2. LITERATURE REVIEW

1. *Agrawal G. P. et al., 2004*, prepared spherical crystals of mefenamic acid (MA) using ammonia diffusion method which involved the use of 25% strong ammonia solution and acetone, chloroform was added with stirring using a three blade agitator in a cylindrical vessel. The physical properties of the spherical crystals like Particle size, Surface area, True density, Bulk density, Angle of repose, Density, Surface tension, Aqueous solubility were compared with those of MA powder. The developed crystals demonstrated good flow and compressibility and had more wettability than the drag powder. The tablets prepared from the spherical crystals had greater mechanical strength and lower friability than tablets made from MA powder.

2. *Chourasia M. K. et al., 2003*, developed spherical crystal agglomerates of Flurbiprofen by spherical crystallization technique using acetone-water-hexane solvent system. The optimization of type, amount and mode of addition of bridging liquid, temperature, and agitation speed was carried out to get maximum amount of spherical crystals. These were characterized for micromeritic properties (particle size and shape, flowability), packability (bulk d.), wettability (contact angle) and compressibility. It was revealed from the study that spherical agglomerates exhibited improved flowability, wettability and compaction behavior.

3. *Di Martino P. et al., 1999* developed & improved dissolution behavior of fenbufen by Different spherical crystallization processes. The solvents and nonsolvents ratios for Fenbufen were selected and iso-Propyl acetate was used as bridging liquid. The results from this method were reproducible batch to batch. The spherical crystals obtained showed a clear improvement in dissolution capacity, probably due to better wettability. Dissolution studies were then carried out on these spherical crystals stored for 1 month at different relative humidities (RHs), the dissolution profiles remained unchanged.

4. *Garekani H. et al., 2000*, studied the effect of polyvinylpyrrolidone (PVP) as an additive during crystallization of paracetamol, significantly influenced the crystallization and crystal habit of paracetamol, due to adsorption of PVP onto the surfaces of growing crystals. From results concluded that the higher molecular weights of PVP (PVP 10000 and PVP 50000) were more effective additives than lower molecular weight PVP (PVP 2000). Paracetamol particles obtained in the presence of 0.5% w/v of PVP 10000 or PVP
50000 had near spherical structure. Particles obtained in the presence of PVP 2000 consisted of fewer microcrystals. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XPD) experiments showed not any structural modification.

5. Gupta V. R. et al., 2007, prepared spherical agglomerates of Celecoxib with polyvinylpyrrollidone (PVP) using acetone, water and chloroform as solvent, non-solvent and bridging liquid, respectively. The results form IR spectroscopy and DSC results indicated the absence of any interactions between drug and additives, XRD studies showed a decrease in crystallinity in agglomerates and, The SEM studies showed that the crystal possesses a good spherical shape with smooth and regular surface. Also, crystals exhibited significantly improved micromeritic properties compared to pure drug. From study it could be concluded that the solubility and in vitro drug release rates increased with an increase in PVP concentration (from 2.5 to 10%).

6. Kawashima Y. et al., 2001, prepared ascorbic acid spherically agglomerated crystals by the spherical crystallization technique. This agglomeration dramatically improved the micromeritic and compaction properties of the original ascorbic acid crystals depended on their fragmentation and plastic deformation during compaction. Support for this mechanism existed because the compacted agglomerated crystals had higher stress relaxation and lower elastic recovery than the original crystals. Spherically agglomerated crystals were tabletted directly without capping by using a single-punch tableting machine under dynamic compaction, although the tensile strength of tablets with spherically agglomerated crystals decreased when the compression speed increased.

7. Kawashima Y. et al., 2003, improved compactibility of ascorbic acid for direct tableting. The ascorbic acid crystals were precipitated by a solvent change method, followed by their agglomerations with the emulsion solvent diffusion (ESD) or spherical agglomeration (SA) mechanism. The micromeritic properties, such as flowability and packability of the spherically agglomerated crystals were preferably improved for direct tableting. The acceptable compact (tablet) with a sufficient strength was produced successfully without capping, although the capping occurred with the original unagglomerated crystals due to their fragmentation and plastic deformation occurred significantly during compression and, this mechanism was supported by higher stress relaxation and less elastic recovery of the compact of agglomerated crystals.
8. **Kawashima Y., et al., 1995**, studied the parameters determining the agglomeration behavior and micromeritic properties of spherically agglomerated crystals of acebutolol hydrochloride prepared by the spherical crystallization technique with a two or three miscible solvent system (i.e., bridging liquid, good solvent, poor solvent). They observed that decreasing amount of water (bridging liquid) in the three-solvent system, the median diameter of agglomerated crystals increased, having a wider size distribution. The median diameter of agglomerates decreased with increasing content of ethanol (good solvent) in the formulation. Spherically agglomerated crystals were produced evenly with the two-solvent system, i.e., water and iso-Propyl acetate (poor solvent), in which the water played both the roles of bridging liquid and good solvent. The median diameter of agglomerates decreased with increasing agitation speed of the system.

9. **Kumar S. et al., 2008**, studied spherical crystallization technique in which crystallization and agglomeration were combined. Spherical agglomeration of Mebendazole (MBZ) was carried out using N, N-Dimethylformamide (DMF), and water as a good and bad solvents respectively, in the presence of different bridging liquids (hexane, octanol, toluene, dichloromethane) and polymers (polyethylene glycol, Crospovidone, starch, Croscarmellose sodium, hydroxylpropyl Methyl cellulose, hydroxylpropyl cellulose (HPC), Ethyl cellulose, Eudragit S100, Eudragit RLPO, Eudragit RD100, Eudragit E), by employing different crystallization conditions such as variation of polymer type, polymer concentration, and rate of stirring. The results of evaluation study revealed that these agglomerates of MBZ exhibited good flow properties, high bulk densities and improved compressibility. Lower elastic:plastic energy (EE/PE) ratio for spherical crystals generated in the presence of Eudragit S100 and HPC indicated better compressibility of spherical crystals.

10. **Malamataris S. et al., 1998**, prepared spherical agglomeration of ibuprofen in the presence of Eudragit® S100 using the solvent-change (ethanol–water) method and applying different crystallization conditions. The results showed crystal yield and drug loading efficiency were not affected by the crystallization conditions, while the mean ‘apparent crystal growth’ rate increases with initial supersaturation ratio and stirring rate; however, the cooling effect is stirring dependent, probably due to changes in the nucleation mechanism. The particle size of agglomerates decreases, while sphericity, surface roughness and intraparticle porosity increase with polymer presence. Also, particle size and sphericity decrease. The effects of Eudragit® on the particle properties
are attributed to the habit and growth rate changes of ibuprofen microcrystals, as well as
to their coating before binding into spherical agglomerates. The size and sphericity
changes due to stirring and cooling are attributed to the polymer binding ability and to
detachment of small fragments from the agglomerate surface.

11. Morishima K. et al., 1994, prepared bucillamine agglomerates by two spherical
crystallization techniques, a spherically agglomeration method and an emulsion solvent
diffusion method. The flow and packing properties of agglomerates were much improved
by this technique compared with those of conventional crystals due to the spherical shape
and smooth surface. Furthermore, spherical agglomerates possessed superior strength
characteristics obtained by the emulsion solvent diffusion method were compressed into
compacts having considerable hardness without capping at high compaction pressure.
The excellent compactibility of agglomerates was attributed to the fragmentation
property and a greater degree of plastic deformation under compression. From the results
it could be concluded that agglomerates made by two methods have quite difference
micromeritic properties due to difference in the distribution of crystal binding point
within the agglomerates.

12. Muatlik S. et al., 2007, enhanced the micromeritic properties, solubility, dissolution rate,
micromeritic properties and bioavailability of Aceclofenac by spherical agglomeration
technique. Acetone-water-dichloromethane was used as a solvent system and polymers
such as water soluble polymers like PVP K30, PVP K90 and sodium alginate were used.
The agglomerates were spherical in structure and formed by cluster of small crystals as
explained by SEM studies. Among other polymers used PVP K90 exhibited improved
solubility, dissolution rate and micromeritic properties of prepared agglomerates. The
preclinical studies showed that optimized agglomerates showed rapid analgesic and anti-
inflammatory activity besides exhibiting improved bioavailability of drug when
compared to pure drug.

technique using a three solvent system comprising acetone: dichloromethane (DCM):
water (bridging liquid, good solvent and bad solvent, respectively). Hydroxypropyl
methylcellulose-50cps (HPMC) in different concentrations was used as hydrophilic
polymer. The effect of speed of rotation and amount of bridging liquid on spherical
agglomeration were studied. The results of various physicochemical evaluations such as
practical yield, drug content, particle size, loss on drying, porosity, IR spectroscopy, differential scanning calorimetry, X-ray diffraction studies, relative crystallinity, scanning electron microscopy, micromeritic properties, solubility and dissolution studies of agglomerates showed improved micromeritic properties as well as dissolution behavior. The optimized agglomerates compressed into tablets by direct compression, having better dissolution rate than that of marketed tablet and pure drug. The 6 months accelerated stability study for agglomerates and tablet formulations were found to be stable. The results of preclinical studies revealed that the agglomerates provided improved pharmacodynamic and pharmacokinetic profiles of drug besides being nontoxic.

14. Nokhodchi A. et al., 2004, studied the influence on dissolution and mechanical behaviour of Carbamazepine recrystallized from ethanol in the presence of various additives. SEMs of untreated and treated carbamazepine crystals showed that the crystal shape of untreated carbamazepine was flaky or thin plate-like, whereas the crystals obtained from alcohol containing no additive, PEG 4000, PVP K30 or Tween 80 were polyhedral prismatic, block-shaped, polyhedral or hexagonal, respectively. The results showed that the higher dissolution rate and compact strength were observed for the crystals obtained in the presence of PVP K30.

15. Paradkar A. R. at el., 2002, carried out spherical crystallization of Celecoxib using the solvent change method in which acetone and water used as good and bad solvent, respectively and DCM as a bridging liquid. To impart strength and sphericity to the agglomerates Hydroxypropylmethylcellulose (HPMC) was used and effect of amount of bridging liquid and speed of agitation was studied using $3^2$ factorial designs. The effect of variables on micromeritic, mechanical, compressional, and dissolution behavior was evaluated by response surface methodology. were evaluated by The infrared spectroscopy, powder X-ray diffraction, and differential scanning calorimetry was carried out to evaluate primary properties of the agglomerates. From the results it was clear that Particle sizes, bulk density, mean yield pressure (MYP), and drug release were found to be significantly affected by either of the two variables.

16. Piera D. M. et al., 2000, prepared spherical propyphenazone crystals by an agglomeration technique using a three solvents system, propyphenazone solvent (ethyl alcohol), non-solvent (demineralized water) and bridging liquid (isopropyl acetate),
several of their ratios were tested by a Sheffe’ ternary diagram. Micromeritic properties of agglomerates such as flowability and compression behavior were improved compared to that of raw crystals. The compression and densification studies, along with tablet SEM analysis, explained the compression mechanism of propyphenazone spherical crystals and have shown that their better tablettability can be due to the small size of individual particles in the agglomerates.

17. Ribardiere A. et al., 1996 prepared ketoprofen agglomerates with a two-solvent system (acetone/demineralized water). The modification of particle texture of formulated agglomerates was studied with low concentration of additives, ethylcellulose; cross-linked PVP and cross-linked CMC, all at a concentration of 1% were give results. Formulations with the methacrylic acid derivatives were found to be incompatible with the operating conditions, in terms of temperature changes, stirring or residence time. Also, an optimization of the formulation with ethylcellulose yielded a controlled release form with 1% of the polymer, whereas, very low concentration increased the drug release.

18. Szabo R. P. et al., 2002, studied one of the crystal growth processes was the production of crystal agglomerates by spherical crystallization. In the study agglomerates of drug materials were developed by means of non-typical (magnesium aspartate) and typical (acetylsalicylic acid) spherical crystallization techniques. They determined specific surface and micro pore volumes of samples. The growth of particle size and the spherical form of the agglomerates resulted in formation of products with good bulk density, flow properties, compactibility and cohesivity properties. The results of evaluation parameters showed that developed crystal agglomerates used for direct and tablet-making and capsule-filling without excipients.

19. Ueda M. et al., 1991, studied Agglomerated crystals of enoxacin polymorph (I) by a novel spherical crystallization technique using ammonia diffusion system (ADS). This technique made it possible to agglomerate amphoteric drugs like (I) which could not be agglomerated by the conventional means. This method included an ammonia water solution of (I) was poured into the mixture of acetone and a water-immiscible solvent such as CH₂Cl₂ under agitation, a small amount of ammonia water was released in the system. The ammonia water played a role both as a good solvent for (I) and a bridging liquid, which collected fine crystals precipitated into spherical agglomerates in one step.
The stability of crystal agglomerates depends on selecting the proper solvents. The agglomeration mechanism follows these steps: acetone in the crystallization solvents enters into droplets of ammonia water and consequently (I) dissolved in the ammonia water is precipitated. While the droplets collect the crystals; simultaneously, a part of the ammonia in the agglomerates diffuses to the outer organic solvent phase.

20. **Yadav A. V. et al., 2009**, prepared polymeric carbamazepin spherical crystals by emulsion solvent diffusion technique, with improved solubility, dissolution rate, and physicochemical properties by ethanol–chloroform–water as the solvent system. In the recrystallization process the hydrophilic polymers like polyethylene glycol, chitosan, and hydrophobic polymer Eudragit RSPO were used. The pure drug CBZ and the prepared spherical crystals of CBZ were characterized in terms of morphology (microscopical photograph), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), drug contents, solubility, dissolution rate, crushing strength, wettability, flowability, and packability was by analysis of tapping process with the Kawakita and kuno equation, which was improved significantly. The results showed that spherical crystals with polyethylene glycol and chitosan showed higher crushing strength when compared with the hydrophobic polymer (Eudragit RSPO).

21. **Nokhodchi A. et al., 2008**, prepared directly compressible agglomerates of naproxen containing disintegrant by spherical crystallization technique. Acetone–water containing hydroxypropyl cellulose (HPC) and disintegrant was used as the crystallization system. In this study croscarmellose sodium (Ac–Di–Sol) was employed as disintegrant. The agglomerates were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (XRPD), and scanning electron microscopy and were evaluated for flow, packing and tableting properties and drug release. The growth of particle size and the spherical form of the agglomerates resulted in 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. DSC and XRPD studies showed that naproxen particles. 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.

22. **Julide A. et al., 1991**, prepared Furosemide-loaded ethyl cellulose microspheres by a spherical crystallization technique. The average diameters were about 330-335 pm and
the drug contents in the microspheres were 65-84%. The size and formation of microspheres can be controlled by the rate of agitation. Furthermore, as the concentration of ethyl cellulose increased, the release rate of furosemide decreased. The results are examined kinetically and the mechanism is discussed. Dissolution data indicated that the release followed the Higuchi matrix model. These results show that furosemide-loaded ethyl cellulose microspheres could be prepared providing a controlled release property.

23. Amit R. T. e al., 2010, studied the effect of different polymers on the solubility and dissolution rate of Felodipine (FL) a poorly water soluble antihypertensive, by spherically agglomeration using acetone, water and dichloromethane as good solvent, poor solvent and bridging liquid, respectively. The quasi-emulsion solvent diffusion technique was used as a method for spherical agglomeration. The hydrophilic polymers like polyvinyl pyrrolidone, polyvinyl alcohol, and polyethylene glycol were used in agglomeration process. The DSC results indicated that decrease in melting enthalpy related to disorder in the crystalline content. PXRD studies also showed changes in crystallanity, IR spectroscopy revealed that there were no chemical changes in the recrystallized agglomerates. The spherical agglomerates with different polymers exhibited marked increase in solubility and dissolution rate as compared with FL. The SEM studies showed that the agglomerates posseeses a good spherical shape. The recrystallized agglomerates also exhibited higher micromeritic properties (bulk density, tapped density and angle of repose).

24. Kulkarni P.K. et al., 2010. Prepared Spherical agglomerates of Mefenamic acid by solvent change method. Crystallization medium used for spherical agglomerates of Mefenamic acid consisted of tetrahydrofuran (good solvent); water poor solvent; iso propyl acetate (bridging liquid) in the ratio of 28.6:100:14.3 ml, respectively. Spherical agglomerates were characterized by differential scanning calorimetry, Infrared spectroscopy, X-ray diffractometry and scanning electron microscopy. Micromeritic and dissolution behavior studies were carried out. Process variables such as amount of bridging liquid, stirring time and duration of stirring were optimazed. Dissolution profile of the spherical agglomerates was compared with pure sample and recrystallized sample. Spherical agglomerates exhibited decreased crystallinity and improved micromeritic properties. The dissolution of the spherical agglomerates was improved compared with pure sample.
25. **Kachrimanis K, et al., 2001**, prepared Spherical crystal agglomeration of ibuprofen in the presence of Eudragit® S100 using the solvent-change (ethanol–water) method and applying different crystallisation conditions such as initial supersaturation under both increasing and constant drug-polymer ratios and different rates of stirring and cooling. The particle size of agglomerates decreases, while sphericity, surface roughness and intraparticle porosity increase with polymer presence. Also, particle size and sphericity decrease, while intraparticle porosity increases with initial supersaturation. The effects of Eudragit® addition on the fundamental particle properties are attributed to the habit and growth rate changes of ibuprofen microcrystals, as well as to their coating before binding into spherical agglomerates. The stirring rate effect on particle size is enhanced by slow cooling, and sphericity becomes maximal at slow cooling and fast stirring. The size and sphericity changes due to stirring and cooling are attributed to the polymer binding ability and to detachment of small fragments from the agglomerate surface. Flow or packing behaviour and densification of agglomerates at low compression are determined by the sphericity changes and their yield pressure by the brittleness due to the incorporated polymer.

26. **Gupta M.M. et al., 2010**, Spherical crystallization is the novel agglomerated technique that can directly transform the fine crystals produced in the crystallization process into a spherical shape. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form. This technique of particle design of drugs has emerged as one the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained interest due to the fact that crystal habit can be modified during crystallization process which would result in better micrometric properties like particle size those can enhance the flowability of the powder drug and prepared spherical crystals can be compress directly without performing granulation, drying and so many steps those are require in wet granulation and in dry granulation process of tablet manufacturing.

27. **Vinay K.M. et al., 2010**, studied Glibenclamide spherical crystal agglomerates via the spherical crystallization technique using dichloromethane-water-chloroform solvent system. 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. These were characterized for micromeritic properties (particle size and shape, flow ability), pack ability (bulk density), wet ability (contact angle) and compressibility. It was revealed from the study that spherical agglomerates exhibited improved flow ability, wet ability and compaction behavior.

28. **Kumar S. et al., 2010.** Studied Mefenamic acid spherical agglomeration (SA). The formulations were characterised by differential scanning calorimetry (DSC) and X-Ray powder diffractometry (XRD) and were investigated for drug content studies, solubility studies, in vitro study and in vivo evaluation of anti-inflammatory activity. The formulations of MFA prepared by spherical agglomeration technique have satisfactory good drug content and the formulations with SLS and HPMC show a significant increase in solubility in case of SA technique. In case of solid dispersion, all carriers show improvement in the dissolution rate of the drug. The DSC studies show no change in the polymorphism in most of the formulations The XRD studies of the formulations show no change in their crystalline form. The formulation containing HPMC & SLS as drug carrier show better anti-inflammatory effect with comparison to pure drug confirming the improved bioavailability of this drug.

29. **Achutha N. U. et al. 2008.** Prepared Aceclofenac agglomerates by spherical crystallization technique using a three solvent system comprising acetone: dichloromethane (DCM): water (bridging liquid, good solvent and bad solvent, respectively). Hydroxypropyl methylcellulose-50 cps (HPMC) in different concentrations was used as hydrophilic polymer. The agglomerates were subjected to evaluations such as practical yield, drug content, particle size, loss on drying, porosity, IR spectroscopy, DSC, XRD, relative crystallinity, SEM, micromeritic properties, solubility and dissolution studies. The agglomerates showed improved micromeritic properties as well as dissolution behaviour in comparison to conventional drug crystals. The optimized agglomerates showed good sphericity as well as high drug release, and were compressed into tablets by direct compression. The dissolution rate tablets 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.

30. **Szabo R. P. et al., 2001,** developed Agglomerates of an aspartic acid salt by means of a non-typical spherical crystallization technique. The control material was commercial
aspartic acid salt with very poor flowability and compressibility. The particle sizes of the samples were measured by sieve analysis. The morphology of the crystals and crystal agglomerates was controlled by SEM. The Carr index, rearrangement constant, plasticity and compressibility values were calculated. The crystallization techniques used resulted in spherical agglomerates of the aspartic acid salt with very good flowability and compressibility parameters.