World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

A review on spherical crystallization: A novel technique in the field of particle engineering

J HASIFUL ARABI [1,*], L SUBRAMANIAN [2] and M RAJESH [3]

[1] *Student, Sankaralingam Bhuvaneswari College of Pharmacy, Sivakasi, Virudhunagar district, Tamilnadu – 626001, India.*
[2] *Associate professor, Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy, Sivakasi, Virudhunagar district, Tamilnadu – 626001, India.*
[3] *Professor and Head of the Department, Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy, Sivakasi, Virudhunagar district, Tamilnadu – 626001, India.*

World Journal of Biology Pharmacy and Health Sciences, 2023, 13(01), 078–093

Publication history: Received on 20November 2022; revised on 03January 2023; accepted on 05January 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.13.1.0281

Abstract

In the production of tablets, the direct compression method is mostly used. In comparison to the traditional wet granulation approach, this cannot be used with sensitive pharmaceuticals and also has a lot more processing limitations. Spherical agglomeration is a novel method for creating pharmaceutical dosage forms that are immediately compressible, the process of spherical agglomeration, which improves the powder's qualities such as particle size, shape, flow characteristics, solubility, and bioavailability of pharmaceutical medicinal ingredients, includes transforming tiny crystals into a spherical shape. The spherical crystallization was improved for use with hydrophilic polymers in order to improve the dissolution properties of pharmaceuticals that are poorly water-soluble. The flow characteristics, particle size analysis, compression, and dissolution behaviour of the spherical agglomerates were also improved. Wet spherical agglomeration (WSA) and the quasiemulsion solvent diffusion method (QESD) are the two most used methods for crystallizing spheres. Additionally, these approaches have two additions: the ammonia diffusion system (ADS) and crystallo-coagglomeration (CCA).The neutralization technique is another method used in this procedure. Any of the aforementioned methods can be employed simultaneously for both crystallization and agglomeration. The crystal physical characteristics, including their shape, polymorphism detection using x-ray powder diffraction (XRD), and thermodynamic characteristics using differential scanning calorimetry (DSC), were examined.

Keywords: Spherical crystallization; Spherical agglomeration; Wet spherical agglomeration; Quasiemulsion solvent diffusion method; Ammonia diffusion system; Crystallo-coagglomeration; X-ray powder diffraction; Differential scanning calorimetry

1. Introduction

Tablets are a relatively common dosage form, making up 70% of all pharmaceutical preparations and at least 50% of all oral drug delivery systems. Direct tableting of pharmaceutical ingredients is a spherical technique for making tablets that has been successfully used to make many medications on a large scale. Simple mixing and compression of powders are used in the manufacture of tablets, which has a variety of advantages in terms of time, money, and energy savings. However, a medication needs to have high micromeritic qualities, such as flowability, in order to be compressed directly. However, crystals with needle or plated shapes have very poor flowability and are challenging to work with. In order to achieve the size enlargement of particles during the crystallization step, Kawashima proposed this method in 1974. He suggested managing crystal agglomeration with regulated features. By demonstrating that spherically dense agglomerates could be generated and were suited for direct tableting, he introduced this process into the

*Corresponding author: J HASIFUL ARABI

pharmaceutical production industry and described it as spherical crystallization. They employed silica sand as their model system, distributed in stirred carbon tetrachloride, and subsequently agglomerated with aqueous calcium chloride solutions. Kawashima employed the spherical crystallization technique to increase the size of drug particles over a period of several years beginning in 1986. By using this technique, the precipitated crystals were agglomerated into spherical particles without the use of binders during the final step of synthesis (recrystallization) [1].

This kind of crystallization allows crystals to be formed directly into compacted spheres by combining crystallization and agglomeration in one step.

Because crystal habit (form, surface, and size as well as particle size distribution) can be altered during the crystallization process, this technique for designing drug particles has recently gained significant attention and importance. It is one of the active research areas currently of interest in pharmaceutical manufacturing.Hence spherical crystallization process can be defined as:

A revolutionary particle engineering method that unites agglomeration and crystallization in a single process to convert crystals directly into compacted spherical form OR

An agglomeration procedure for increasing the flowability, solubility, and compactability of crystalline pharmaceuticals by converting them directly into compact spherical forms[2].

The key factors that affect spherical crystallization include the solvents and their composition, the amount of bridging liquid, the agitation rate, the initial particle size, the feeding rate, the stirring rate, the temperature, and the concentration of the solid, among others. These factors affect the productivity as well as the product's strength, shape, and particle size distribution. Earlier research on the effects of the aforementioned characteristics used other materials as model compounds [3].

The spherical crystallization technique, one of many methods for creating microparticles, has drawn increased attention since it creates microparticles with the necessary qualities that can be used as a directly compressible material. To create spherical matrices of pharmaceuticals with sustained release, the spherical crystallization approach can be changed into an easy and less expensive procedure. In order to create microspheres with longer release and increased bioavailability, the spherical crystals of several medicines, including furosemide, ibuprofen and ketoprofen were directly changed during spherical crystallization using acrylic polymers[4].

Figure 1 Scanning electron microraph of spherical agglomerates [5]

The traditional drug manufacturing procedure (granulation) involves the following steps:

Crystallization; filtration; drying; blending of formulated powders; granulation; drying; tableting.

This is a slow and time-consuming process, whereas in spherical crystallization the process could be reduced to:

Crystallization, filtration, drying, dry blending, and tableting[6].

Additionally, several weakly soluble medications, such as celecoxib and fenbufen, are said to have improved detectability, bioavailability, and dissolving rates as a result of this method [7].

The spherical crystallization method also uses a bridging liquid that acts as a granulating fluid to give compressibility [8].

So, the process of spherical crystallization aids in achieving superior flowability and compressibility. In order to alter their release patterns, several medications have also been recrystallized using the spherical agglomeration approach [9]

2. Need for spherical crystallization

It is the approach of choice for low-dose medications that are water soluble and compressible. This procedure alters the drug's crystallization behaviour, which has an impact on a number of morphological, rheological, and technological elements of pharmacological behaviour and, consequently, dosage form bioavailability. A medicinal powder's flowability, packing, compaction, syringability, suspension stability, and dissolving properties can all be affected by the crystal habit of the powder. Some poorly soluble medications benefit from this method's improved wettability, bioavailability, and dissolving rate [10].

2.1. Advantages of spherical crystallization process

- In comparison to other size enlargement methods, this is the simplest.
- There are fewer unit operations required.
- The need for manpower is limited because there are fewer operations.
- Economic
- Proper GMP considerations
- It has been traditionally used for improving flow, compressibility, solubility, and bioavailability.
- This technique could enable subsequent processes such as separation, filtration, drying, etc. to be carried out more efficiently.
- By using this technique, the physicochemical properties of pharmaceutical crystals are improved for pharmaceutical processing, i.e., milling, mixing, and tableting, because of their excellent flowability and packability.
- This technique may convert crystalline forms of a drug into a different polymorphic form with better bioavailability.
- For masking the bitter taste of the drug.
- The preparation of microsponge, microspheres, and nanospheres, as well as nanoparticles and micropellets as novel particulate drug delivery systems [11].

2.2. Disadvantages of spherical crystallization process

- The selection of a solvent is a tedious process.
- It is challenging to maintain process parameters (stirring rate, temperature, and agitation) [11].

3. Principle of spherical crystallization

- This process involves pouring the saturated solution of the drug in a good solvent (in which the drug is soluble) into a poor solvent (in which the drug is slightly soluble).
- A third solvent, called the "bridging liquid," is added in small amounts to promote the formation of agglomerates. Bridging liquid wets the crystal surface, causing binding, and promotes the formation of liquid bridges between drug crystals, allowing spherical agglomerates to form.
- Poor and good solvents should be freely miscible, and the affinity between the solvents must be stronger than the affinity between the drug and the good solvent.
- The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals [12].

3.1. The spherical crystallization process's steps include:

Four steps were suggested by Bermer and Zuider for the growth of an agglomeration.

3.1.1. Flocculation Zone

In this zone, the bridging liquid displaces the liquid from the surface of the crystals, which are brought into 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, and this stage of the agglomeration process, where the ratio of liquid to void volume is low and air is the continuous phase, is known as the pendular state. The mutual attraction of particles is brought about by the surface tension of the liquid and the liquid bridges. The capillary stage is reached when all the void space within the agglomerate is completely filled with liquid. An intermediate state known as the funicular state exists between the pendular and capillary stages. The cohesive strength of agglomerate is attributed to the bonding forces exerted by the pendular bridges and capillary suction pressure [13].

3.1.2. Zero Growth Zone

Loose floccules get transferred into tightly packed pellets, during which the entrapped fluid is squeezed out followed by the squeezing of the bridging liquid onto the surface of small flocs, causing a poor space in the pellet to be completely filled with the bridging liquid. The driving force for the transformation is provided by the agitation of the slurry, which causes liquid turbulence and pellet-pellet and pellet-stirrer collisions [13].

3.1.3. Fast Growth Zone

The fast growth zone of the agglomerates takes place when sufficient bridging liquid has been squeezed out of the surface of the small agglomerates. This formation of large particles following random collisions of well-formed nuclei is known as coalescence. Only if the nucleus has a slight excess of surface moisture does a collision occur. This gives the nucleus plasticity and promotes particle deformation and subsequent coalescence. Another reason for the growth of agglomerates' size is attributed to growth mechanisms that describe the successive addition of material onto already formed nuclei [13].

3.1.4. Constant Size Zone

In this zone, agglomerates cease to grow or even show a 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 shattering. The rate-determining step in agglomeration growth occurs in zero growth zones when bridging liquid is squeezed out of the pores as the initial floccules are transformed into small agglomerates. The rate-determining step is the collision of particles 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 the interfacial tension between the bridging liquid and the continuous liquid phase, the contact angle, and the ratio of the volumes of the bridging liquid and solid particles [13].

4. Techniques of spherical crystallization

Spherical crystals can be obtained by two different techniques:

- The typical spherical crystallization technique
- The non-typical spherical crystallization technique.

The non-typical spherical crystallization technique can also be considered the traditional crystallization process (salting out, cooling, precipitation, etc.). This process is carried out by controlling the physical and chemical factors [14].

In typical spherical crystallization, three different solvents are used. A good solvent for dissolving the medication, a bridging liquid for partial dissolution and wetting properties, and a bad solvent for being immiscible with the drug ingredient [15].

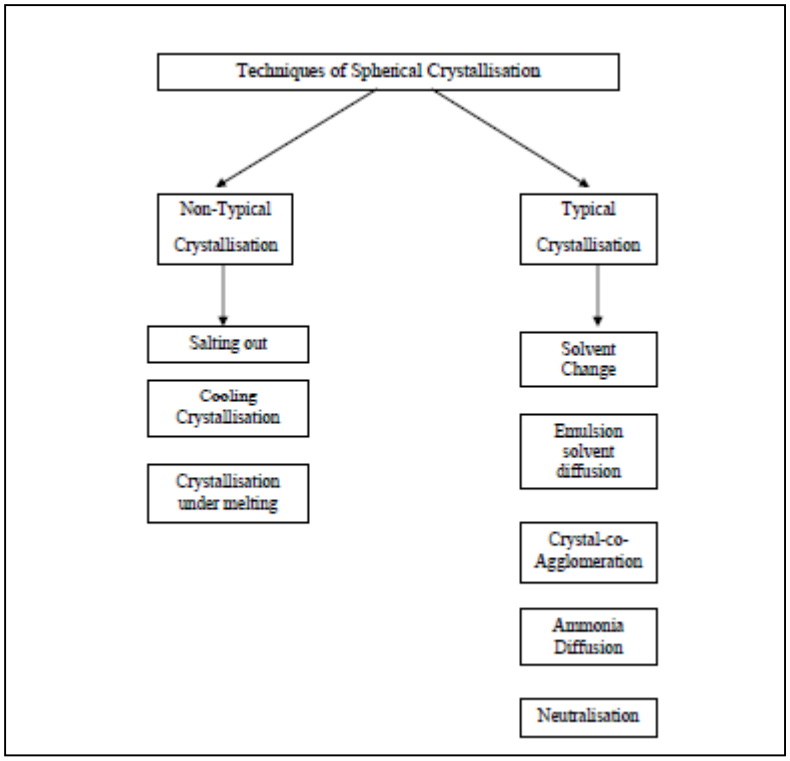

Figure 2 Techniques of spherical crystallization [14]

5. Types

5.1. Wet spherical agglomeration or solvent change

Here, the good and bad solvents are easily miscible and their interaction (binding force) is stronger than that of the drug with the good solvent, causing crystals to precipitate right away. Due to capillary negative pressure and the tension at the liquid-solid interface, bridging liquid gathers the suspended crystals in the system by creating liquid bridges between the crystals. The WSA approach has three steps. Here, the good and bad solvents are easily miscible and their interaction (binding force) is stronger than that of the drug with the good solvent, causing crystals to precipitate right away. Due to capillary negative pressure and the tension at the liquid-solid interface, bridging liquid gathers the suspended crystals in the system by creating liquid bridges between the crystals. The three steps of the WSA approach are depicted in Fig.

The first is choosing the crystallization technique, such as thermal (temperature drop or evaporation), physicochemical (addition of another solvent, salting out), or chemical reaction. The second stage is selecting a wetting agent that will not mix with the crystallization solvent. The third and final process involves hardening the agglomerates.

Drawback of this system is that it produces the low yield, due to co-solvency effect of crystallization solvent. The bridging liquid, the stirring speed and the concentration of solids are the other factors which need to be taken care of [16].

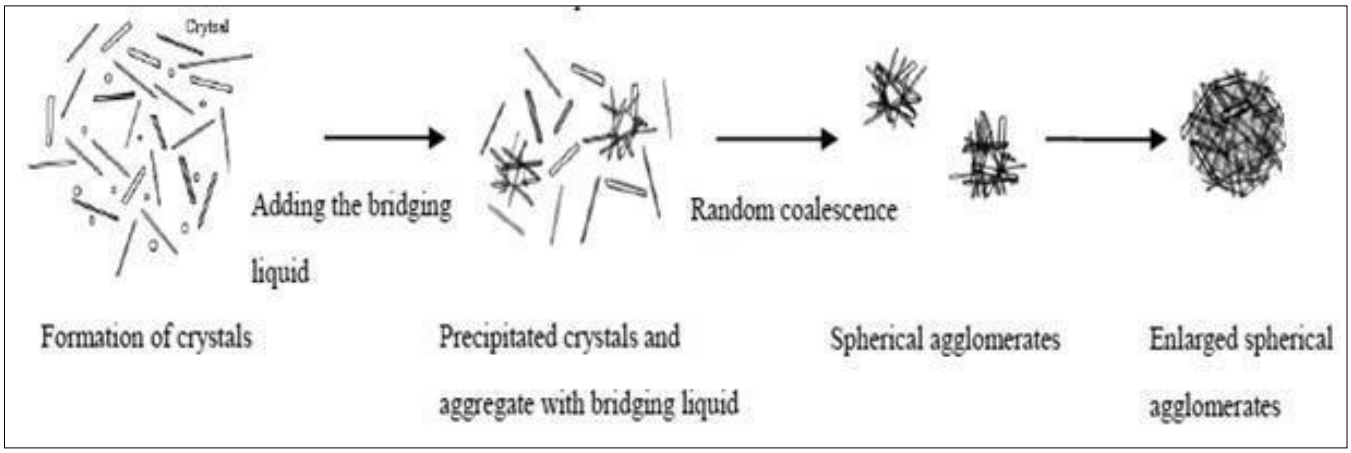

Figure 3 steps involved in spherical agglomeration [16]

Chow *et al* postulated some general guide lines for the spherical agglomeration of drugs.

- A salt solution of high concentration without common ions can be employed as the bridge liquid for molecules that are water soluble, while a water-immiscible organic solvent is utilised as the external medium.
- Water is used as the exterior phase and an organic solvent that is not miscible with water is used as the bridging liquid for molecules that are soluble in one or more organic solvents.
- A saturated aqueous solution of the molecule can act as the exterior phase and an organic solvent mixture as the bridging solvent for compounds that are only soluble in water-miscible organic solvents.
- A water-immiscible organic solvent can serve as the exterior phase and a 20% calcium chloride solution as the bridging liquid for substances that are insoluble in water or any organic solvents. Additionally, since the powders are insufficiently soluble in the bridging liquids to allow binding by recrystallization and fusion, a binding agent like PVP or PEG is needed for agglomeration [17].

5.2 Quasi-Emulsion Solvent Diffusion (QESD) or emulsion solvent diffusion

Kawashima first mentioned quasi-emulsion solvent diffusion (QESD) or emulsion solvent diffusion (ESD) in 1989.

When using this procedure, the medication and the good solvent interact more strongly than the good solvent and the poor solvent. Therefore, even though the solvents are generally miscible, a good solvent drug solution is distributed in a bridging liquid, resulting in quasi-emulsion droplets. This causes the interfacial tension between the bridging liquid and the excellent solvent to increase. Drug crystallization results from the counter-diffusion of the poor solvent into the droplets when the drug's solubility in droplets containing poor solvent declines. Good solvent diffuses out of the emulsion droplets in the poor solvent's outer phase. The remaining excellent solvent in the droplets serves as a connecting liquid to aggregate the crystals that are produced. Then, spherical crystal agglomerates are formed if the process parameters are set accordingly.

Finding an appropriate addition to maintain the system's emulsification and enhance the diffusion of the poor solute into the dispersed phase can be challenging, which is a drawback of this approach [18].

A water-soluble medication, salbutamol sulphate, can be crystallized into spheres using the QESD method. For the purpose of producing spherical particles with a size range of 80-500 mm, the type of solvent, antisolvent, and emulsifier to be used, as well as the concentration of emulsifier to be used, are determined. Further research is done on the solvent/antisolvent ratio and the temperature difference (DT) between the two. It was found that the DT value has no effect on the production of spherical particles when salbutamol sulphate is included. This behaviour might be explained by a sizable salbutamol sulphate metastable zone in water. Lastly, the effect of maturation time and emulsifier concentration on the size of spherical particles is studied. The findings indicate that in order to regulate the size of the recovered particles, these two parameters must be fixed [19].

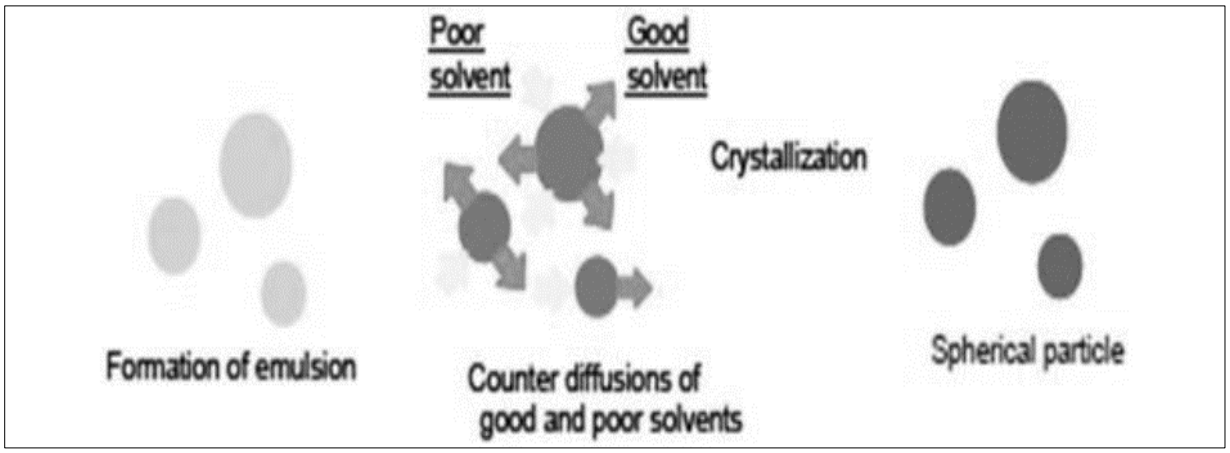

Figure 4 Steps involved in quasi emulsion solvent diffusion [18]

5.3 Neutralization method

In this process, tiny crystals are formed and then aggregated. This method was used to create spherical crystals of the anti-diabetic medication tolbutamide. A NaOH solution was used to dissolve the medication. Tolbutamide was precipitated out by adding aqueous solutions of HPMC and HCl to the tolbutamide NaOH solution to neutralize it. After adding the bridging liquid drop wise at a rate of 10 ml/min, the tolbutamide crystals clumped together.

According to Sano et al., tolbutamide agglomerates prepared by neutralization technique have a higher specific surface area, greater wettability, and a faster dissolution rate than agglomerates prepared by emulsion solvent diffusion and solvent change method. The agglomerates prepared by the neutralization method were instantly permeated with water, showing strikingly greater wettability. The reason for the superior wettability of agglomerated crystals and tablets reported is due to the fact that, at the time of agglomeration, hydrophilic polymer (HPMC) in the crystallization solvent adheres firmly to the agglomerated crystals [20].

5.4 Ammonia Diffusion System (ADS)

This technique is usually meant for amphoteric drugs, which cannot be agglomerated by conventional procedures [21].

The good solvent in this case is an ammonia-water mixture, and the bad solvent is chosen based on how soluble the medication is. The ammonia-water mixture serves as a bridging liquid as well [22, 23].

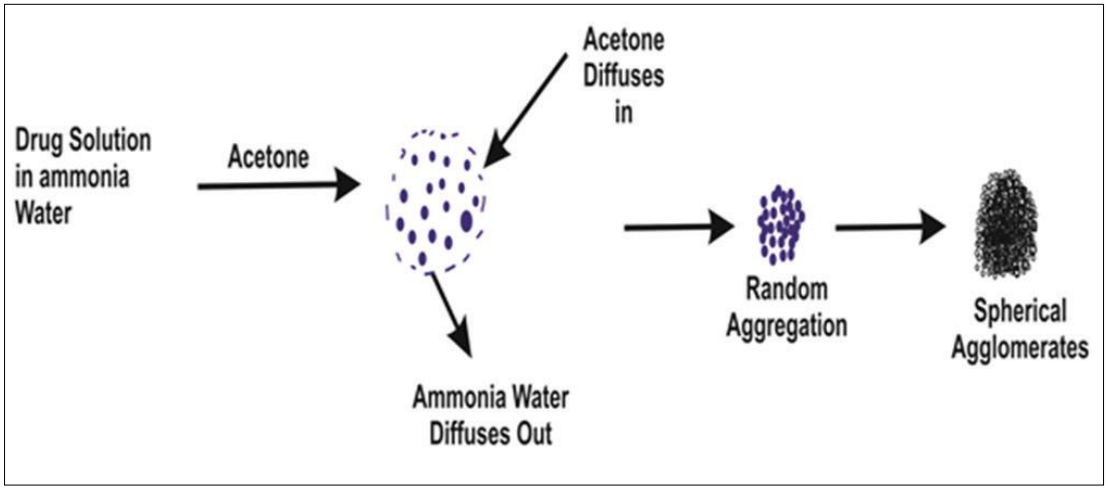

Figure 5 Ammonia diffusion system[24]

Three stages make up the entire procedure. The medication is first precipitated when the droplets gather the crystals after it has been dissolved in ammonia water. Ammonia in the agglomeration simultaneously diffuses to the surrounding

organic solvent. Spherical agglomerates are created as a result of the liquid's diminished capacity to serve as a bridging liquid. By using this technique, the agglomerated crystals of numerous amphoteric medicines have been created.

Drawback of this method is that it is only meant for amphoteric drugs which cannot be agglomerated by conventional methods [24].

5.5 Crystallo-co-agglomeration

Kadam and colleagues developed crystallo-co-agglomeration in an effort to get beyond the restrictions of spherical crystallization procedures, which were limited to size enlargements of single high-dose medications exclusively. A drug is crystallized and agglomerated with an excipient or with another drug in this version of the spherical crystallization techniques mentioned above. Similar to spherical agglomeration, this approach solubilizes the drug with a good solvent, crystallizes it with a poor solvent, and forms liquid bridges during agglomeration with a bridging liquid that is immiscible with the poor solvent.

The drawback of this method is that choosing a solvent solution for the crystal-co-agglomeration technique is quite difficult due to the differences in the physicochemical properties of the drug molecules and the excipients [25].

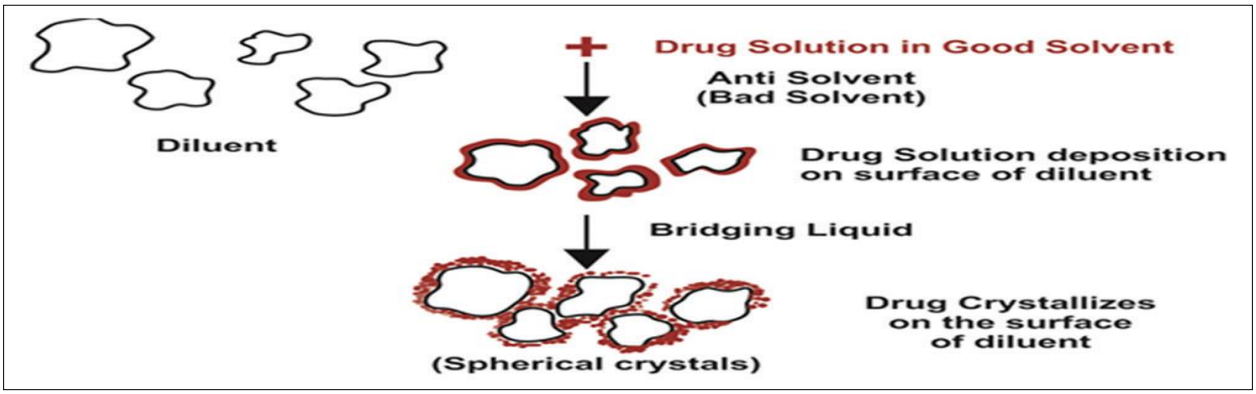

Figure 6 Crytsallo-co-agglomeration process for preparation of spherical crystals [26]

6 Solvent selection

Spherical agglomeration is more significant than the other methods due to its simplicity of usage and the ease with which the solvents can be chosen. The quasi-emulsion method trails behind other techniques.

Guidelines for choosing solvents and moving on with various techniques For the spherical agglomeration of various types of solids, the suggested solvents and agglomeration techniques (Chow and Leung, 1996) The terms SA and QESD stand for spherical agglomeration and quasi-emulsion solvent diffusion [17].

Table 1 Drug solubility and selection of solvents, bridging liquid and method [17]

Drug solubility	Continuous phase	Bridging liquid	Method used
Soluble in water	Water-immiscible Organic solvent	20% calcium chloride solution	Spherical agglomeration
Soluble in organic solvents	Water	Water-immiscible Organic solvent	Spherical agglomeration
Soluble in water-miscible organic solvents	Saturated aqueous solution	Organic solvent mixture	Quasi-emulsion solvent diffusion.
In Soluble in water or any organic solvent	Water-immiscible Organic solvent	20% calcium chloride Solution+ binding agent	Spherical agglomeration

7 Factors affecting the agglomeration process

7.2 Role of solvents

The solvent's characteristics as well as the quantity and make-up of the bridging liquid have an impact on how spherical the agglomerates are. The general rule in a normal SA process indicates that as the amount of bridging liquid increases, so does the size of the agglomeration.[14] The size of the agglomerates do not appear to vary with additional additions of bridging liquid, according to observation, after a certain volume has been supplied to the system [27].

7.3 Role of temperature

A crucial part of the agglomeration process is the attainment of the ideal temperature. The crystals did not agglomerate and had high fine content at temperatures greater than room temperature. Agglomerates formed at lower temperatures were bigger than those formed at ambient temperature, which plainly affects their solubility and mechanical strength [28].

7.4 Role of agitation

It is obvious that the particle size of the agglomerates is greatly influenced by agitation. The shape and size of the product will change if the rate and length of agitation are altered. Agglomerates are sheared by increased agitation rates, which leave behind smaller, finer agglomerates or none at all. Lower rates of agitation will result in spheres with irregular sizes, defeating the purpose of the approach. For the manufacture of satisfying products, the agitation speed must be optimized [29].

7.5 Role of additives

Polymers like polyethylene glycol, polyvinyl pyrrolidone, and hydroxypropyl methyl cellulose slow down the nucleation process. These polymers stop crystals from spontaneously aggregating, giving spherical agglomerates plenty of time to develop. The polymers' altered crystal habits cause them to interfere with sphericity and particle size [30].

7.6 Duration of residence of agglomerates in crystallization medium

It has been observed that larger agglomerates are generated as the time that agglomerates spend in the crystallization media increases [30].

8 Physico chemical characterization of spherical agglomerates:

The following criteria must be used to assess the spherical crystals since they have a substantial impact on the design and production of medicinal dosage forms:

8.2 Particle size and size distribution

Particle size and distribution can be determined using a straightforward sieve analysis. The Ro-Tap sieve shaker, however, makes it possible to use particle size analysis. An image analyzer is employed in spherical technology to calculate the particle's size and volume [31].

8.3 Particle shape/surface topography

Following methods are used:

8.3.1 Optical microscopy

By viewing the crystals under an optical microscope, spherical crystal forms can be investigated. A variety of magnifications, including 10X, 45X, 60X, and others, are used to make the observations [32].

8.3.2 Electron scanning microscopy

Scanning electron microscopy is used to analyse the surface topography and crystal type (polymorphism and crystal habit) of the spherical crystals [32].

8.3.3 X-ray powder diffraction

This is an important technique for establishing batch-to-batch reproducibility of a crystalline form. Technique is used to determine the crystal form in agglomerates. An amorphous form does not produce a pattern. The X-rays scattered in a reproducible pattern of peak intensities at a distinct angle (2θ) relative to the incident beam. Each diffraction pattern is characteristic of a specific crystalline lattice for a compound [32].

8.3.4 Fourier Transform Infrared spectrometer (FTIR)

Due to the inclusion of new stretching frequencies brought on by the salvation, it is significantly more helpful for recognising solvates and anhydrous forms than polymorphs [32].

8.3.5 Differential scanning calorimeter (DSC)

DSC calculates the heat gain or loss brought on by alterations in a sample's physical or chemical composition. DSC can be used to analyse changes in the characteristics of agglomerates made from a combination of medicines and polymers [32].

8.3.6 Thin layer chromatography (TLC)

It establishes the relationship between the drug and polymer in spherical agglomerates and investigates the stability of the drug in various solvents [32].

8.4 Residual solvent determination by gas chromatography

By using gas chromatography, the agglomerates are examined for solvent residue that might have remained trapped during the agglomeration process [33].

8.5 *In vitro* dissolution studies

Studies are carried out by adding medium to the spherical crystals in the capsule shell to confirm the better disintegration. Dissolution investigations will show that agglomerates have an advantage over pure drugs [34].

8.6 Stability studies

To verify that the agglomerates will remain stable during the shelf life of the final dosage form that will be commercialized, stability tests should be carried out in accordance with ICH criteria [34].

8.7 Drug loss in supernatant liquid

In particular for the CCA approach, the liquid supernatant is analysed for the medication that is lost after the whole procedure has been completed. If there is a substantial quantity of drug loss, there may not be enough excipient available to deposit the medicine [35].

8.8 Micromeritic properties

Particle size distribution, roundness, angle of repose, Carr's index, Hausner's ratio, compactibility, and packability are examples of micromeritic qualities. Densities are physical traits that depend on the dimensions, morphology, and spherical crystals that are produced as the end result [36].

8.9 Practical yield

By crushing and dissolving a specified amount of the generated agglomerates in an appropriate solvent, and then analysing the results using an ultraviolet spectrophotometer, the practical yield of the agglomerates can be ascertained. based on a straightforward mathematical operation [35];

$$\text{Practical yield (\%)} = \frac{\text{Weight of product}}{\text{Weight of feed}} \times 100$$

8.10 Mechanical properties

8.10.1 Friability of agglomerates

Each batch of plastic balls and agglomerates has a sample placed on a sieve, which is then shaken for a predetermined amount of time. The mean geometric diameter is determined for each time period.

Percentage friability index (FI) as a function of time can be calculated at each time using the following equation

$$FI= [(dg)_t /(dg)_0] \times 100$$

Here, $(dg)_t$ = mean geometric diameter after time *t*

$(dg)_0$ = mean geometric diameter at initial time [36].

8.10.2 Compression properties

The preparation of the tablet often makes use of this feature. Compaction is another name for this action. When the porosity shifts,

Plastic behaviour: compact powder deforms under compression and is tapped into close packing.

Unexpected expansion under stress is known as dilatant behaviour, and some substances show more porosity when compressed than powder and packed closely [37].

8.10.3 Strength analysis

The mechanical toughness of single agglomerates was assessed by compression in materials on a testing apparatus. The agglomerate was positioned as shown in Figure 2, and a steady movement of the upper plane towards the lower plane at a speed of 0.5 mm/min was used to apply a load that gradually increased. The powder bed was compacted after 100 to 150 mg of agglomerates (8.2 mm in diameter) was added to the steel cup.

$F= (\pi d2/4) \times \sigma$

$\varepsilon = l/d$

The measured force (F), stress (σ), strain (ε)[37].

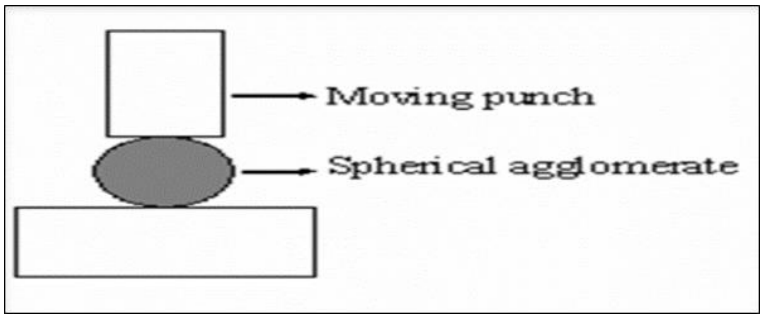

Figure 7 Compression of the spherical agglomerates [37]

8.11 Heckel analysis

The subsequent In order to analyze and evaluate the compatibility of agglomerated crystals, Heckel's equation was applied.

$In [1/(1-D)] = KP+A$

Where: D is the relative density of the tablets under compression Pressure

K is the slope of the straight portion of the Heckel Plot

The reciprocal of K is the mean yield is the mean yield pressure (Py).

The following equation gives the intercept obtained by extrapolating the straight portion of the plots

A=1n [1/(1-D0]+B

Where: D0 is the relative density of the powder bed when P=0.

The following equation gives the relative densities corresponding to A and B.

DA=1-e-A DB=DA-D0 [38].

9 Applications of spherical crystallization in pharmaceuticals

9.1 To improve the flowability and compressibility

Agglomerates have been shown to possess qualities that make them appropriate for direct compression tableting. Crystals can be produced through sublimation, solvent evaporation, vapour diffusion, thermal processing, crystallization from melt precipitation by a change in pH, growth in the presence of additives, or grinding. Thus, the innovative agglomeration technology that, during the crystallization process, converts the crystals themselves directly into a compacted spherical form has been desired. Making advantage of Spherical crystallization appears to be a successful alternate method for producing direct compression-ready particles. Numerous medications exhibit unfavourableflowability and compressibility as a result of various crystal habits. So these problems can be solved by converting them into agglomerated crystals by changing the crystal habit and spheronization so as to increase the flowability and compressibility [39].

9.2 To mask the bitter taste of drug

To cover up the medication's unpleasant taste, microcapsules are created. Since spherical material may be uniformly coated with a relatively small amount of polymer, they are appropriate for coating grains. To cover up the bitter taste, the following medications were made into microcapsules [39].

9.3 To increase the solubility and dissolution rate of poorly soluble drug

Some medications with limited water solubility and a slow dissolution profile have been said to respond well to spherical crystallization, according to research [39].

9.4 Microparticles by spherical crystallization

For sustained drug release, spherical crystallization using acrylic polymers was used to create a variety of drug microparticles. The traditional approach of generating microspheres, which involves co-precipitating drugs and polymers to create functional drug delivery systems based on the characteristics of the polymer, is less beneficial than spherical crystallization. As a simple and less expensive process, the spherical crystallization technique can be modified to create spherical matrices of prolonged release drugs as an alternative to traditional methods. It offers many benefits, such as the avoidance of harmful organic solvents and additives and the avoidance of raising the system's temperature as in the phase separation method. Additionally, the produced matrix spheres can be directly compressed, skipping the tiresome and drawn-out granulation process [40].

Table 2 Summarizes the different techniques and solvents used in preparing spherical agglomeration of drugs

Drugs	Solvent system			Technique
	Good solvent	Bad solvent	Bridging liquid	
NSAIDS				
Aceclofenac [41]	Acetone	Water	Dichloromethane	SA
Aspirin [42]	Acid Buffer	Methanol	Chloroform	SA
Acetyl salicylic acid [43]	Ethanol	Water	Carbon tetrachloride	SA
Celocoxib [44]	Acetone	Water	Chloroform	SA
Fenbufen [45]	THF	Water	Isopropyl acetate	SA
Ibuprofen [46]	Ethanol	Water	Ethanol	SA
Ibuprofen-Talc [47]	Dichloromethane	Water	Dichloromethane	CCA
Indomethacin [48]	Dimethyl formamide	Water	Chloroform	SA
Ketoprofen [49]	Isopropyl acetate	Water	Chloroform	SA
ketoprofen-Talc [50]	Dichloromethane	Water	Dichloromethane	CCA
Mefenamic acid [51]	Ammonia water	Acetone	Ammonia water	ADM
Naproxen [6]	Acetone- Ethanol	Water	Chloroform	SA
Antibiotics				
Ampicillin trihydrate [52]	Ammonia water	Acetone	Dichloromethane	ADM
Cefuroxime Axetil [53]	Acetone	Water	Dichloromethane	QESD
Roxythromycin [54]	Methanol	Water	Chloroform	SA
Antidiabetic				
Glibenclamide [55]	Dichloromethane	Water	Chloroform	SA
Tolbutamide [56]	Ethanol	Water	Isopropyl alcohol	ESD,NT
Bronchodialator				
Aminophylline [57]	Ethanol	Water	Chloroform	SA
Theophylline[58]	Ethylene diamine	Sodium chloride	Water	SA
Antifungal				
Gresiofulvin [9]	Dichloromethane	Water	Dichloromethane	QESD
Antiepileptic				
Carbamazepine [59]	Ethanol	Water	Chloroform	QESD
Antihypertensive				
Felodipine [60]	Acetone	Water	Dichloromethane	QESD
Antiallergic				
Tranilast[61]	Acetone	Water	Dichloromethane	SA

10 Conclusion

Spherical crystallization has emerged as a significant technology in recent years that not only streamlines the stages necessary in direct compression of tablets but also offers improved flowability over the initial pure amorphous medication. The spherical crystal, which is a cheap technique, The solvent change method, the quasi-emulsion solvent, the ammonia diffusion system, and the neutralisation method are all used in the formation of spherical crystals. This method takes less time than wet granulation since it crystallises, aggregates, and spheronizes in one process. Spherical crystals have a higher solubility in aqueous solvents, increasing the bioavailability of poorly soluble medications, particularly Biopharmaceutical Classification System class II medications, where the bioavailability is dissolution rate limited and the in vivo performance is improved when compared to that of the pure medication as well as the marketed formulation, in addition to exhibiting no preclinical toxicity. However, it is necessary to monitor the organic solvent residues for compliance with legal requirements after the production of agglomerates. Techniques for spherical crystallization can be used successfully as an alternative. Creating microparticles involves Appropriate polymers can be used to get a sustained release of API from the microparticles or compacts of them. By using a spherical crystallization technique instead of the laborious and time-consuming traditional method, sustained-release API microparticles can be created. This approach offers the potential to produce directly compressed tablets of poorly compressible and water-soluble pharmaceuticals with higher bioavailability if the production scale can be increased.

Compliance with ethical standards

Acknowledgments

The authors wish to acknowledge and thanks to Dr.P.Solairaj, M.Pharm, Ph.D, Principal and Management of Sankaralingam Bhuvaneswari College of Pharmacy, Sivakasi, Virudhunagar district, Tamilnadu – 626001, India.

Disclosure of conflict of interest

No conflict of interest.

References

[1] Maghsoodi M. Role of solvents in improvement of dissolution rate of drugs: crystal habit and crystal agglomeration. Adv Pharm Bull 2014;1:1-6.

[2] Ujwala R, Redasani K, Kothwade S. Preparation and *in-vitro* evaluation of loperamide hydrochloride spherical crystals by emulsion solvent diffusion technique. Int J Pharm PharmSci 2013;5:409-13.

[3] Paradkar A.R, Pawar A.P, Mahadik K.R, Kadam S.S. Spherical crystallization: A novel particle design technique. Indian Drugs. 1993, 31(6): 229-331.

[4] Kawashima Y, Niwa T., Takeuchi H., Hino T., Ito Y., Control of prolonged drug release and compression properties of ibuprofen microspheres with acrylic polymer, Eudragit RS, by changing their intraparticle porosity. Chem. Pharm. Bull., 1992, 40(1), 196-201.

[5] Kuriki ST, Handa T, Takeuchi H, Kawashima Y. Particle design of tolbutamide in the presence of soluble polymer or surfactant by the Spherical crystallization technique: Improvement of dissolution rate. J. Pharm. Sci 76(6), pp 471-474

[6] Maghsoodi M, Hassan-ZadehD,Barzegar-Jalali M, Nokhodchi A and Martin G. Improved Compaction and Packing Properties of Naproxen Agglomerated Crystals Obtained by Spherical Crystallization Technique. *Drug Dev. Ind. Pharm* 2007; 33: 1216-1224.

[7] Gupta VR, Mutalik S, Patel M, Girish K. Spherical crystals of celecoxib to improve solubility,dissolution rate and micromeritic properties. *Acta Pharm*. 2007; 57: 173–184.

[8] GP, Bhadra S, Kumar M, Jain S, Agrawal S. Spherical Crystallization of Mefenamic Acid. *Pharm. Tech*. 2004; Feb: 66-76.

[9] Yadav VB, Yadav AV. Effect of Different Stabilizers and Polymers on Spherical Agglomerates of Gresiofulvine by Emulsion Solvent Diffusion (ESD) System. *Int. J. Pharm. Tech. Res*. 2009; 1(2):149-150.

[10] Krishna E, Gupta V, Jyothi S. Spherical crystallisation-a modern technique for direct compression of pharmaceutical substances. Asian J Pharm Clin Res 2012;5:114-7.

[11] Dixit M, Kulkarni P, Johri A. Spherical agglomerates of mefanamic acid by solvent change method. Int J Pharm Sci 2011;2:111-25.

[12] Parida R. Evaluation parameters for spherical agglomerates formed by spherical crystallisation technique. Int J Pharma Bio Sci 2010;1:1-10.

[13] Chouracia M.K., Jain A. Potential of guar gum microspheres for target specific drug release to colon. *Indian Drugs*. 2004; 41 (6): 319-29.

[14] Martino P, Bartheleny C, Pina F. Improved dissolution behaviour of fenbufen by spherical crystallisation. Drug Dev Ind Pharm 1999;25:1073-81.

[15] Yadav VB, Yadav AV. Polymeric Recrystallized Agglomerates of Cefuroxime Axetil Prepared by Emulsion Solvent Diffusion Technique. *Trop. J. Pharm. Res*. 2009; 8(4): 361-369.

[16] Nokhodchi A, Maghsoodi M, Hassanzadeh D. An Improvement of Physicomechanical Properties of Carbamazepine Crystals .*Iran. J. Pharm. Res*. 2007; 6(2): 83-93.

[17] Chow AHL, Leung MWM. A study of the mechanisms of wet spherical agglomeration of pharmaceutical powders. *Drug Dev. Ind. Pharm*. 1996; 22(4): 357-371.

[18] Espitalier F, Biscans B. Spherical crystallisation modelling of emulsion solvent diffusion technique. Powder Technol 1997;1:1-3.

[19] M. NOCENT, L. BERTOCCHI, F. ESPITALIER, M. BARON, G. COUARRAZE Definition of a Solvent System for Spherical Crystallization of Salbutamol Sulfate by Quasi-Emulsion Solvent Diffusion (QESD) Method Journal of Pharmaceutical Sciences, Vol. 90, 1620±1627 (2001).

[20] Sano A, Kuriki T, Kawashima Y, Takeuchi H, HinoT, Niwa T, Particle design of Tolbutamide by the spherical crystallization technique IV, Improved of dissolution and bioavailability of direct compression tablets prepared using Tolbutamide agglomerated crystals, Chem.Pharm.Bull, 40, 1992, 3030-3035.

[21] Hector GP, Jorge B, Carlo A., Preparation of Norfolxacin spherical agglomerates using the ammonia diffusion system. J. Pharm. Sci.,1998, 87(4): 519-523.

[22] Agrawal GP, Bhadra S, Kumar M, Jain S, Agrawal S., Spherical Crystallization of Mefenamic Acid. Pharm. Tech., 2004, 66-76.

[23] Gohel MC, Parikh RK, Shen H, Rubey RR., Improvement in flowability and compressibility of AmpicillineTrihydrate by spherical crystallization. Ind. J. Pharm. Sci., 2003, 634-637.

[24] Ueda M, Nakamura Y, Makita H, Imasato I, Kawashima Y. Particle design of enoxacin by spherical crystallizaion technique. I principle of ammonia diffusion. Chem Pharm Bull 1990;38:2537-41.

[25] Kawashima Y, Cui F. Improvement in flowability and compressibillty of pharmaceutical crystals for direct tabletting by Spherical crystallisation with a two solvent system. Powder Technol 1994;78:151-157.

[26] Garala KC, Patel JM, Dhingani AP, Dharamsi AT. Preparation and evaluation of agglomerated crystals by crystallo-co-agglomeration: An integrated approach of principal component analysis and Box-Behnken experimental design. Int J Pharm 2013;452:135-56.

[27] Maghsoodi M. Role of solvents in improvement of dissolution rate of drugs: Crystal habit and crystal agglomeration. Adv Pharm Bull 2015;5:13-8.

[28] Katta J, Rasmuson AC. Spherical crystallization of benzoic acid. Int J Pharm 2008;348:61-9.

[29] Deshpande MC, Mahadik KR, Pawar AP, Paradkar AR. Evaluation of spherical crystallization as a particle size enlargement technique for aspirin. Ind J Pharm Sci 1997;59:32-40.

[30] Raghavan SL, Trividic A, Davis AF, Hadgraft J. Crystallization of hydrocortisone acetate: Influence of polymers. Int J Pharm 2001;212:213-21.

[31] Andreou JG, Stewart PJ, Morton DV. Short-term changes in drug agglomeration within interactive mixtures following blending. Int J Pharm 2009;372:1–11.

[32] Mullin JW. 1993. Metastable zone widths. In:Crystallization, third edition. Oxford, UK: Butter-worth-Heinemann. pp. 189-193.

[33] Dixit M, Kulkarni PK, Vaghela RS. Effect of different crystallization techniques on the dissolution behavior of ketoprofen. Trop J Pharm Res 2013;12:317-22.

[34] Pusapati RT, Kumar MK, Rapeti SS, Murthy T. Development of co-processed excipients in the design and evaluation of atorvastatin calcium tablets by direct compression method. Int J Pharm Investig 2014;4:102-6.

[35] Raval MK, Patel JM, Parikh RK, Sheth NR. Dissolution enhancement of chlorzoxazone using cogrinding technique. Int J Pharm Investig 2015;5:247-58.

[36] Gupta MM, Srivastava B. Enhancement of flow property of poorly flowableaceclofenac drug powder by preparation of spherical crystals using solvent change method and making drug powder suitable for direct compression. Int J Curr Pharm Rev Res 2010;1:12-23.

[37] Garg N, Pandey P, Kaushik D, Dureja H. Development of novel multifunction directly compressible co-processed excipient by melt granulation technique. Int J Pharm Investig 2015;5:266-74.

[38] Garg J, Khatry S, Arora S. Spherical crystallization: an overview. Int J Pharm Technol 2012;4:1909-28.

[39] Tiwari S, Verma P. Spherical crystallization–a novel drug delivery system. Int J Pharm Life Sci 2011;2:1065-8.

[40] Spherical crystallization: A novel technique for designing sustained release microparticlesKishorRavjibhaiSorathia et al. / Journal of Pharmacy Research 2012,5(10),4943-4946.

[41] Usha AN, Mutalik S, Reddy MS, Ranjith AK, Kushtagi P, Udupa N. Prepartion and invitro preclinical and clinical studies of aceclofenac spherical agglomerates. Eur J Pharm Biopharm. 2008; 70, pp 674-683.

[42] M.C. Deshpande, KR Mahadik, AP Pawar, AR Paradkar. Ind J Pharm Sci. 1997; 59 (1), pp 32-34.

[43] H. Goczo, R.P. Szabo, M. HasznosNezdei, et al. Chem Pharm Bull. 2000; 48(12), pp 1877-81.

[44] V.R. Gupta, M. Srinivas, M.M. Patel, G.K. Jani. Acta Pharm. 2007; 57, pp 173-184.

[45] P.D. Martino, C. Barthelemy, F. Piva, E. Joiris, C. Marthelemy. Drug Dev.Ind.Pharm. 1999; 25 (10), pp 1073-1081.

[46] Y. Kawashima, T. Niwa, T. Handa, H. Takeuchi, T. Iwamoto. J Pharm Sci. 1989; 78(1),pp 68-72.

[47] Pawar A, Paradkar A, Kadam S, Mahadik K. Agglomeration of Ibuprofen with Talc by Novel Crystallo-Co-AgglomerationTechnique. AAPS PharmSciTech. 2004;5(4), pp 1-6.

[48] Mudit Dixit*1, P. K. Kulkarni1, Spherical agglomeration of Indomethacin by solvent change method International Journal of Pharma Research and Development 2005;2(9), pp 33-43.

[49] Mudit dixit*, Dr.P. K. Kulkarni and Ashwini G Kini Spherical agglomeration of Ketoprofen by solvent change method International Journal of Pharmaceutical Sciences Review and Research 2010;4(3), pp 129-135.

[50] Chavda V, Maheshwari RK. Tailoring of ketoprofen particle morphology via novel crystallo- coagglomeration technique to obtain a directly compressible material. Asian J. Pharm. 2008;2(1), pp 61-67.

[51] Agrawal GP, Bhadra S, Kumar M, Jain S, Agrawal S. Spherical Crystallization of Mefenamic Acid. Pharm. Tech. 2004 February, pp 66-76

[52] Gohle MC, Parikh RK, Shen H, Rubey RR. Improvement in flowability and compressibility of AmpicillineTrihydrate by spherical crystallization. Ind J Pharm Sci. 2003, pp 634-37.

[53] Yadav1 VB, Yadav AV. Polymeric Recrystallized Agglomerates of Cefuroxime Axetil Prepared by Emulsion Solvent Diffusion Technique. Trop. J. Pharm. Res. 2009;8(4), pp 361-369.

[54] Bermer GG, Zuiderweg FG. Proceedings of international symposium of fine particles. AIME, New York. 1992, pp 1524-46.

[55] Vinay K. Mishra1, Sumeet Dwivedi 2* Method development for spherical crystallization of glibenclamide and evaluation of micromeritic properties Drug Invention Today 2010;2(2), pp 119- 122.

[56] Sano A, Kuriki T, Kawashima Y, Takeuchi H, Hino T, NiwaT.Particle design of Tolbutamide by the spherical crystallization technique IV, Improved of dissolution and bioavailability of direct compression tablets prepared using Tolbutamide agglomerated crystals, Chem. Pharm. Bull. 1992;40, pp 3030-3035.

[57] Kawashima Y,AokiS,TakenakaH,Miyake .Y.Preparation of spherically agglomerated crystals of Aminophylline. J.Pharm Sci1984;73(10), pp 1407- 1410.

[58] Kawashima Y. Development of spherical crystallization technique and its application to pharmaceutical systems. Arch Pharm. Res. 1984;7(2), pp 145-151.

[59] Nokhodchi A, Maghsoodi M, Hassanzadeh D. An Improvement of Physicomechanical Properties of Carbamazepine Crystals . Iran. J. Pharm. Res. 2007 6(2), pp 83-93.

[60] Amit R. Tapas1*, Pravin S. Kawtikwar2 Polymeric recrystallized spherical agglomerates of felodipine by quasi-emulsion solvent diffusion method Pelagia Research Library Der Pharmacia Sinica 2010;1(1), pp 136-146.

[61] Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y, Furuyama S, Characterization of polymorphs of Tranilast anhydrate and Tranilast monohydrate when crystallization by two solvents changes spherical crystallization technique, J. Pharm. Sci. 1991;80(5), pp 472-478