 2 phase even though drug is molecularly dispersed	2	Sekiguchi K and Obi N (1961)
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differ less than 15% from The matrix (solvent) diameter. In that case the drug and matrix are Substitutional. Can be continuous or Discontinuous. When discontinuous: 2 phase even though drug is molecularly dispersed	1 or 2	(Rastogi and Verma, 1956); (Wilcox et al., 1964)
	Interstitial Solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) Diameter. Usually limited miscibility, Discontinuous. Example: Drug in Helical interstitial space of PEG.	2	(Chiou & Reigelman, 1971) (Chiou & Reigelman, 1969)
IV	Glass suspension	A	C	Particle size of dispersed phase	2	(Chiou & Reigelman,

				dependent on cooling/ evaporation Rate. Obtained after crystallizations Of drug in amorphous matrix.		1971) (Sarkari M et al., 2002)
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/ evaporation rate may solid dispersion is of this Type.	2	(Chiou & Reigelman, 1971) (Sarkari M et al., 2002)
VI	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or	1	Simonelli AP et al., 1969

*A: matrix in the amorphous state, C: matrix in the crystalline state
**A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix.

VI. COMMON METHODS USED FOR PREPARATION OF SOLID DISPERSION

- Fusion method
- Solvent method
- Melting solvent method
- Supercritical fluid method
- Electro spinning method. 12
- Solvent evaporation method
- Melt agglomeration method
- Lyophillization Techniques
- Spray-Drying method
- Dropping method solution
- Melt extrusion method
- Gel entrapment technique
- Kneading technique
- Co-precipitation method
- Co-grinding method

➢ FUSION METHOD

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. The first solid dispersions are created for pharmaceutical applications were prepared by the fusion method.

ADVANTAGE

- The main advantage of direct melting method is its simplicity and economy.
- In addition melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier.

DISADVANTAGES

- Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible when they mix well at the heating temperature.
- When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion.
- In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions[13&14].

➢ SOLVENT METHOD

The first step in the solvent method is the preparation of a solution containing both matrix and material and drug. The second step involves the removal of solvent resulting in the formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges. First challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution and solid dispersions are obtained.

ADVANTAGES

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

DISADVANTAGES

The disadvantages include the higher cost of preparation, the difficulty in completely removing liquid solvent and possible adverse effect of the supposed negligible amount of the solvent on the chemical stability of the drug are some of the disadvantages of this method[14].

- **MELTING SOLVENT METHOD**

In this method drug is first dissolved in a suitable liquid solvent solution is then incorporated directly into the melt of polyethylene glycol obtainable below 70^0c without removing the liquidsolvent. It has been shown that 5-10 %(w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property.

ADVANTAGES

- In this method that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

DISADVANTAGES

- As the practical point of view, the melting-solvent method is limited to drugs with a low therapeutic dose, e.g. Below 50 mg.
- Moreover, it is impossible that the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol.
- The feasibility of the method has been demonstrated on spironolactone polyethylene glycol 6000 systems[13].

- **SUPERCRITICAL FLUID METHODS**

Supercritical fluid methods are mostly applied with carbon dioxide, which h is used as either a solvent for drug and matrix or as an ant solvent. When supercritical C02 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as "solvent free". The technique is known as Rapid Expansion of Supercritical Solution.

ADVANTAGES

- The supercritical anti solvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize and form particles.
- The general term for this process is precipitation with compressed anti oven. More specific examples of PCA are Supercritical Anti Solvent when supercritical CO2 is used or Aerosol Solvent Extraction System, and solution Enhanced Dispersion by supercritical fluids.

DISADVANTAGES

- Usually organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix which are more in cost[15&16].

- **ELECTROSPINNING METHOD**

Electros pining is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through millimeter scale nozzles. This process involves the application of a strong electrostatic field over a conductive capillary attaching to reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical

Value, a charged polymer jet is ejected from the apex of cone. The ejected charge jet is then carried to the collection screen via the electrostatic force. The Columbic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried.

ADVANTAGES

- This technique has tremendous potential for the preparation of Nano fibers and controlling the release of biomedicine.

Process is simplest, the cheapest.

- This technique can be utilized for the preparation of solid dispersions in future.

DISADVANTAGES

- Less economical for all the drugs and carriers[17&18].

➢ **SOLVENT EVAPORATION METHOD**

Solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is latter evaporated[19-21]. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature[22]. A basic process of preparing solid dispersions of this type consists of dissolving the drug and thy polymeric carrier in a common solvent, such as ethanol, chloroform mixture of ethanol and dichloromethane .Normally, the resulting films are pulverized and milled[20,23].

➢ **MELT AGGLOMERATION METHOD**

This technique has been used to prepare where in the binder acts as a carrier. In addition, are prepared either by Heating 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 might be preferable to the high melt agglomeration because it is easier to control the temperature and because a high binder content can be incorporated in the agglomerates. In addition the melt in procedure also results in homogenous distribution of drug agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion. The mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles[15].

➢ **LYOPHILLIZATION TECHNIQUES**

Lyophillization has been thought of a molecular mixing technique. The drug and carrier are co dissolved in a common solvent, Frozen and sublimed to obtain a lyophilized molecular dispersion.

➢ **SPRAY-DRYING METHOD**

Drug is dissolved in suitable solvent and 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 evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved[24].

➢ **DROPPING METHOD SOLUTION**

The dropping method, developed by Ulrich et al., (1997) to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods. For laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvent and, therefore, has none of the problems associated with solvent evaporation. 24

➢ **MELT EXTRUSION METHOD**

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g. sustained-release pellets[24].

➢ **GEL ENTRAPMENT TECHNIQUE**

Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then drug for example is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved[24].

➢ **KNEADING TECHNIQUE**

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

- **CO-PRECIPITATION METHOD**

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

- **CO-GRINDING METHOD**

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Ex. chlordiazepoxide solid dispersion was prepared by this method[24].

VII. CARRIER USED IN SOLID DISPERSION[3,25,26,27]

The selection of the carrier has the influence on the dissolution characteristics of the dispersed drugs, since the dissolution rate of one component from the surface is affected by the other component in a multiple component mixture. Therefore, a water soluble carrier results in a faster release of the drug from the matrix. A poorly soluble or insoluble carrier leads to slower release of a drug from the matrix. If the active drug present is a minor component in the dispersion, faster release of a drug can be achieved from matrix.

- **POLYETHYLENE GLYCOL (PEG)[2]**

GENERAL CHARACTERISTICS OF PEGS

Polyethylene glycols (PEG) are polymers of ethylene oxide, having a molecular weight (MW) in the range 200- 300000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500-20000 are usually employed. As the MW increases, so does the viscosity of the PEG. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents. The melting point of the PEGs of interest lies under 650C in every case (e.g. the m.p. of PEG 1000 is 30-400C, the m.p. of PEG 4000 is 50-58^{0}C and the m.p. of PEG 20000 is 60-63^{0}C) [28]. These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Dissolution rate of a relatively soluble drug like aspirin can be improved by formulating a solid dispersion in PEG 6000[29].

INFLUENCE OF THE PEG CHAIN LENGTH

PEGs of MW 4000-6000 are the most frequently used for the manufacture of solid dispersions, because in this MW range the water solubility is still very high, but hygroscopy is not a problem and the melting points are already over 50^{0}C. If PEG with low a MW is used, the product changes it's consistency and gives a sticky consistency that is difficult to formulate product[30]. PEGs with higher MW have also been used with success, products containing PEG 8000[31] and 10000[32] showed enhanced dissolution rates compared to the pure drug. Phenylbutazone/PEG solid dispersions indicated that the release is dependent on the PEG MW[33].

INFLUENCE OF DRUG/PEG RATIO

If the percentage of the drug is too high, it will form small crystals within the dispersion rather than remaining molecularly dispersed. On the other hand, if the percentage of the carrier is very high, this can lead to the complete absence of crystallinity of the drug and thereby enormous increases in the solubility and release rate of the drug[34].

- **POLYVINYLPYRROLIDONE (PVP)**

GENERAL CHARACTERISTICS OF PVP

Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3000000. These can be classified according to the K value, which is calculated using Fikentscher's equation[35]. The glass transition temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (TG) is high; for example, PVP K25 has a TG of 155^{0}C[36]. For this reason PVPs have only limited application for the preparation of solid dispersions by the hot melt method. PVP is suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wettingand thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid[37].

INFLUENCE OF THE PVP CHAIN LENGTH

The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given concentration[35].

DRUG/PVP RATIO

Solid dispersion prepared with high proportions of PVP tend to exhibit a higher drug solubility and release rate than those with high proportions of drug. For albendazole, for example, it has been shown that an increase in the %PVP in the dispersion leads to an increase in the release rate[38].

When the carrier comprised 81% of the dispersion, no crystalline areas could be detected and the release rate of the compound was rapid. Interestingly, when the %carrier was further increased, the release rate became slower. In the case of Piroxicam/PVP solid dispersions[39], the release rate increased with the %PVP up till a ratio of drug/carrier of 1:4, after which it fell again (at ratios of 1:5 and 1:6).

- **POLYVINYLALCOHOL (PVA), CROSPOVIDONE (PVP-CL), POLVINYLPYRROLIDONE-POLYVINYLACETATE COPOLYMER (PVPPVA)**

These three polymers belong to the polyvinyl group. Whereas polyvinyl alcohol (PVA) and vinylpyrrolidone/vinylacetate (PVP-PVA) copolymers are both water soluble, crospovidone swells when dispersed in water. The use of PVA/PVP copolymers as carriers in solid dispersions has been shown to lead to enormous increases in the drug release rate. Studies with the cytostatic drug HO-221 showed that the PVA/PVP solid dispersed not only dissolved 25 times faster than the drug powder, but also enhanced the bioavailability in beagles by a factor of 3.5[40]. Even though crospovidone does not dissolve in water, it can also be used as a carrier to improve drug release rates. For example, a 1:2 ratio of furosemide to crospovidone led to an increase in the dissolution rate by a factor of 5.8[41], in comparison with either the drug powder or a physical mixture of furosemide with crospovidone.

VIII. CELLULOSE DERIVATIVES

GENERAL CHARACTERISTICS OF CELLULOSE DERIVATIVES

Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by ß-1, 4-glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl- (MC), hydroxypropyl- (HPC), hydroxypropylmethyl- (HPMC) and many other semisynthetic types of cellulose. Since each glucose unit has three hydroxyl groups that can be derivatized, the average substitution grade (SG). A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and Hydroxypropylmethylcellulose phthalate (HPMCP) [42].

- **HYDROXYPROPYLMETHYLCELLULOSE (HPMC)**

HPMCs are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4-32% are derivatized with hydroxypropyl groups. The molecular weight of the HPMCs ranges from about 10000 to 1500000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane[43]. A poorly soluble weak base with incomplete bioavailability showed that the release rate and the bioavailability in beagles could be improved through preparation of a solid dispersion in HPMC[44]. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids and benidipine[45].

- **HYDROXYPROPYLCELLULOSE (HPC)**

Hydroxypropylmethylcellulose exhibits good solubility in a range of solvents, including water (up till 400C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37000 (Type SSL) to 1150000 (Type H) [46]. The release rate improved as the proportion of HPC was increased and when lower MW HPCs were used as the carrier.

- **CARBOXYMETHYLETHYLCELLULOSE (CMEC)**

CMEC also belongs to the cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5-6, with lowest dissolution pH being dependent on the grade of the CMEC. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at pH values of 6.8[47].

- **HYDROXYPROPYLMETHYLCELLULOSE PHTHALATE (HPMCP)**

HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). Their solubility in organic solvents is also type-dependent. Their MWs range from 20000 to 2000000[48].

- **POLYACRYLATES AND POLYMETHACRYLATES**

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. Commonly they are referred today the trade name Eudragit[49]. Eudragit E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pH, while Eudragit L can be used when it is desirable to avoid release in the stomach. When benipidine was formulated as a evaporate with Eudragit E, the rate of dissolution was much higher than from the pure drug powder[45].

- **UREA**

In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea[10]. Although urea is not often used as a carrier these days. In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000[49].

- **SUGAR, POLYOLS AND THEIR POLYMERS**

Chitosan a derivative of the polysaccharide chitin which is formed by deacetylation at the N position has also been used as a carrier in solid dispersions. Both chitosan and its salt form, chitosan glutamate, were able to improve the release of nifedipine by a factor of two to three compared to the drug powder[42].

- **EMULSIFIERS**

Two mechanisms are possible here for release behavior of drug: improvement of wetting characteristics and solubilization of the drug. Bile salts and their derivatives are natural surfactants that are built from a steroidal skeleton in the liver and which are important to the emulsification of fats and oils in the diet. As with other surfactants, they can enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate[50].

- **ORGANIC ACIDS AND THEIR DERIVATIVES**

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin[51].

- **SURFACE ACTIVE AGENTS[52]**

Surface-active agents are substances that at low concentrations adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface and the interfacial tension. Surface-active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. The surface active carriers are said to be amphipathic in nature. , surface active carriers may be included to the thermodynamic activity, solubility, diffusion, disintegration, and dissolution rate of drug.

IX. MECHANISM OF INCREASED DISSOLUTION RATE BY SOLID DISPERSION[53,57]

1. Reduction in particle size.
2. Solubilization effect (use of carriers).
3. Increased wettability and dispensability by carriers
4. Formation of metastable dispersion with reduced lattice energy for faster dissolution.
5. Ex. Dissolution energy for furosemide is 17Kcal/mol while Dissolution energy for 1:2 furesamide: PVP co-precipitate is 7.3Kcal/mol.

X. MARKETED PREPARATIONS OF SOLID DISPERSION[57]

- Solid dispersion of VALDECOXIB (NSAID) using PVP by Solvent Evaporation Method[54].
- Solid dispersion of TERBINAFINE HYDROCHLORIDE (synthetic allyl amine derivative, broad spectrum antifungal activity when used orally/topically) using polyvinyl pyrollidone K30 by Solvent Evaporation method[55].
- Surface Solid Dispersion Of GLIMEPIRIDE (third generation sulphonylurea, Antidiuretic drug which stimulates insulin release) using crospovidone, pregelatinised starch, croscarmellose sodium and Avicel PH 101 by Solvent Evaporation method[56].

XI. LIMITATIONS OF SOLID DISPERSIONS

Although a great research interest in solid dispersion in the past four decades, the commercial Utilization is very limited. Problems of solid dispersion involve

- The physical and chemical stability of drugs and vehicles.
- Method of preparation.
- Reproducibility of its physicochemical properties.
- Formulation of solid dispersion into dosage forms.
- Scale-up of manufacturing processes

XII. CHARACTERIZATION OF SOLID DISPERSION SYSTEM[2,42]

The most important methods which are used for characterization are thermo analytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug.

Methods for the characterization of solid dispersions are as following

- Dissolution testing.
- Thermo analytical methods: differential thermo analysis and hot stage microscopy.
- Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change.
- X-Ray diffraction.
- Spectroscopic methods, e.g. IR spectroscopy, NMR spectroscopy.
- Microscopic methods including polarization microscopy and scanning electron microscopy.

XIII. APPLICATIONS OF SOLID DISPERSION[5]

- 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.
- Polymorphs in a given system can be converted into isomorphous, solid solution,
- Eutectic or molecular addition compounds.

XIV. CONCLUSION

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs[2]. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling. Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

REFERENCES

[1]. Youn YS, Improved intestinal delivery of salmon calcitonin by Lys18- amine specific PEGylation: Stability, Permeability,Pharmacokinetic behavior and in vivo hypocalcemic efficacy. J. Contr. Rel.2006; 114: 334–342.

[2]. Patil RM, Maniyar AH, Kale MT, Akarte AM, Baviskar DT, Solid Dispersion: Strategy to enhance solubility, Int.J Pharm Sci. Review &Reasearch. 2011; 8(2): 66-73.

[3]. ShethNS,Formulation and evaluation of solid dispersion of Olanzepine, Int.J Pharm Sci. Review & Reasearch.2011; 2(3): 691-697.

[4]. ArunachalamA,KarthikeyanM,KonamK,Prasad HP, SethuramanS,Ashutoshkumar S, Solid Dispersions:A Review, Current PharmaResearch.2010; 1(1): 82-90.

[5]. DhirendraK,LewisS,Udupa N andAtin K, Solid Dispersions: A Review, Pak.J.Pharm.Sci. 2009; 22(2):234-246.

[6]. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995; 12: 413-420.

[7]. Ford JL, The current status of solid dispersions. Pharm ActaHelv. 1986; 61: 69-88.
[8]. Ozeki T, Yuasa H, Kanaya Y. Application of the solid dispersion method to the controlled release of medicine. IX. Difference in the release of flurbiprofen from solid dispersions with poly (ethylene oxide) and hydroxypropylcellulose and the interaction between medicine and polymers, Int J Pharm. 1997; 115: 209-217.
[9]. GiriTK,AlexanderA,Tipathi DK, Physicochemical Classification and Formulation Development Of Solid Dispersion Of Poorly Water Soluble Drugs: An Updated Review, Int.J.PharmBio. Arch., 2010; 1(4): 309-324.
[10]. Sekiguchi K, Obi N, Studies on Absorption of Eutectic Mixture. I. A comparison of the behaviour of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man, Chem. Pharm. Bull. 1961; 9: 866-872.
[11]. Mogal SA, Gurjar PN , Yamgar DS, KamodAC,Solid dispersion technique for improving solubility of some poorly soluble Drugs. 2012; 4(5): 1574-1586.
[12]. PATIDAR K, KSHIRSAGAR MD, SAINI V, JOSHI PB, SONI M; Solid Dispersion Technology: A Boon for Poor Water Soluble Drugs, Ind.J.Novel drug del. 2011; 3(2): 83-90.
[13]. Sayyad A, Sawant SD. Techniques of solubility enchancement of poorly soluble drug with special emphasis on solid dispersion, Journal of pharmacy research. 2010; 3: 2494- 2501.
[14]. Sekiguchi K, Studies on absorption of eutectic mixture. Pharma bull 1961; 9: 866- 872.
[15]. Horter D, Dressman JB, Physiochemical properties on dissolution of drug in the gastrointestinal tract. Adv Drug Del Rev, 1997; 25: 3-14. 16.
[16]. Goldberg AH, Galbaldi M, Kaning KL. Increasing in resolution rates and gastrointestinal via solid solution and eutectic mixture experimental evaluation of griseofulvin-succinic acid solution. J Pharm sci 1966; 55: 4870-4920.
[17]. Chiou WL, Rielman S, Pharmaceutical application of solid dispersion system. J Pharm.sci.1971; 78: 10-12.
[18]. Sharma DK, Joshi SB, Solubility enhancement strategies for poorly water soluble drugs in solid dispersion. Asian Journal of pharmaceutics 2007; 1: 7-8.
[19]. Hasegawa S, Effects of water content in physical mixture and heating temperature on crystallinity of troglitazone-PVP K30 solid dispersions prepared by closed melting method, Int. J. Pharm. 2003; 302: 103–112.
[20]. Lloyd GR, A calorimetric investigation into the interaction between paracetamol and polyethlene glycol 4000 in physical mixes and solid dispersions, Eur. J. Pharm. Biopharm. 2003; 48: 59–65.
[21]. Rodier E, A three step supercritical process to improve the dissolution rate of Eflucimibe, Eur. J. Pharm. Sci. 2005; 26: 184–193.
[22]. Won DH, Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical antisolvent precipitation process, Int. J. Pharm. 2005; 301: 199– 208.
[23]. Yoshihashi Y, Estimation of physical stability of amorphous solid dispersion using differential scanning calorimetry, J. Therm. Anal. Calorim. 2006; 85: 689– 692.
[24]. Nikghalb LA, Singh G, Singh G, Kahkeshan KF , Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs, volume. 2012; 2(10): 170-175.
[25]. Patidar Kalpana, Drug Invention Today. 2010; 2(7): 349-357.
[26]. Remingtons Pharmaceutical Sciences, 1980.vol.1&2
[27]. AnselC.Howard, Allen V. Loyd, PopovichA.Nicholas, Pharmaceutical dosage forms and drug delivery systems. 2000; 7: 248-252.
[28]. Price JC, Polyethylene glycol In: Wade A, Weller PJ (Eds.) Handbook of Pharmaceutical Excipients, American Pharmaceutical Association/The Pharmaceutical Press, Washington, DC/London.1994; 355-361.
[29]. Asker AF, Whitworth CW, Dissolution of acetylsalicylic acid from acetylsalicylic acidpolyethylene glycol 6000 coprecipitates, Pharmazie. 1975; 30: 530-531.
[30]. Shah JC, Chen JR, Chow D, Preformulation study of etoposide. 2, increased solubility and dissolution rate by solid-solid dispersions, Int. J. Pharm. 1995; 31: 103-111.
[31]. Perng CY, Kearney AS, Patel K, Palepu NR, Zuber G, Investigation of formulation approaches to improve the dissolution of SB- 210661, a poorly water soluble 5- lipoxygenase inhibitor, Int. J. Pharm. 1998; 17: 31-38.
[32]. Khan GM, Zhu JB, Preparation, characterization, and dissolution studies of ibuprofen solid dispersions using polyethylene glycol (peg), talc, and peg-talc as dispersion carriers, Drug Dev, Ind. Pharm. 1994; 24: 455-462.
[33]. Ford JL, Stewart AF, Dubois JL, The properties of solid dispersions of indomethacin or phenylbutazone in polyethylene glycol, Int. J. Pharm. 1986; 28: 11-22.

[34]. Lin CW, Cham TM, Effect of particle size on the available surface area of nifedipine from nifedipine-polyethylene glycol 6000 solid dispersions, Int. J. Pharm. 1996; 127: 261- 272.
[35]. Walking WD, Povidone, In: Wade A, Weller PJ (Eds.), Handbook of Pharmaceutical Excipitients, American Pharmaceutical Association/The Pharmaceutical Press, Washington, DC/London. 1994; 392-399.
[36]. BuÈhler V, Soluble Kollidon Grades (Povidone, Polyvidone): Tablet Coatings, Kollidon: Polyvinylpyrrolidone for the Pharmaceutical Industry, BASF, Ludwigshafen, 1993; 106- 115.
[37]. Itai S, Nemoto M, Kouchiwa S, Murayama H, Nagai T, Influence of wetting factors on the dissolution behavior of flufenamic acid, Chem. Pharm. Bull. 1985; 33: 5464-5473.
[38]. Torrado S, Torrado JJ, Cadorniga R, Preparation, dissolution and characterization of albendazole solid dispersions, Int. J. Pharm. 1996; 140: 220-250.
[39]. Tantishaiyakul V, Kaewnopparat N, Ingkatawornwon S, Properties of solid dispersions of piroxicam in polyvinylpyrrolidone K-30, Int. J. Pharm. 1996; 143: 59-66.
[40]. Kondo N, Iwao T, Hirai K, Fukuda M, Yamanouchi K, Yokoyama K, Miyaji M, Ishihara Y, Kon K, Ogawa Y, Mayumi T, Improved oral absorption of enteric coprecipitates of a poorly soluble drug, J. Pharm. Sci. 1994; 83: 566-570.
[41]. Shin S, Oh I, Lee Y, Choi H, Choi J, Enhanced dissolution of furosemide by coprecipitating or cogrinding with crospovidone, Int. J. Pharm. 1998; 175: 17-24.
[42]. Leunar C, Dreessan J, Improving drug solubility for oral delivary using solid dispersion, European journal of Pharmaceutics and Biopharmaceutics. 2000; 50: 47-60.
[43]. Harwood RJ, Johnson JL, Hydroxypropylmethylcellulose, In: Wade A, Weller PJ (Eds.), Handbook of Pharmaceutical Excipients, American Pharmaceutical Association/The Pharmaceutical Press, Washington, DC/London. 1994; 229- 232.
[44]. Kohri N, Yamayoshi Y, Xin H, Iseki K, Sato N, Todo S, Miyazaki K, Improving the oral bioavailability of albendazole in rabbits by the solid dispersion technique, J. Pharm. Pharmacol. 1999; 155: 159-164.
[45]. Suzuki H, Miyamoto N, Masada T, Hayakawa E, Ito K, Solid dispersions of benidipine hydrochloride. 1, Preparations using different solvent systems and dissolution properties, Chem. Pharm. Bull. 1996; 44: 364-371.
[46]. Harwood RJ, Johnson JL, Hydroxypropylcellulose, In: Wade A, Weller PJ (Eds.), Handbook of Pharmaceutical Excipients, American Pharmaceutical Association/The Pharmaceutical Press Washington, DC/London. 1994; 223-228.
[47]. Hasegawa A, Kawamura R, Nakagawa H, Sugimoto I, Physical properties of solid dispersions of poorly watersoluble drugs with enteric coating agents, Chem. Pharm. Bull. 1985; 33: 3429-3435.
[48]. Lee JC, Hydroxypropyl methylcellulose phthalate, In: Wade A, Weller PJ (Eds.), Handbook of Pharmaceutical Excipients, American Pharmaceutical Association/The Pharmaceutical Press, Washington, DC/London. 1994; 233-237.
[49]. Portero, Remunanlopez C, Vilajato JL, Effect of chitosan and chitosan glutamate enhancing the dissolution properties of the poorly water soluble drug nifedipine, Int. J. Pharm.1998; 175: 75-84.
[50]. Stoll RT, Bates TR, Nieforth KA, Swarbrick J, Some physical factors affecting the enhanced blepharototic activity of orally administered reserpinecholanic acid coprecipitates, J. Pharm. Sci. 1969; 58: 1457-1459.
[51]. Chiou WL, Riegelman S, Preparation and dissolution characteristics of several fastrelease solid dispersions of griseofulvin, J. Pharm. Sci.1969; 58(12): 1505-1510.
[52]. Chaudhari P, Current trends in solid dispersions techniques, Pharminfo.net. 2006; 4(3): 458-469.
[53]. James Swarbrick, Encyclopedia of Pharmaceutical Technology, 3rd Edition. 2006; 777 - 779.
[54]. Modi, P, Enhancement of dissolution profile by solid dispersion (Kneading) Technique, AAPS pharmasciTech. 2006; 7(3): 68-72.
[55]. Kumar N, Jain AK, Singh C, Kumar R, Development, Characterization & Solubility Study of solid Dispersion Of Terbinafine Hydrochloride By Solvent Evaporation Method,sianpharmaceutics.info. 2008; 3(2): 154-158.
[56]. Kiran T, Shastri N, Ramkrishna S, Sadanandam M, Surface Solid Dispersion Of Glimipiride For Enhancement of Dissolution Rate, International journal of pharmatech research. 2009; 1(3): 822-831.
[57]. Sngh MC, Sayyad AB, Sawant SD, Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion. 2010; 3(10): 2494-2501.

Prosun Kanti Ghosh Different Methods Used In Solid Dispersion"." IOSR Journal of harmacy (IOSRPHR), vol. 8, no. 07, 2018, pp. 28-38.