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Spherical Crystallization in Solubility Enhancement

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1.1 Introduction

Solubility is the property of a solute to dissolve in a solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance depends upon number of factors like properties of solute and solvent, temperature, pressure and so on. The solvent is any state of matter, solid liquid and gas but considering pharmaceuticals generally a solvent used is liquid, which can be a pure substance or a mixture of two liquids (Myrdal et al., 2007). The extent of solubility ranges widely, from Very soluble to practically insoluble as per the criteria given in United States Pharmacopoeia and Indian Pharmacopoeia (USP 2007 and IP 1996). Solubility is not to be confused with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. For example, zinc is insoluble in hydrochloric acid, but does dissolve in it by chemically reacting into zinc chloride and hydrogen, where zinc chloride is soluble in hydrochloric acid. Solubility does not also depend on particle size or

other kinetic factors; given enough time, even large particles will eventually dissolve (Martin et al., 2011).

The major focus in formulation and development is on solubility enhancement as it leads with poor bioavailability specifically for Class II drugs as per BCS classification. Solubility is one of the important parameters can directly be correlated with achieving required pharmacological response as it is rate determining step for bioavailability of Class II drugs (Behera et al., 2010). Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs shows poor drug absorption leads to poor bioavailability consequently to poor or ineffective drug action. The improvement of drug solubility thereby its oral bioavailability is one of the hurdle for drug development process especially for oral-drug delivery system. This it can be one of the foremost and big challenges from few decades to a pharmaceutical industry. There are various approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form. Some of the methods are as given below (Savjani et al., 2012).

Table 1.1 Different methods for solubility enhancement.

	Name of the Method		
	Physical Modifications	**Chemical Modifications**	**Miscellaneous Methods**
Examples	1. Particle size reduction like micronization and nanosuspension. 2. Modification of the crystal habit like polymorphs, amorphous form and cocrystallization.	1. Change of pH 2. Use of buffer 3. Derivatization 4. Complexation 4. Salt formation.	1. Supercritical fluid process 2. Use of adjuvant like surfactant, solubilizers cosolvency 3. Hydrotrophy.

Table 1.1 *Contd…*

Name of the Method			
	Physical Modifications	**Chemical Modifications**	**Miscellaneous Methods**
	3. Drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.		

1.2 Mechanism of Solubility

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug is represented through various concentration expression such as parts, percentage, molarity, molality, volume fraction, mole fraction.

Spontaneous passage of poorly water soluble solute molecules into an aqueous solution of surfactant is termed as solubilisation. As difference molecules interact, both repulsive and attractive forces are operative. The intramolecular forces and valence bond are given below:

(i) Intermolecular forces:
Dipole-dipole interaction (Keesome interactions)
Dipole- induced dipole interaction (Debye interactions)
Induced-dipole interaction-Induced-dipole interaction
(London dispersion forces)
Ion-dipole interaction
Hydrogen bonds

(ii) Valence Bonds:
Electrovalent bond
Covalent bond
Homo-polar bond
Ionic bond
Heteropolar bond

1.3 Factors Influencing Solubility of Drugs

Solute related: Nature of solute – Size, Shape and surface area. Physicochemical properties – melting point, heat of fusion, molar volume and pKa, Physical forms: Salt, crystalline state and polymorphism.

Solvent related: Nature of the solvent, i.e., Polarity, pH of the medium, volume of solvent employed.

Environment related: Temperature and pressure.

Formulation related: Other ingredients.

Influence of particle size, shape and surface area: Solubility increases with decreasing particle size. Since surface area of solids in contact with the medium increases, rapid dissolution is obtained. This increase in solubility ceases when the particle size reaches a particular point. Hence, particle size is critical and beyond a particular value, the solubility of solid decreases. Such a change arises because of the presence of an electrical charge on the particle, which is predominat in small particles. Symmetric molecules may be less soluble than unsymmetric ones. If crystals are compact, they possess high lattice energy and therefore, wiil be lowered.

Influence of physicochemical properties of drugs: The melting points of solids are indicators of molecular cohesion and hence are useful for predicting the trend in a series of similar compounds. The other parameters are molar heat of fusion, entropy of fusion and molar volume. These are discussed in the theories of solutions.

Dissociation constant of drug is useful in predicting the extent of ionisation depending on the pH of the environment. In general, the ionised species have greater aqueous solubility than the unionised species.

Physical Forms of Drugs

Some of the general principles are: Amorphous forms of drugs have greater aqueous solubility than the crystalline forms.

Among crystals, metastable forms of drugs have greater aqueous solubility than the stable forms.

Anhydrous forms of drugs have greater aqueous solubility than hydrates forms.

Organic solvates of drugs have greater aqueous solubility than unsolvated forms.

Salt forms of drugs have greater aqueous solubility than non-salt forms, provided common ion effect is not influenced.

Influence of solvents: In the formulation, water or vegetable oils are normally used as solvents. The solubility of the drug is due to the polarity of the solvent that is dipole movement. In addition, hydrogen bonding between solute and solvent is essential. Therefore, structural features and presence of nonpolar and polar groups in the molecule are important. Syrups and liquid oral solutions are manufactured using water. The simple maxim of like-dissolve-like is the guiding principle.

Table 1.2 Influencing of solvent on solubility.: i.v.: Intra venous.

Solvent	Nature of Solute	Examples of Drugs	Dosage forms
Water(Polar)	Polar Substances	Vitamin B1 & B2	Elixer
	Strong Electrolytes	Sodium chloride	i.v. infusion
	Weak Electrolytes	Sodium Phenobarbitone	Injection
	Nonelectrolytes	Dextrose	i.v. injection
Oil(nonpolar)	Nonpolar substances	Progesteron	Oil injection

Poorly water soluble drugs are normally dissolved in non-aqueous vehicles such as liquid paraffin, arachis oil and ethyl oleate. In most cases, a mixture of solvents is used for maximum solubility of drugs.

Influence of pH of the medium: Most of the drugs are weak electrolytes. Weak acids and weak bases undergo ionisation in solution. Drugs are more soluble in water when they are in ionised form. Unionised drugs are poorly water soluble. The extent of ionisation of drug in a solution depends on the dissociation constant and the pH of the medium. For example, alkaloidal salts are more soluble in acidic pH and begin to precipitate as the pH increases. On the other hand, phenobarbitone is more soluble in alkaline Ph and begins to precipitate as the pH decreases.

The relationship between pHp (of the preparation), solubility and pKa value of the drug is expressed as:

$$\text{Acidic drugs: } pHp = pKa + \log s - s_{0/} s_0$$

$$\text{Basic drugs: } pHp = pKa + \log s_{0/} S - s_0$$

Where pKa = dissociation constant of drug, s_0 = solubility of unionised form, moles/litre, S = overall solubility of drug, moles/litre.

If pH of the solution is known, solubility of drugs can be calculated using equations(1) and (2). Similarly minimum pH can be determined in order to maintain a solution of known concentration without precipitation.

Influence of Cosolvents: Frequently a solute is more soluble in a mixture of solvents rather than in a single solvent. The solvents,which are used to increase the solubility of a drug in water are called as cosolvents. The phenomenon is known as cosolvency. Ethanol, propylene glycol, glycerine, PEG 300, and PEG 400(polyethylene glycols) are the commonly used cosolvents, since these are water miscible. The concept of cosolvency is applied in the manufacture of liquid dosage forms such as syrups, elixirs, injections, creams and lotions. In addition, solvents such as benzyl alcohol, dimethyl sulphoxide(DMSO) Dimethyl acetamide (DMA) and Dimethyl formamide(DMF) are used as supplementary solvents.

Influence of Temperature: Increase in temperature involves the absorption of heat and it influences the solubility of the drugs.

If the dissolution involves positive hit of solution, a rise in temperature leads to an increase in solubility of solid. Example is potassium nitrate in water.

Conversely if the dissolution of a solid involves the liberation of heat then an increase in temperature leads to decrease in solubility. Example is calcium acetate in water.

Influence of Surfactants: Surface active agents enhance the solubility of poorly water-soluble drugs due to the formation of micelles. This phenomena is known as micellar solubilisation. For Example, Solubility of procaine is enhanced by 25% in aqueous buffer, owing to the formation of surfactant micells.

Influence of other ingredients: Several ingredients of diverse nature are added in the formulation of dosage forms.

Common ion effect: The solubility of a sparingly soluble electrolyte is decreased by the addition of a second electrolyte that posses a similar ion to the first. The phenomenon is known as common ion effect. The behaviour is predicted from the concept of solubility product.

Effect of other electrolytes: The solubility of a sparingly soluble electrolytes may be increased by the addition of a second electrolyte that

does not posses same ions. The ions produced by dissociation of electrolytes are strongly associated with oppositely charged ions.

1.4 Spherical Crystallization

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement solubility. The various parameters optimized were type, amount and mode of addition of bridging liquid, temperature and agitation speed to get maximum amount of spherical crystals. It was revealed from the studies that spherical agglomerates exhibited improved solubility and bioavailability of drugs in pharmaceuticals (Patil et al., 2010).

The spherical crystallization can enable subsequent process such as separation, filtration and drying to be carried out more efficiently. The potential and achievements of the spherical crystallization techniques in pharmaceutical fields were described as follows.

Aminophylline agglomerates has been prepared by (Kawashima *et al.,* 1982[a]) by SA method using Chloroform-Ethanol-Water as solvent system. Agglomerates prepared were found to be spherical with improved micromeritic properties. The resultant Aminophylline agglomerates were free flowing and directly compressible due to their spherical shape.

Salicylic acid agglomerates has been prepared by (Kawashima *et al.,* 1984[c]), by SA method using ethanol-water-chloroform as solvent system. The crystallinity of the agglomerated Salicylic acid decreased when the amount of ethanol in the solvent mixture was decreased. The wettability of agglomerated crystals increased when the amount of ethanol in the solvent mixture was decreased and this enhances the dissolution rate of the crystals. The remarkable improvement in the flow and packing of the agglomerated crystals enabled the direct compression of the crystals

Tolbutamide agglomerates has prepared by (Sano *et al.*, 1987), by NT method using aqueous solution of sodium hydroxide with polymer and 1M hydrochloric acid as a solvent system. Prepared agglomerates were compared with raw crystals for dissolution rate, flowability, solubility. The study has shown increased dissolution rate, flowability, and solubility of agglomerated crystals than raw crystals.

Furosemide agglomerates has prepared by Julide, 1989 by SA method using different polymers like Eudragit L100, Eudragit S100, Eudragit RL100, Eudragit RS100 and got the following results. The most

release retardant effect was obtained by using Eudragit RS 100. Dissolution data showed that the release followed Higuchi matrix model kinetics. Thus controlled release Furosemide agglomerates were successfully prepared by spherical agglomeration.

Ibuprofen agglomerates has prepared by (Kawashima *et al.,* 1989) and (Kawashima *et al.,* 1991) by ESD method using Ethanol-Water with sucrose fatty acid ester as solvent system and that of Tranilast were prepared by SA method using Ethanol/Acetone-Water-Chloroform/ Dichloromethane as a solvent system. Agglomerates were spherical with improved micromeritic properties. Also remarkable improvement in flowability, packability compressibility and *in-vitro* dissolution were observed.

Naproxen agglomerates were prepared by (Gordon *et al.,* 1990) by SA method using Acetone-Water, Bridging liquid: (Hexanol, Octanol, Toluene) as a solvent system. Agglomerates prepared were found to be spherical with improved micromeritic properties and flow characteristics of agglomerates, which are directly compressible.

Enoxacin agglomerates were prepared by (Ueda *et al.,* 1991) by ADM using Ammonia water - Acetone - Dichloromethane as solvent system. Agglomerates were spherical with improved particle size. Also significantly improved flowability and packability without much delay in their dissolution rate were observed compared with untreated pure drug crystals.

Ibuprofen agglomerates were prepared by (Kawashima *et al.,* 1992[a]) by ESD method using solvent system as ethanol with Eudragit RS 100. The resultant microsponges had a higher porosity and tortuosities. Microsponges compressibility was much improved over the physical mixture of drug and polymer owing to plastic deformation of their sponge like structure. The more porous microsponges produced stronger tablet.

Tranilast and Ibuprofen were prepared by (Kawashima *et al.,* 1992[b]) by using solvent system: Ethanol, acetone, water, chloroform, DCM. The developed multiple-unit intragastric floating system for involving hollow microspheres (microballoons) has shown excellent buoyant properties achieving a longer-lasting and more reliable release of drugs. This gastrointestinal transit-controlled preparation is designed to float on gastric juice with a specific density of less than one. This property results in delayed transit through the stomach, which could be applicable for a drug absorbed mainly at the proximal small intestine, such as riboflavin. Optimum preparation temperature with respect to

microballoon cavity formation and factors influencing the buoyancy properties of microballoons were examined. Different drugs, which exhibited distinct water solubility, were tested in terms of entrapment within microballoons. The efficiency of drug entrapment into microballoons and the buoyancy properties of the microballoons were also investigated. Hollow microspheres were prepared by the emulsion solvent diffusion method using enteric acrylic polymers with drug in a mixture of dichloromethane and ethanol. It was found that preparation temperature determined the formation of cavity inside the microsphere and the surface smoothness, determining the floatability and the drug release rate of the microballoon. The drugs incorporated in the solidified shell of the polymer were found to be partially or completely amorphous. The flowability and packability of the resultant microballoons were much improved compared with the raw crystals of the drug.

Tolbutamide agglomerates has prepared by (Sano *et al.,* 1992) by NT/ ESD / SA methods using solvent system:

NT: 1N sodium hydroxide, 1N hydrochloric acid, 2% Hydroxy propyl methyl cellulose solution.

SA: Ethanol, IPA, drug and 0.025% sucrose fatty acid ester aqueous solution.

ESD: Dimethyl formamaide, 0.025% sucrose fatty acid ester aqueous solution.

The Tolbutamide dissolution rate from the physical mixtures and tablets increased in the order of ESD < SA < NT in direct proportion to an increase in the specific surface area of the agglomerated crystals. *In-vivo* studies in beagle dogs, the physical mixture and tablet of agglomerated crystals show significantly higher value than those of bulk in area under the curve of plasma concentration (AUC-8hr), C_{max}, especially high value were obtained with the NT physical mixture and tablet.

Captopril agglomerates has prepared by (Jayaswal *et al.,* 1993) by ESD method using solvent system dichloromethane, Alcohol, 0.1N HCl with polymers Eudragit RL100, Eudragit RS100 and Ethyl cellulose. He has observed that increase in the concentration of polymer decreases the release rate significantly. The most retardant effect was obtained using Eudragit RS100. Also increase in stirring rate has increased the drug release rate.

Acebutolol HCl agglomerates has prepared by (Kawashima *et al.,* 1994[b]) by ESD method using water and isopropyl acetate as solvent

system. Spherically agglomerated crystals prepared by the ESD technique with a two-solvent system exhibit improved flowability and packability for direct tabletting. The main factor in the improvement of these micromeritic properties was a significant reduction in interparticle friction, due to their spherical shape and a lower static electricity charge. Compressibility of the agglomerates was much improved, due to the increased interparticle bonding of agglomerates fractured during compression.

Bucillamine agglomerates has prepared by (Morshima *et al.,* 1994) by SA / ESD methods using Ethanol- Dichloromethane-water as solvent system. Agglomerates were spherical with improved physicochemical properties compared with raw crystals of the drugs like particle size, flowability, packability and compressibility.

Acebutolol hydrochloride agglomerates has prepared by (Kawashima *et al.,* 1995) by ESD method using ethanol - water - isopropyl acetate as solvent system. The behavior of spherical crystallization via a quasi-emulsion produced by pouring the good solvent solution of the drug into the poor solvent has determined by the diffusion rates of good solvent or/and bridging liquid from the emulsion droplet into the dispersing medium. The agitation speed of the system is the main parameter determining the average diameter of agglomerated crystals.

Acetaminophen agglomerates were prepared by (Garcia *et al.,* 1996) by SA method using aqueous solution of cross-linking agent as a solvent system. It has reported that the physical properties and the drug release from spheres varied according to the amount of drug entrapped into the spheres, level of polymer in the dispersion and the cross-linking agent used. The level of polymer in the dispersion was critical in controlling the drug release. Its ability to undergo gelation enables a gel matrix to be formed and consequently control the drug release.

Dibasic calcium phosphate agglomerates were prepared by (Takami *et al.,* 1996) by Solvent change method using Water-Aqueous solution of phosphoric acid and citric acid as a solvent system. Agglomeraes formed were spherical and adequately porous and has shown remarkable improvement in flowability, compressibility and rate of dissolution.

Aspirin agglomerates were prepared by (Deshpande *et al.,* 1997) by SA method using Acid buffer-Methanol-Chloroform as a solvent system. Agglomerates prepared were found to be spherical with improved micromeritic properties Also agglomerates has shown significantly

improved flow property, compressibility and stability compared with raw crystals of the aspirin.

Norfloxacin agglomerates were prepared by (Hector *et al.,* 1998) by ADM method using Ammonia water-Acetone-Dichloromethane as solvent system. Agglomeretaes prepared were found to be spherical with improved micromeritic properties. The resultant Norfloxacin agglomerates were free flowing and directly compressible due to their spherical shape.

Ibuprofen agglomerates were prepared by (Kachirmanis *et al.,* 1998) by SA method using solvents ethanol and water with polymer Eudragit S100. He has reported the improved micromeritic properties, flow properties with improved packing behavior and densification of Ibuprofen agglomerates at low compression.

Insulin nanospheres were prepared by (Kawashima *et al.,* 1999) by ESD method using acetone, 0.01 M hydrochloric acid, water and 0.01 M sodium hydroxide solution with polymers as a solvent system. It was observed that Eighty five percent of the drug was released from the nanospheres at the initial burst, followed by prolonged releasing of the remaining drug for a few hours. The aqueous dispersions of PLGA nanospheres administered pulmonarily to the guinea pig via nebulization, reduced significantly the blood glucose level over 48 h, compared to the nebulized aqueous solution of insulin as a reference. This result could be attributed to the deposition of nanospheres widely spread through the whole lung and the sustained release of insulin from the deposited nanospheres.

Fenbufen agglomerates were prepared by (Martino *et al.,* 1999) by SA method using Tetrahydrofuran- isopropyl acetate- demineralized water with isopropyl acetate as solvent system. Agglomeretaes prepared were found to be spherical with improved micromeritic properties. Improvement in dissolution capacity, probably due to better wettability in presence of bridging liquid (isopropyl acetate) has been reported.

Paracetamol agglomerates were prepared by (Garekani *et al.,* 2000) by salting out method using Ethanol-Water with PVP as a solvent system. It was found that PVP is an effective additive during crystallization of paracetamol and significantly influenced the crystallization process and changed the crystal habit. These effects were attributed to adsorption of PVP onto the surfaces of growing crystals. It was found that the higher molecular weights of PVP (PVP 10 000 and PVP 50 000) were more effective additives than lower molecular weight PVP (PVP 2000).

Acetyl salicylic acid agglomerates were prepared by (Goczo *et al.,* 2000) by SA method. Agglomerates are having excellent flow properties and favorable compactability, cohesiveness and tabletability value.

Propyphenazone agglomerates were prepared by (Martino *et al.,* 2000) by SA method using ethyl alcohol-isopropyl acetate-demineralized water as solvent system. The result has indicated the improvement in flowability contributes to making the filling of the die easier and more precise and thus gives more reproducible results. Increase in tabletability and compatibility properties, helps to obtain a material for direct compression. The prepared agglomerated crystals were small, favorable to compression.

Cyclosporine naoparticles were prepared by (Gref *et al.,* 2001) by ESD method using dichloromethane and water with polymers as a solvent system. Polylactic acid (PLA)-poly ethylene glycol (PEG) particulate carriers with different particle sizes can be designed as new Cyclosporine carriers, showing promising characteristics as compared with conventional PLA micro-and nanoparticles. Cyclosporine-loaded PLA-PEG micro-and nanoparticles provide new opportunities to improve present marketed Cyclosporine formulations, to improve Cyclosporine-based therapies in the areas of Cyclosporine biomedical application.

Ketoprofen agglomerates were prepared by Comoglu *et al.,* 2002 by ESD method using ethyl alcohol with Eudragit RS 100 as an internal phase and water containing PVA as an external phase. Results indicated that microsponge compressibility was much improved over the physical mixture of the drug and polymer and owing to the plastic deformation of sponge-like structure, microsponges produce mechanically strong tablets.

KSR-59 steroid agglomerates were prepared by (Ikegami *et al.,* 2002) using acetone and water as a solvent system. The primary crystals in the agglomerates produced by the bridging liquid in agitated aqueous medium grew until the dispersing medium was saturated with the bridging liquid as well as growing the agglomerates. The growth rates of primary crystals and agglomerates increased with an increase in the temperature and/or a reduction in the agitation speed of the system. The growth of primary crystals in the spherical agglomerates was explained by a crystallization and fusion mechanism. The primary crystals were mechanically stronger than their agglomerates so that the agglomerates were disintegrated easily into the primary crystals, which retained their original size, under the shear force generated on being mixed with carrier particles for dry powder inhalations.

Ketoprofen agglomerates were prepared by (Comoglu *et al.,* 2003) by ESD method using ethyl alcohol with polymer-Eudragit RS 100 and triethylcitrate as an internal phase and water containing PVA as an external phase. The effects of different mixing speeds, drug-polymer ratios, solvent-polymer ratios on the physical characteristics of the microsponges as well as the *in-vitro* release rate of the drug from the microsponges were investigated. All the factors studied had an influence on the physical characteristics of the microsponges. *In-vitro* dissolution results showed that the release rate of ketoprofen was modified in all formulations.

Flurbiprofen agglomerates were prepared by (Chourasia *et al.*, 2003) by SA method using acetone-water-hexane as a solvent system. The results have shown that the agglomerates were spherical. Also the spherical agglomerates exhibited improved flowability, wettability and compaction behavior.

Nitrendipine agglomerates were prepared by (Cui *et al.*, 2003) by ESD method. Nitrendipine was dissolved with HP-55, EuRS, EC, Aerosil, triethyl citrate in a mixed organic solution containing ethanol, acetone and dichloromethane and the external phase used was distilled water. He has observed the improvement in micromeritic properties. Also the release rate of nitrendipine from the microspheres could be modulated as desired by adjusting the formulations of the microspheres and preparation conditions. The markedly improved bioavailability of nitrendipine indicating effectiveness of method for designing sustained-release microspheres with water-insoluble drugs. HP-55 could be used as a desired enteric agent to prepare solid dispersions in the pharmaceutical field to enhance the solubility and dissolution rate of the drug.

KSR-592 steroid agglomerates were prepared by (Ikegami *et al.*, 2003) using hexane, ethanol and cooled water with ethyl acetate as a solvent system. The dry powder inhalations formulation with these agglomerates exhibited ideal fluidity and provided a larger fine particle fraction than the formulation with agglomerates consisting of a-form (plate-like) crystals. The air-flow rate of inhalation had no effect on the disintegration properties of these agglomerates, suggesting a reliable inhalation performance *in-vivo*. Further, an *in-vivo* test of the aerosolized KSR-592 (β-form) crystals having the same particle size distribution as those in the aerosol. Inhaled KSR-592 (β-form) crystals were found to be uniformly deposited in the lungs of Brown Norway rat sensitized by ovalbumin (OA) and suppressed the increase in eosinophil number in the lungs after OA challenge.

Ampicillin trihydrate agglomerates were prepared by (Gohle *et al.*, 2003) using ADM method using Ammonia water-Acetone-Dichloro-methane as a solvent system. Agglomeretaes prepared were found to be spherical with improved micromeritic properties, compressibility and compaction property. Tablet prepared from agglomerates showed comparable drug release with that of obtained from marketed product.

Ascorbic acid agglomerates were prepared by (Kawashima *et al.*, 2003) by SA method using purified water (good Solvent) and ethyl acetate (poor solvent). The micromeritic properties like flowability and packability of the spherically agglomerated crystals were preferably improved for direct tableting. The improved compaction properties of the agglomerated crystals were due to their fragmentation and plastic deformation occurred significantly during compression.The spherically agglomerated crystals were tableted directly without capping.

Riboflavin agglomerates were prepared by (Sato *et al.*, 2003) using dichloromethane and ethanol with polymers as an internal phase and water with PVA as an external phase. The prepared agglomerates were able to float in the stomach sufficiently in the fed condition. This phenomenon could prolong the gastric residence time and delay drug arrival at the absorption site; consequently, the sustained pharmacological action could be provided. Microballoons (MB) enabled increased absorption rate of drug as the floating MB in the stomach gradually sank and arrived at the absorption site. MB multiple unit floating systems should be possibly beneficial with respect to sustained pharmacological action.

Nitrendipine agglomerates were prepared by (Yang *et al.*, 2003) by ESD method using, Acetone, Dichloromethane, Aerosil, Eudragit RS as internal phase and water as an external phase. He has revealed that the agglomerates have desired micrimeritic properties. The release profiles of the agglomerates were modulated with adjusting the ratio of the retarding agent to the dispersing carrier. The relatively high recovery and incorporation efficiency of agglomerates showed an advantage over the other conventional method of preparing microspheres.

Cystatin nanoparticles were prepared by (Cegnar *et al.*, 2004) by ESD method using ethyl acetate / dichloromethane and acetone (1:1) with Cystatin and PLGA as an internal phase and and water with PVA (5%, w/v), trehalose and a mixture of sugars as an external phase. The protein activity was preserved more in the case when protectants were in direct contact with cystatin, protecting it during the whole nanoparticle (NP) formation. Furthermore, NP-entrapped cystatin is more stable than a

solution of free cystatin and that the stability is increased by the selection of optimal PLGA derivatives.

Roxythromycin agglomerates were prepared by (Chouracia *et al.*, 2004[b]) using SA method using Methanol-Chloroform-Water as solvent system. Prepared agglomerates were compared with raw crystals for flowability, packability, wettability. Agglomerates have shown improved flowability, packability, wettability in comparison to conventional drug crystals.

Cyclosporine naoparticles were prepared by (Dai *et al.*, 2004) using ESD method using ethanol and water with polymers as a solvent system. In vitro release experiments revealed that the nanoparticles exhibited perfect pH-dependant release profiles. The relative bioavailability of Cyclosporine was markedly increased, with these results; the potential of pH-sensitive nanoparticles for the oral delivery of Cyclosporine was confirmed.

Aspirin, Salicylic acid, Ethoxybenzamide, Indomethacin and Riboflavin agglomerates were prepared by (Sato *et al.,* 2004) using dichloromethane and ethanol with polymers as an internal phase and water with PVA as an external phase. In the case of aspirin, salicylic acid and ethoxybenzamide, the drug release profiles of microballoons proved linear relationships by Higuchi plotting. However, indomethacin and riboflavin release profiles did not follow the Higuchi equation. When the loading amount of riboflavin was higher than the solubility in the mixture of dichloromethane and ethanol, the drug release profiles of the microballoons displayed an initial burst release. The insoluble riboflavin in the mixture of dichloromethane and ethanol adsorbed on to the microballoon surface in the crystal state. Such riboflavin crystals were released preferentially at the initial stage of the release test, which was attributable to the initial burst. In addition, by incorporating a polymer such as hydroxy propyl methyl cellulose within the shell of microballoons, the release rate of riboflavin from the microballoons could be controlled while maintaining high buoyancy.

Nitrendipine agglomerates were prepared by (Yang *et al.*, 2004) by ESD method using, internal phase: acetone / ethanol as good solvent , dichloromethane as bridging liquid with pH-dependent polymers like Acrylic resins Eudragit E-100, hydroxy propyl methyl cellulose phthalate, hydroxy propyl methyl cellulose and water as an external phase. The drug dissolution behavior of the system under the stimulated gastrointestinal pH conditions revealed the gradient-release characteristics. The dissolution profiles and content of the systems stored

at 40^{o}C 75% RH were unchanged during a 3-month period of accelerating storage conditions. The results of the bioavailability testing in six healthy dogs suggested that the pH-dependent gradient-release delivery system could improve efficiently the uptake of the poorly water-soluble drug and prolong the T_{max} value *in-vivo*.

Roxithromycin agglomerates were prepared by (Gao *et al.*, 2006) by ESD method using ethanol, acetone (good solvent) and dichloromethane (bridging liquid) with roxithromycin, polymer- Eudragit and silica as internal phase and water containing 1% of PVA as an external phase. He has quoted the following findings. The bitter taste of roxithromycin was masked by the microspheres produced with Eudragit S100. The DSC and XRD study showed that the drug was in an amorphous state in the microspheres. The microspheres masking the bitter taste of the drug could be incorporated into a suitable dosage form for oral administration in the future. The opposite electric groups between drug and polymer can take better effects on taste-masking with the interaction, but must be considered the chemical stability on the interaction between them.

Benzoyl peroxide agglomerates were prepared by (Jelvehgari *et al.*, 2006) by ESD method using Dichloromethane with ethyl cellulose as an internal phase and water containing PVA as an external phase. The microsponges were spherical in shape with pores because of the diffusion of solvent from the surface of the microparticles and thus the particles were designated as microsponges. Drug: polymer ratio, stirring rate, volume of dispersed phase influenced the particle size and drug release behavior of the formed microsponges. Increase in drug: polymer ratio resulted in a reduction in the release rate of Benzoyl peroxide which was attributed to a decreased internal porosity of the microsponges.

Flurbiprofen agglomerates were prepared by (Orlu *et al*., 2006) by ESD method using dichloromethane with ethyl cellulose as an internal phase and water containing PVA as an external phase. Agglomerates were spherical in shape and showed high porosity values. Mechanically strong tablets prepared for colon specific drug delivery was obtained owing to the plastic deformation of sponge-like structure of microsponges.

Mefenamic Acid and Nabumetone agglomerates were prepared by (Viswanathan *et al.*, 2006) by ESD method using Dimethylformamide (DMF) - distilled water - Chloroform (for Mefenamic Acid) and Ethanol - distilled water - cyclohexane/n-hexane with hydroxy propyl methyl cellulose and lecithin as a solvent system (for Nabumetone). It has shown

that the incorporation of polymer HPMC during agglomeration significantly enhanced the dissolution rate of mefenamic acid while incorporation of solubilizing agent lecithin improved the solubility of nabumetone. Thus, spherical agglomeration is an important technique for improving direct compressibility of pharmaceutical powders.

Cefuroxime axetil nanoparticles has prepared by (Zhang *et al.*, 2006) by SA method using ethyl acetate, methylene chloride, chloroform, formic acid, isopropyl ether and acetone as a solvent system. The cefuroxime axetil nanoparticles produced via the controlled nanoprecipitation are amorphous with a narrow particle size distribution. The dissolution of nanosized cefuroxime axetil is significantly enhanced compared with the spray-dried cefuroxime axetil. In conclusion, the controlled nanoprecipitation method offers a direct process to obtain drug nanoparticles of controllable size, amenable for continuous and consistent production.

Celecoxib agglomerates were prepared by (Gupta *et al.*, 2007) by SA method using Acetone-Water with PVP-chloroform as solvent system. Spherical agglomerates of celecoxib prepared with PVP exhibited improved micromeritic properties in addition to improving the solubility and dissolution rate. This technique may be applicable for producing oral solid.

Benzoyl peroxide agglomerates has prepared by (Nokhodchi *et al.*, 2007[a]) by ESD method using Dichloromethane as an internal phase and water containing PVA as an external phase. It was noted that the morphology and particle size of microsponges were affected by drug: polymer ratio, stirring rate and the amount of emulsifier used. Increase in the ratio of drug: polymer resulted in a reduction in the release rate of Benzoyl peroxide from the prepared microsponges.

Carbamazepine agglomerates has prepared by (Nokhodchi *et al.*, 2007[b]) by SA method using ethanol-water with isopropyl acetate as a solvent system. The micromeritic properties of the agglomerated crystals like flowability, packability and compactibility were dramatically improved. The compression of treated carbamazepine samples resulted in successful direct tableting without capping.

Oridonin naoparticles has prepared by (Xing *et al.*, 2007) by ESD method using acetone, ethanol and water as a solvent system. The release of oridonin from the PLA nanoparticles was in a biphasic way, which could be expressed well by the Higuchi equation. When these

formulations of nanoparticles injected, could obtain prolonged circulation time and accumulate in liver, spleen and lung.

Benzoic acid agglomerates has prepared by (Katta *et al.*, 2008) by ESD method using ethanol - chloroform - water as a solvent system. Prepared spherical agglomerates appear in the larger size fractions. The agglomerate size increases with increasing initial solute concentration and increasing agitation rate up to a certain level, but there is no significant influence found on the mechanical properties. A higher fraction of spherical agglomerates is obtained when the bridging liquid is initially mixed into the feed solution, instead of being added to the agitated solution afterwards.

Mebendazole agglomerates has prepared by (Kumar *et al.*, 2008[a]) by SA method using Dimethylformamide (DMF), water and hexane, octanol, or toluene as a solvent system. These agglomerates of Mebendazole exhibited good flow properties, high bulk density and improved compressibility. These agglomerates also showed improved dissolution compared to Mebendazole, however the crystals from Eudragit had a poor drug release because of its pH dependent release property, which failed to release in acidic medium. Such technique can successfully be employed to generate ready - to - formulate API, thus saving on time and effort at the formulator's end.

Mebendazole agglomerates has prepared by (Kumar *et al.*, 2008[b]) by SA method using Dimethylformamide (DMF), water with PVP and sodium lauryl sulphate as a solvent system. It has shown that the presence of additives like PVP and sodium lauryl sulphate shows the impact on crystallization and leading to modified performance. Sodium lauryl sulphate improves the dissolution while PVP gives negative impact on dissolution process.

Indomethacin nanocrystals has prepared by (Makhlof *et al.*, 2008) by ESD method using ethanol and water with β-cyclodextrin as a solvent system. The prepared Indomethacin nanocrystals showed a uniform particle size distribution with an average diameter in the range of 300–500 nm. Compared to the commercial drug powder, fast and complete dissolution of Indomethacin was achieved as a result of particle size reduction to the nano - order and polymorphic change to a meta-stable form.

Aceclofenac agglomerates has prepared by (Mutalik et al., 2008) by SA method using chitosan in 1% glacial acetic acid, water or sodium

citrate solution as a solvent system. Aceclofenac-chitosan crystals have shown enhancement in aqueous solubility and dissolution rate. The prepared crystals also exhibited exceptional stability and better *in-vivo* performance in comparison with pure drug.

Naproxen agglomerates has prepared by (Nokhodchi *et al.*, 2008) by SA method using acetone–water containing polymer as a solvent system. The study showed the formation of products with good flow and packing properties. The improved compaction properties of the agglomerated crystals were due to their fragmentation occurred during compression. The dissolution rate of naproxen from tablets made of naproxen–(Ac–Di–Sol) agglomerates was enhanced significantly because of including the disintegrant in to the particles. This was attributed to an increase in the surface area of the practically water insoluble drug when exposed to the dissolution medium.

Aceclofenac agglomerates has prepared by (Usha *et al.,* 2008) by ESD method using acetone: dichloromethane (DCM): water with hydroxy propyl methyl cellulose as a solvent system. The dissolution rate of prepared tablets of agglomerates was better than that of marketed tablet and pure drug. The optimized agglomerates and tablet formulations were found to be stable for 6 months under accelerated conditions. The results of preclinical studies revealed that the agglomerates provided improved pharmacodynamic and pharmacokinetic profiles of drug besides being nontoxic. The results of pharmacokinetic studies of optimized tablet in human subjects indicated improved pharmacokinetic parameters of drug in comparison with that of marketed tablet.

Gliclazid agglomerates has prepared by (Varshosaz *et al.*, 2008) by ESD method using Acetone-Water as solvent system. Higher dissolution rate of agglomerates were observed as compared to untreated sample. Changing the concentration of drug and stabilizing agent changed the size of crystals. However, dissolution efficiency was more affected by drug concentration and stabilizing agent type.

Ciprofloxacin agglomerates has prepared by (Hong Zhao *et al.*, 2009) by NT method using 0.1N HCl as internal phase and NaOH as external phase. Ciprofloxacin dry powder can form uniform spherical particles with diameter of 3-4 μm and exhibited great improved aerosol performance. Spherical aggregates with ultrafine primary ciprofloxacin particles can be obtained and exhibited great improved aerosol performance with fine particle fraction (FPF) up to 60%.

Mefenamic acid agglomerates has prepared by (Kulkarni *et al.*, 2011) by ADM method using ammonia water, acetone and dichloromethane as a solvent system. The spherical crystals demonstrated good flowability and compressibility and had more wettability than the drug powder. The tablets prepared from the spherical crystals had greater mechanical strength and lower flowability than tablet made from Mefenamic acid powder.

1.5 Methods of Spherical Crystallization

The spherical crystallization or particle spherical agglomeration method employs three solvents first is substance dissolution medium, second is partially dissolution medium for the substance and third one is immiscible with the substance (Paradkar et al., 1994).

Spherical crystallization is a solvent exchange crystallization method in which crystal agglomeration is purposely induced through the addition of third solvent known as bridging liquid. Crystal agglomeration, which is usually avoided during normal processing, is performed in a controlled fashion during spherical crystallization to bring about improved flow and compaction properties of the material (Paradkar et al., 1994). These properties are highly advantageous for pharmaceutical production. Currently optimization of spherical crystallization is difficult as the mechanism and effect of process parameters are unclear. In process monitoring of the chord length distribution (CLD) to track the rate and degree of change in particle dimension and particle count can provide insight into the dynamics of spherical crystallization. The main requirement in spherical crystallization system is that, it should require a small amount of bridging liquid. The proportion of bridging liquid in the given system can be determined by plotting a ternary or solubility diagram of the bridging liquid in the given system. Following are the methods to prepare the spherical crystals:

1. Spherical Agglomeration Method (SA)
2. Emulsion Solvent Diffusion method (ESD)
3. Ammonia diffusion system (ADS)
4. Neutralization Technique (NT).
5. Traditional crystallization process (TCP).

1.5.1 Spherical Agglomeration Method (SA)

In the spherical agglomeration method a near saturated solution of the drug in the good solvent is poured into the poor solvent. Provided that the poor and good solvents are freely miscible and the affinity between the solvents is stronger than the affinity between the drug and the good solvent, crystals will precipitate immediately. Under agitation, the bridging liquid (the wetting agent) is added (Kawashima, 1994[a]). The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid act to adhere the crystals to one another (Kawashima et al., 1984[b]). The SA method has been applied to several drugs and it has been found that the product properties are quite sensitive to the amount of the bridging liquid. Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles (Bausch et al., 1994). Also the choice of bridging liquid, the stirring speed and the concentration of solids (or of the solute) are of importance. The viscosity of the continuous phase has an effect on the size distribution of the agglomerates. The choice of bridging liquid has an influence on the rate of agglomeration and on the strength of the agglomerates.

1.5.2 Emulsion Solvent Diffusion (ESD)

In the emulsion solvent diffusion the affinity between the drug and the good solvent is stronger than that of the good solvent and the poor solvent. The drug is dissolved in the good solvent and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets. The method is considered to be simpler than the SA method, but it can be difficult to find a suitable additive to keep the system emulsified and to improve the diffusion of the poor solute into the dispersed phase (Sano et al., 1992).

1.5.3 Ammonia Diffusion Method (ADM)

In this method, the mixture of three partially immiscible solvent i.e., acetone, ammonia water, dichloromethane was used as a crystallization system. In this system ammonia water acted as bridging liquid as well as good solvent, Acetone was the water miscible but a poor solvent, thus Drug precipitated by solvent change without forming ammonium salt. Water immiscible solvent such as hydrocarbons or halogenated

hydrocarbons e.g., dichloromethane induced liberation of ammonia water (Kawashima et al., 1995).

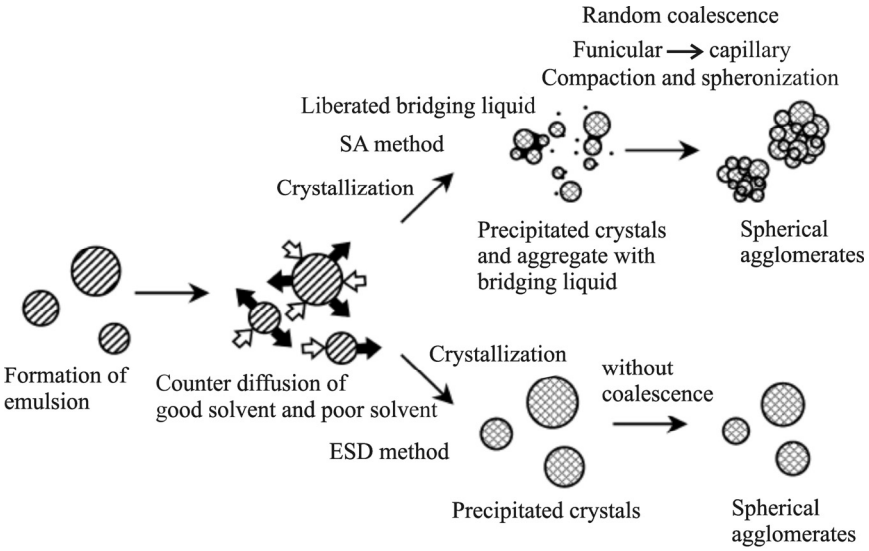


Fig. 1.1 Mechanism of formation of spherical agglomerates by spherical agglomeration (SA) and emulsion solvent diffusion (ESD) method.

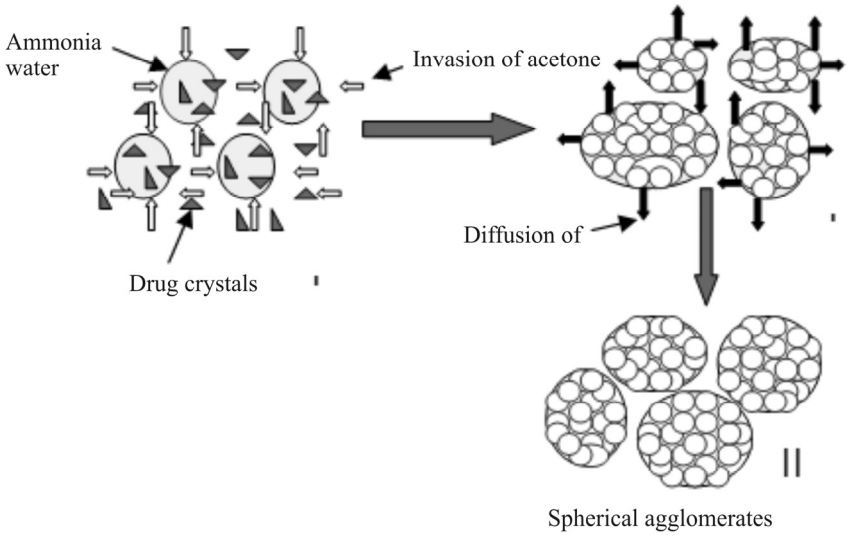


Fig. 1.2 Mechanism of formation of spherical agglomerates by ammonia diffusion method (ADM).

1.5.4 Neutralization Method (NT)

This process involves the formation of fine crystals and their agglomeration. The spherical crystallization of antidiabetic drug tolbutamide was reported by this technique. The drug was dissolved in sodium hydroxide solution. Aqueous solution of Hydroxypropyl methylcellulose and hydrochloric acid was added to neutralize sodium hydroxide solution of tolbutamide and the tolbutamide was crystallized out. The bridging liquid was added drop wise at a rate of 10 ml/min followed by agglomeration of the tolbutamide crystals.

The agglomerates of tolbutamide prepared by neutralization technique were found to have more specific surface area, more wettability and hence better dissolution rate as compared to the agglomerates prepared by emulsion solvent diffusion method and solvent change method. The agglomerates prepared by the neutralization method were instantaneously permeated with water showing strikingly greater wettability. The reason for this superior wettability of agglomerated crystals and tablet is due to fact that, at the time of agglomeration process, hydrophilic Hydroxy-propyl methylcellulose in the crystallization solvent adheres firmly to the agglomerated crystals (Chouracia et al., 2004).

1.5.5 Traditional Crystallization Process (TCP)

These methods also can be used to produce spherical crystal agglomerates, which are carried out by controlling the physical and chemical properties and can be called the non-typical spherical crystallization process (Chouracia et al., 2004). These are

- Salting out precipitation.
- Cooling crystallization.
- Crystallization from the melting.

1.6 The Principle Steps Involved in the Process of Spherical Crystallization

Bermer and Zuider Wag proposed four steps in the growth of agglomeration (Chouracia et al., 2004).

1.6.1 Flocculation Zone

In this zone, the bridging liquid displaces the liquid from the surface of the crystals and these crystals are brought in close proximity by agitation; the adsorbed bridging liquid links the particles by forming a lens bridge

between them. In these zones, loose open flocs of particles are formed by pendular bridges.

1.6.2 Zero Growth Zone

Loose flocs get transferred into tightly packed pellets, during which the entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocs causing poor space in the pellet of completely filled with the bridging liquid. The driving force for the transformation is provided by the agitation of the slurry causing liquid turbulence, pellet-pellet and pellet-stirrer collision.

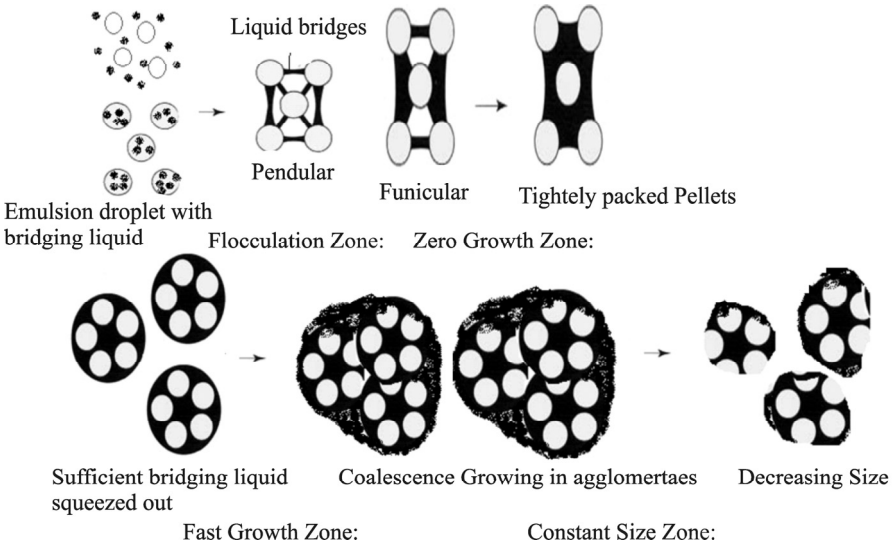


Fig. 1.3 Steps involved in the mechanism of spherical crystallization.

1.6.3 Fast Growth Zone

The fast growth zone of the agglomerates takes place when sufficient bridging liquid has squeezed out of the surface on the small agglomerates. This formation of large particles following random collision of well-formed nucleus is known as coalescence. Successful collision occurs only if the nucleus has slight excess surface moisture. This imparts plasticity on the nucleus and enhances particle deformations and subsequent coalescence. Another reason for the growth of agglomerates size is attributed to growth mechanisms that describe the successive addition of material on already formed nuclei.

1.6.4 Constant Size Zone

In this zone agglomerates cease to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomeration. The size reduction may be due to attrition, breakage and shatter. The rate determining step in agglomeration growth occurs in zero growth zones when bridging liquid is squeezed out of the pores as the initial flocs are transformed into small agglomerates. The rate determining step is the collision of particle with the bridging liquid droplets prior to the formation of liquid bridges. The rate is governed by the rate of agitation. The strength of the agglomerates is determined by interfacial tension between the bridging liquid and the continuous liquid phase, contact angle and the ratio of the volumes of the bridging liquid and solid particles.

1.7 Factors Controlling the Process of Agglomeration (Kulkarni et al., 2002)

1.7.1 Solubility Profile

The selection of solvent is dictated by solubility characteristic of drug. A mutually immiscible three solvent system consisting of a poor solvent (suspending liquid), good solvent and bridging liquid are necessary. Physical form of product i.e. whether micro-agglomerate or irregular macro-agglomerates or a paste of drug substance can be controlled by selection of proper solvent proportions. The proportion of solvent to be used is determined by carrying out solubility studies and constructing triangular phase diagram to define the region of mutual immiscibility by using Ternary diagram.

1.7.2 Mode and Intensity of Agitation

High speed agitation is necessary to disperse the bridging liquid throughout the system. Any change in agitation pattern or fluid flow would be reflected as change in force acting on agglomerate, which ultimately affects the shape of agglomerate. The extent of mechanical agitation in conjugation with the amount of bridging liquid determines the rate of formation of agglomerate and their final size. At increasing stirring rate the agglomeration was reduced because of increasing disruptive forces (Bos et al., 1987). Higher stirring rate produce agglomerates that are less porous and more resistant to mechanical stress, and the porosity decreases when the concentration of solid increases (Blandin et al., 2003).

1.7.3 Temperature of the System

Study revealed that the temperature has a significant influence on the shape, size and texture of the agglomerates. The effect of temperature on spherical crystallization is probably due to the effect of temperature on the solubility of drug substance in the ternary system.

1.7.4 Residence Time

The time for which agglomerates remain suspended in reaction mixture affect their size shape and strength. Optimum residence time for the agglomeration of recrystallized crystals was required. Below the optimized residence time the incomplete agglomeration occurs due to incomplete diffusion of good solvent and bridging liquid from the formed droplets in the dispersion medium. At longer residence time the formed agglomerates were break down and the size of the agglomerated particles decreases. This might be due to the solubilization of the agglomerates by the bridging liquid that diffuses out from them.

1.8 Applications of Spherical Crystallization in Solubility Enhancement In Pharmaceuticals

Spherical crystallization has been described as a very effective technique in improving the solubility and dissolution behavior of drugs having low water solubility and a slow dissolution profile. Various drugs whose solubility is improved by spherical crystallization method were listed in Table 1.3.

Table 1.3 List of drugs on which various spherical agglomeration techniques have been tried for improving solubility.

Sr. No.	Drug	Method	Reference
1	Aceclofenac	SA	Patil et al., 2012
2	Fenbufen	SA	Martino et al.,1999
3	Flurbiprofen	SA	Chourasia et al., 2003
4	Tranilast	SA	Kawashima et al., 1992
5	Mefenamic Acid	SA	Viswanathan et al., 2006
6	Nabumetone	SA	Viswanathan et al., 2006
7	Tolbutamide	SA	Sano et al., 1992
8	Carvedilol	ESD	Tapas et al., 2012
9	Simvastatin	SA	Varshosaz et al., 2011
10	Etoricoxib	ESD	Dash et al., 2011
11	Loperamide hydrochloride	ESD	Bagmar et al., 2013
12	Naproxen	ESD	Saritha et al., 2012.

1.9 Case Study

The surface area of drug available for dissolution is dependent on its particle size and ability to be wetted by luminal fluids. This particle size, which is critical to drug dissolution rate, is dependent on the conditions of crystallization or on methods of comminution such as impact milling and fluid energy milling. The comminution techniques can produce particles which are highly heterogeneous, charged and cohesive, with the potential to cause problems in downstream processing and product performance. Spherical crystallization technique is developed for the controlled crystallization of drugs to produce high purity powders with well-defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature and surface energy (Savjani et al., 2012). By manipulating the processing conditions (use of different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangement.

For example, in the study of Pioglitazone Hydrochloride (PGH) and Glibenclamide (GLM) Spherical Agglomerates it has been observed the drastic improvement in the solubility by spherical crystallization with and without selected additives. (Patil et al., 2011 and Patil et al., 2012 respectively)

The agglomerates of the drug were prepared by ESD method as given below:

PGH / GLM (10 g) was dissolved in a mixture of 60 ml methanol (good solvent) and 40 mL chloroform (bridging liquid). The resultant solution was poured in to 500 mL of distilled water (poor solvent) containing 1% / 2% / 3% w/v of PEG/PVP/β-CD/EU/GG/XG with stirring at 800 revolutions per minute (rpm) for 20 min at 25°C. The obtained recrystallized agglomerates were collected by vaccum filtration and dried in an oven at 60° C for 4 h. The dried crystals were stored in a dessicator at room temperature before use. Above process was repeated more than 10 times to obtain adequate materials for characterization and to observe repeatability. Formulation codes with proportion of polymers used for spherical agglomeration of PGH and GLM are as given in table 3 (a) and 3 (b) respectively.

Table 1.4 (a) Formulation codes with proportion of the polymers used for spherical agglomeration / tablets of PGH.

Sr. No.	Formulation Code	Polymers used (%)					
		PEG	β-CD	EU	GG	XH	PVP
1	PP	-	-	-	-	-	-
2	PA1	1	-	-	-	-	-
3	PA2	-	1	-	-	-	-
4	PA3	-	-	1	-	-	-
5	PA4	-	-	-	1	-	-
6	PA5	-	-	-	-	1	-
7	PA6	-	-	-	-	-	1
8	PB1	2	-	-	-	-	-
9	PB2	-	2	-	-	-	-
10	PB3	-	-	2	-	-	-
11	PB4	-	-	-	2	-	-
12	PB5	-	-	-	-	2	-
13	PB6	-	-	-	-	-	2
14	PC1	3	-	-	-	-	-
15	PC2	-	3	-	-	-	-
16	PC3	-	-	3	-	-	-
17	PC4	-	-	-	3	-	-
18	PC5	-	-	-	-	3	-
19	PC6	-	-	-	-	-	3

FC: Formulation codes

Table 1.4 (b) Formulation codes with proportion of the polymers used for spherical agglomeration / tablets of GLM.

Sr. No.	Formulation Code	Polymers used (%)					
		PEG	β-CD	EU	GG	XH	PVP
1	GP	-	-	-	-	-	-
2	GA1	1	-	-	-	-	-
3	GA2	-	1	-	-	-	-
4	GA3	-	-	1	-	-	-
5	GA4	-	-	-	1	-	-
6	GA5	-	-	-	-	1	-
7	GA6	-	-	-	-	-	1

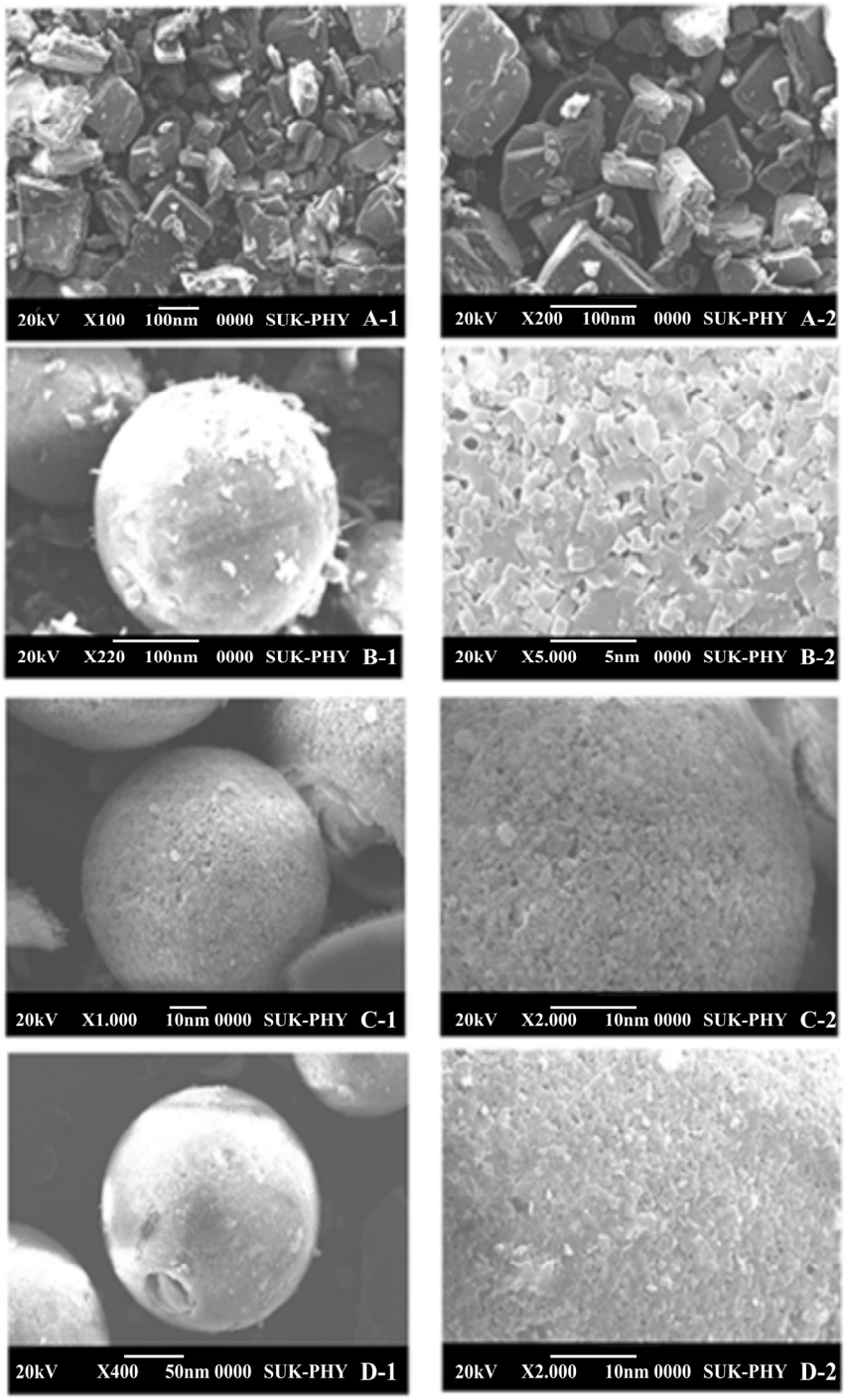
Table 1.4(b) *Contd…*

Sr. No.	Formulation Code	Polymers used (%)					
		PEG	β-CD	EU	GG	XH	PVP
8	GB1	2	-	-	-	-	-
9	GB2	-	2	-	-	-	-
10	GB3	-	-	2	-	-	-
11	GB4	-	-	-	2	-	-
12	GB5	-	-	-	-	2	-
13	GB6	-	-	-	-	-	2
14	GC1	3	-	-	-	-	-
15	GC2	-	3	-	-	-	-
16	GC3	-	-	3	-	-	-
17	GC4	-	-	-	3	-	-
18	GC5	-	-	-	-	3	-
19	GC6	-	-	-	-	-	3

FC: Formulation codes

The agglomeretes prepared were spherical as shown in figure 4 and 5. Solubility of raw crystals and spherical agglomerates of PGH were determined in distilled water and in pH 2 KCl buffer while solubility of raw crystals and spherical agglomerates of GLM were determined in distilled water and in pH 8 phosphate buffer. Excess amount of sample were added in 20 mL solvent and were continuously shaken (300 rpm) at 25 ± 0.5°C for 48 h and sonicated using sonicator for 2 h. Samples were filtered through 0.45 μm filters and concentration of drug was determined spectrophotometrically at 269 nm for PGH and 239 nm for GLM on UV-Visible spectrophotometer.

Solubility study of PGH and GLM are as given in table 4. Solubility of spherical agglomerates was significantly increased than raw crystals of PGH and GLM may be due to improved porosity, decreased primary particle size and polymorphic transition of drug in agglomerates as demonstrated by DSC and XRD studies. It was higher for agglomerates with β-CD and lower for agglomerates with PVP might be due the reason that hardly any agglomeration had occurred with PVP. No significant difference was observed for all parameters of the agglomerates with different concentrations of polymers. Thus stable spherical crystals of PGH and GLM were successfully prepared by emulsion solvent diffusion method. Solubility was dramatically improved for plane agglomerates and agglomerates with additives might be due to improved wettability.


20kV X100 100nm 0000 SUK-PHY A-1
20kV X200 100nm 0000 SUK-PHY A-2
20kV X220 100nm 0000 SUK-PHY B-1
20kV X5.000 5nm 0000 SUK-PHY B-2
20kV X1.000 10nm 0000 SUK-PHY C-1
20kV X2.000 10nm 0000 SUK-PHY C-2
20kV X400 50nm 0000 SUK-PHY D-1
20kV X2.000 10nm 0000 SUK-PHY D-2

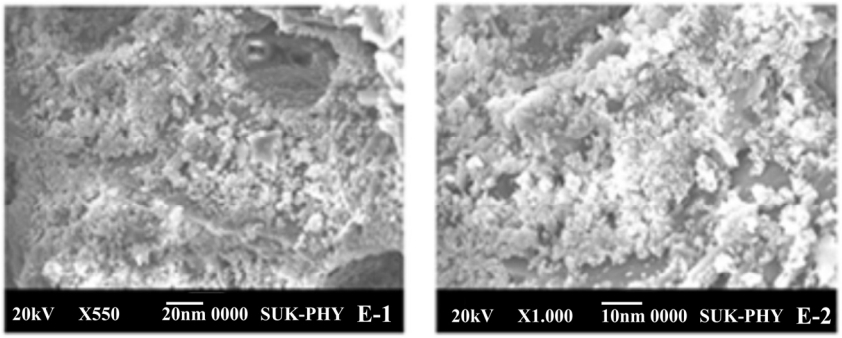
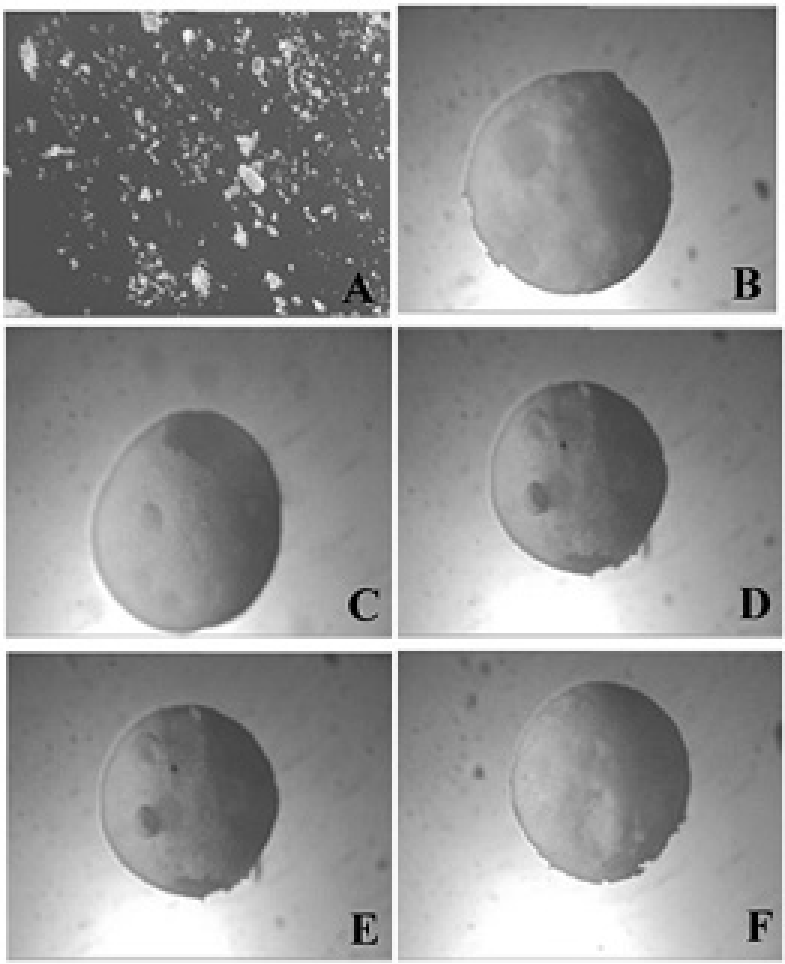


Fig. 1.4 SEM microphotographs of A-1, A-2: PGH, B-1, B-2: PP, C-1, C-2: PC1, D-1, D-2: PC2, E-1: E-2: PC3.



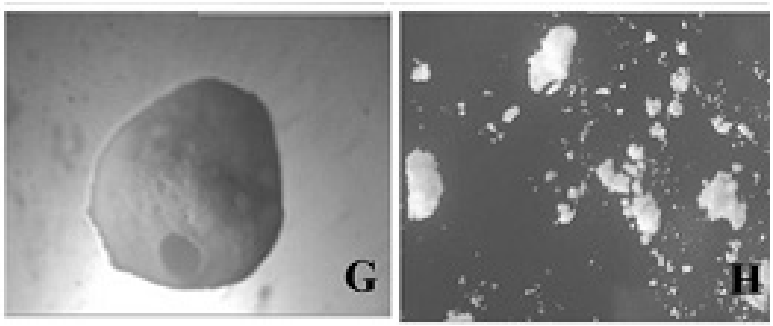


Fig. 1.5 Microphotographs of GLM (A) and its Spherical agglomerates; B: GP, C: GC1, D: GC2, E: GC3, EF: GC4, G: GC5, H: GC6

Table 1.5 Solubility study of PGH and GLM spherical agglomerates.

FC	Solubility (µg/ml)		FC	Solubility (µg/ml)	
	Water	pH 2 KB		Water	P. B. pH 8
PGH	30.86 ± 1.2	109.05 ± 2.3	GLM	22.76 ± 1.2	98.34 ± 2.3
PP	76.50 ± 1.6 **	227.84 ± 3.1 **	GP	74.56 ± 1.6 ***	212.32 ± 3.1 ***
PA1	81.27 ± 2.5 **	258.27 ± 1.8 **	GA1	82.24 ± 2.5 ***	238.81 ± 3.3 ***
PA2	98.06 ± 1.8 **	396.96 ± 4.3 **	GA2	93.24 ± 1.8 ***	398.76 ± 4.3 ***
PA3	82.97 ± 2.1 **	268.27 ± 2.1 **	GA3	84.12 ± 2.1 ***	243.61 ± 2.1 ***
PA4	78.97 ± 1.1 **	248.13 ± 3.2 **	GA4	84.76 ± 1.1 ***	248.13 ± 3.2 ***
PA5	68.97 ± 2.2 **	238.31 ± 2.6 **	GA5	73.84 ± 2.2 ***	222.32 ± 3.6 ***
PA6	71.97 ± 1.9 **	255.37 ± 2.9 **	GA6	49.32 ± 1.4 ***	137.78 ± 1.9 ***
PB1	78.65 ± 2.1 **	136.21 ± 1.4 *	GB1	22.76 ± 1.2 ***	238.34 ± 2.6 ***
PB2	91.57 ± 1.7 **	412.56 ± 3.1 **	GB2	102.56 ± 1.6 ***	412.39 ± 3.8 ***
PB3	89.65 ± 2.0 **	368.27 ± 2.7 **	GB3	104.12 ± 2.7 ***	243.61 ± 2.4 ***
PB4	84.16 ± 1.6 **	308.36 ± 2.3 **	GB4	93.24 ± 1.6 ***	398.36 ± 3.3 ***
PB5	84.17 ± 1.1 **	248.13 ± 3.0 **	GB5	84.76 ± 1.1 ***	241.13 ± 3.2 ***
PB6	78.47 ± 1.2 **	158.41 ± 1.6 **	GB6	53.59 ± 2.3 ***	212.32 ± 1.6 ***
PC1	81.37 ± 1.9 **	268.77 ± 3.2 **	GC1	99.36 ± 1.8 ***	307.18 ± 1.9 ***
PC2	96.45 ± 1.4 *	455.22 ± 1.4 *	GC2	122.76 ± 1.2	498.34 ± 2.2
PC3	91.48 ± 1.6 **	247.54 ± 3.7 **	GC3	164.26 ± 1.6 ***	292.32 ± 3.7 ***
PC4	88.17 ± 2.1 **	368.07 ± 2.4 **	GC4	197.22 ± 2.1 ***	401.31 ± 2.1 ***
PC5	89.32 ± 1.9 **	408.96 ± 1.3 **	GC5	123.44 ± 1.8 ***	298.71 ± 4.1 ***
PC6	80.23 ± 2.1 **	211.43 ± 3.8 **	GC6	84.76 ± 1.1 ***	248.13 ± 2.2 ***

KB: Potassium Chloride Buffer, P.B.: Phosphate Buffer pH 8.
Significantly different from the value for raw crystals of PGH at $p < 0.001$ (***), $p < 0.01$ (**) and $p < 0.05$ (*).

1.10 Conclusion

The major focus in formulation and development is on solubility enhancement of poor bioavailability specifically for Class II drugs as it can directly be correlated with achieving required pharmacological response as it is rate determining step for bioavailability of Class II drugs. Different methods are available for solubility improvement but Spherical crystallization is suitable method from pharmaceutical view point. Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs along with solubility. Spherical crystallization has been described as a very effective technique in improving the solubility and dissolution behavior of drugs having low water solubility and a slow dissolution profile. The use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable. The various parameters optimized were type, amount and mode of addition of bridging liquid, temperature and agitation speed to get maximum amount of spherical crystals. From the case study and the available references it can be concluded that spherical crystallization is one of the effective technique to improve solubility consequently dissolution rate and bioavailability may leads to reduction of dose of a drug which is advantageous for cost effectiveness and better patient compliance.

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