IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
April 2023 Vol.:27, Issue:1

Improvement of Physicochemical Properties of Drugs by Particle Engineering: A Spherical Crystallization Approach

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Ashok T. Jadhav[1]*, Sanjay S. Pekamwar[2]

[1] *School of Pharmacy, SRTM University, Nanded, 431606, Maharashtra, India.*

[2] *School of Pharmacy, SRTM University, Nanded, 431606, Maharashtra, India.*

Submitted: 21 March 2023
Accepted: 27 March 2023
Published: 30 April 2023

Keywords: Spherical crystallization, crystal-co-agglomeration, quasi-emulsion solvent diffusion, ammonia diffusion Method, neutralization Technique.

ABSTRACT

The most convenient and preferred route of administration is an oral route over other routes. Tablets are the readily acceptable and preferred dosage form for the oral route of administration. We can define tablets as easy to take but difficult to make in the dosage form. There are several factors are as flow properties, crystal habit, and compatibility of the powder which are rate-limiting steps. The challenges in the formulation development of the tablets are converting the raw material into the powder having desired physical properties such as compressibility and flowability. To achieve this prerequisite for good tableting properties a series of operations is required which leads to more documentation and may lead to regulatory compliance issues as the process steps increase the validation of the process becomes lengthy. The techniques like spherical agglomeration, quasi-emulsion solvent diffusion, ammonia diffusion method, neutralization technique, and crystal-co-agglomeration.

INTRODUCTION:

Solubility, dissolution, and gastrointestinal permeability are basic characteristics that govern the rate and amount of medication absorption as well as its bioavailability, as has been well explained. A drug's water solubility is a critical feature that affects its absorption after oral administration [1]. It also determines if a drug can be administered parenterally and is important in changing and assessing drug properties during the drug development process. Although aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, and sensitivity to efflux mechanisms all affect a drug's oral bioavailability, aqueous solubility and drug permeability are also key factors. The size and form of the particles have a significant impact on the separation process and it has a direct impact on the yield and quality of the crystals. The flowability, packing, compatibility, drinkability, physical stability, and dissolution profile of a pharmacological molecule are all affected by particle orientation, which is impacted by crystal habit [2]. One of the popular, convenient pharmaceutical dosage forms is the Tablet which covers almost 70 % of all dosage forms administered [3]. The dosage form is more popular due to its ease of administration, acceptability, Stability of formulation and ease of handling, manufacturability, and cost-effectiveness. The quality and efficiency of the tablet are majorly driven by properties of small particles such as crystal habit, bulk density, the flowability of the API, and powder for formulating the final dosage form [4, 5]. Moreover, the performance of the solid dosage form is also depending on the solubility and rate of dissolution of the pharmaceutical dosage form. The formulation development should be aimed at the achievement of dual objectives of formulation of a directly compressible dosage form and enhancement of its bioavailability by increasing its solubility [5]. Solubility profile, agitation mode and intensity, system temperature, and residence time are all factors that influence the agglomeration process. During the crystallization process, this crystal habit can be changed. Certain micrometric and physicochemical qualities (such as solubility, rate of dissolution, and bioavailability) can be altered as a result of such changes in the crystal habit. Spherical crystallization has many uses in medicines, that enhance the compressibility, flowability, solubility, and dissolution of drugs with poor solubility characteristics. Spherical crystallization is one of the efficient methods to modify the crystal habit in one step. There are several methods of spherical crystallization are available includes the Spherical- agglomeration (SA), Quasi-emulsion solvent diffusion (QESD), Ammonia diffusion method (ADM), Neutralization technique (NT), and Crystallo-co-agglomeration (CAA) [6, 7]. Evaluation of spherical crystalization to

be done for drug content, saturation solubility, particle size, flow property and compressibility, shape and morphology of crystals, in vitro dissolution study, and powder X-ray diffraction study [7. 8].

Importance of Spherical Crystallization (SC):

"During the crystallization process, spherical crystallization is an aggregation mechanism that converts crystals straight into compact spherical shapes," says the author. Spherical crystallization is a novel agglomeration technique that may instantly transform small crystals generated during the crystallization process into a spherical shape. To formulate solid dosage forms, developing novel methods to increase the bioavailability of drugs with poor aqueous solubility is a huge challenge. The two most common techniques for improving the bioavailability of poorly soluble drugs are the mechanical micritization of crystalline drugs and the incorporation of surfactants during the crystallization process. Micronization affects the flow and compressibility of crystalline powders, which can lead to formulation issues. Surfactant addition resulted in a less significant increase in water solubility. Kawashima developed a spherical crystallization approach to solving this challenge, which improved the flow and direct compressibility of a variety of microcrystalline medicines.

Applications of Spherical Crystallization [3]

1. Micromeritic properties of the drug crystals improve drastically.

2. Spherical crystallization improves the wettability and dissolution rate of drugs having poor solubility.

3. In spherical crystallization, we can convert crystalline API into an amorphous form which results in better solubility in terms of better bioavailability.

4. Spherical crystals have improved flow properties which helps in the direct compression of the tablets.

5. Spherical crystallization improves the compatibility and friability of the tablets which helps in the improvement of the aesthetic properties of the formulation.

6. Spherical crystals can be compressed directly with fewer diluents.

7. Reduction in production cost of formulation dies to direct compression process.

8. Reduces unit operation for tablet manufacturing and reduces GMP burden.

9. With the crystal-co-agglomeration technique, we can do the crystallization of fixed drug combinations together.

Limitations of Spherical Crystallization [3]

1. The choice of solvent is a crucial factor.

2. The solvent quantity may be huge as per the solubility of the drug.

3. Optimization of process parameters is a tedious process.

Solvents in Spherical Crystallization [2]

Usually, three types of solvents are employed in the process. These are good solvents, bridging solvents, and poor solvents.

1) Good solvent:

A good solvent is one in which the medicine is soluble in a large amount of it. It's ideal for use as a drug solvent. The solubility of the medication and its affinity/miscibility with the bridging liquid is utilized to select a suitable solvent.

2) Bridging solvent:

To make the agglomerates, the crystals in the liquid suspension were agitated in the presence of the bridging liquid. While cementing the agglomerated particle, the bridging liquid must be immiscible in the suspending medium. The finely divided solid crystals in the liquid suspension initially separated from one another, but bridges between the solid crystals were formed by adding a small amount of bridging liquid that preferentially wets the surface of solids, and the solid crystals eventually agglomerated into a spherical form.

3) Poor solvent:

The poor solvent is sometimes known as an anti-solvent or bad solvent. The poor solvent must not be miscible with the solvent system (good solvent and bridging liquid) and must have a higher affinity than the drug and the solvent. Because it is utilized to increase the solubility of poorly soluble medicines, water is the most recommended anti-solvent in this

procedure. The solvent system and its composition are usually determined through trial and error.

Spherical Crystallization:

Bremer and Zuider Wag demonstrated the following four-step responsible for agglomeration reaction [9].

1. Zone of Flocculation
2. Zone of Zero Growth
3. Zone of Fast Growth
4. Zone of Constant Size

1) Zone of Flocculation

In this step, crystal surface liquid was brought together to bridge the gap between crystals by agitating the solvent. The lens bridges are established in between particles by adsorbing liquid links and the loose open flocs are formed.

2) Zone of Zero Growth

In the Zero growth zone, the loose open flocks formed in the flocculation zone get transferred into a compact pellet. In this process, small flocks are covered with the liquid that emerged from the squeezing of entrapped fluid resulting in filling empty spaces using liquid bridging. The main force behind this is turbulence due to agitation, pellets-pellets, and stirrer-pellets collision.

3) Zone of Fast Growth

This phase occurs due to the squeezing of bridging liquid from small agglomerate surfaces to larger particles. These particles form coalescence which is the result of collision from the nucleus. This phenomenon of collision essentially requires an excess of moisture.

4) Zone of Constant Size

Here the cessation of size expansion of the agglomerates takes place. The rupture of the agglomerate is get balanced by coalescence. The size reduction results in place due to attrition, breakage, and shatter.

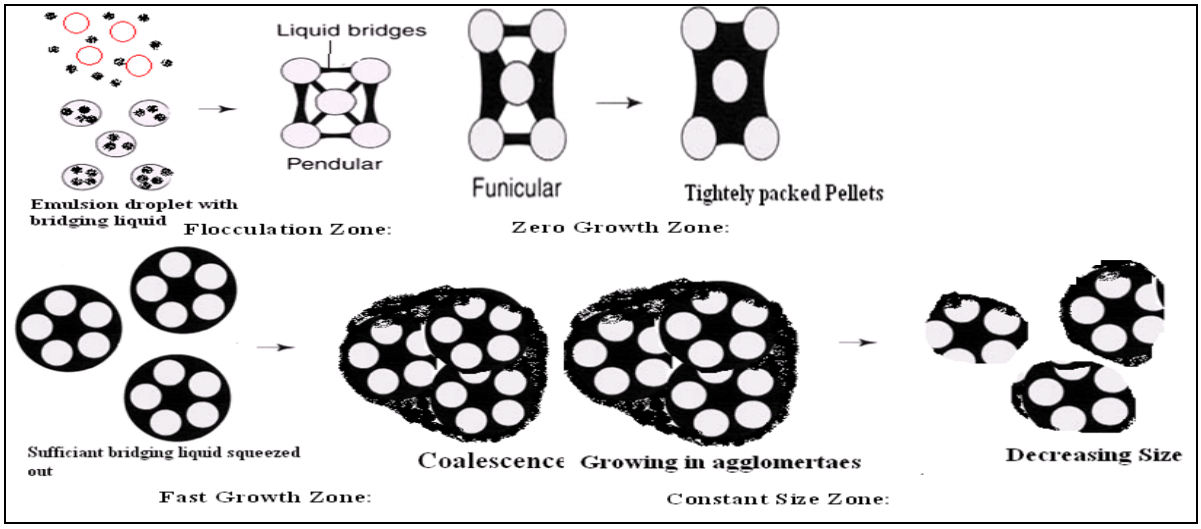

Figure no 1: Schematic representation of the Spherical Crystallization process.

Methods of spherical crystallization [8]

Several methods of spherical crystallization are available which are as follows.

1. Spherical Agglomeration method (SA)
2. Quasi-Emulsion Solvent Diffusion Method (QESD)
3. Ammonia diffusion method (ADM)
4. Neutralization Technique (NT).
5. Crystallo-Co-Agglomeration (CAA)
6. Salting out method (SO).

1. Spherical Agglomeration method (SA):

Spherical agglomeration is a particle engineering approach that includes structuring small crystals into spherical shapes to improve the powder's physical characteristics, including

particle size, shape, flow characteristics, solubility, and bioavailability of pharmaceutical drug substances [11]. Kawashima Y. 1982 introduced spherical crystallization and prepared Salicylic acid crystals [11]. In this method, the drug is dissolved in a water system with ethanol and chloroform acting as the poor solvent, good solvent, and bridging liquid respectively. A third liquid known as bridging liquid that has limited miscibility with the poor solvent but has a strong affinity for the drug is introduced in a controlled manner to the crystallization vessel as the drug solution is put into the poor solvent and crystallization of the API occurs simultaneously. As a result, it creates a bridge between the particles and causes binding. In this procedure, it is important to remember that the good solvent and poor solvent should have a stronger affinity than the good solvent and drug. In spherical agglomeration, crystal formation, crystal growth, and agglomeration take place simultaneously [12]. The prerequisite for spherical agglomeration is a selection of the solvent. In spherical crystalization, we need to select three types of solvent whether it is good, poor, or bridging liquid. Bridging liquid works as a wetting agent and preferably bridging liquid must not be miscible with poor solvent. Spherical agglomeration takes place when a drug's saturated solution is mixed with a poor solvent. At this point, if both solvents are miscible and show good affinity then it leads to crystalization. Here bridging liquid and agitation force play an important role [12]. In this procedure, it is important to remember that the good solvent and poor solvent should have a stronger affinity than the good solvent and drug.

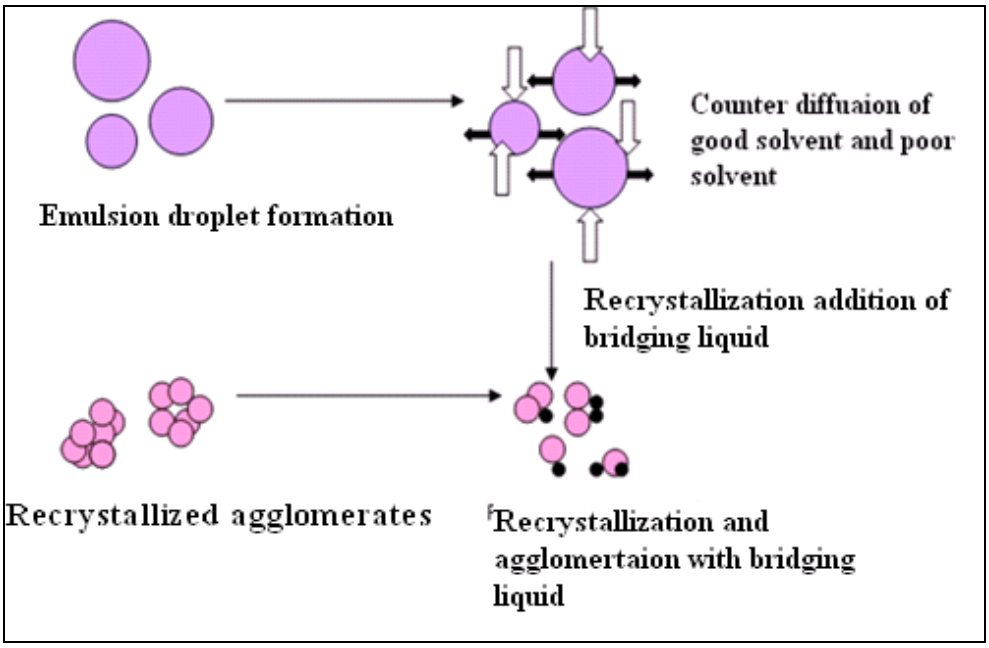

Figure no 2: Mechanism of recrystallized agglomerates formation by spherical crystallization.

The spherical crystallization process leads to the formation of small crystals and their agglomerates. The change of solvent system and salting-out effect is the driving force for spherical crystallization. Thus, formed larger particles are spherical with a controlled level of bridging liquid and agitation. Salicylic acid agglomerates were generated using the solvent change technique by using ethanol as a good solvent and water as a bad solvent using chloroform as a bridging liquid [12]. Propyphenazone crystals are prepared by using ethyl alcohol as a good solvent demineralized water as a bad solvent and isopropyl acetate act as a liquid for bridging [13].

2. Quasi-Emulsion Solvent Diffusion Method (QESD)

Depending on the crystallization method selected, agglomeration occurs with or without the addition of any binding liquid during the quasi-emulsion solvent diffusion phase. Although both of the solvents are somewhat miscible, in this case, crystallization is accomplished by adding a solution of the active ingredient in a good solvent to a vessel containing a poor solvent. When the drug solution is introduced to the insufficient solvent, a quasi-emulsion is created under the effect of agitation. In this procedure, the interaction between a good solvent and a drug is stronger than that between a good solvent and a poor solvent. The effective solvent serves as a bridging liquid in this situation, and droplet crystallization occurs when it diffuses out of the emulsion. The production of a quasi-emulsion is achieved using partially mixed systems such as bridging liquid-poor solvent systems or excellent solvent-bridging liquid-poor solvent systems in this approach. When a drug solution in bridging liquid (or plus good solvent) is poured into a poor solvent (dispersion medium) under agitation, counter diffusion occurs, and quasi-emulsion droplets of bridging liquid or good solvent form emulsion droplets in the dispersing medium, causing crystallization and agglomeration. The emulsion is stabilized using stabilizers in the Quasi-Emulsion Solvent Diffusion Method. Stabilizers are utilized, and the right polymers guarantee good crystallization [14].

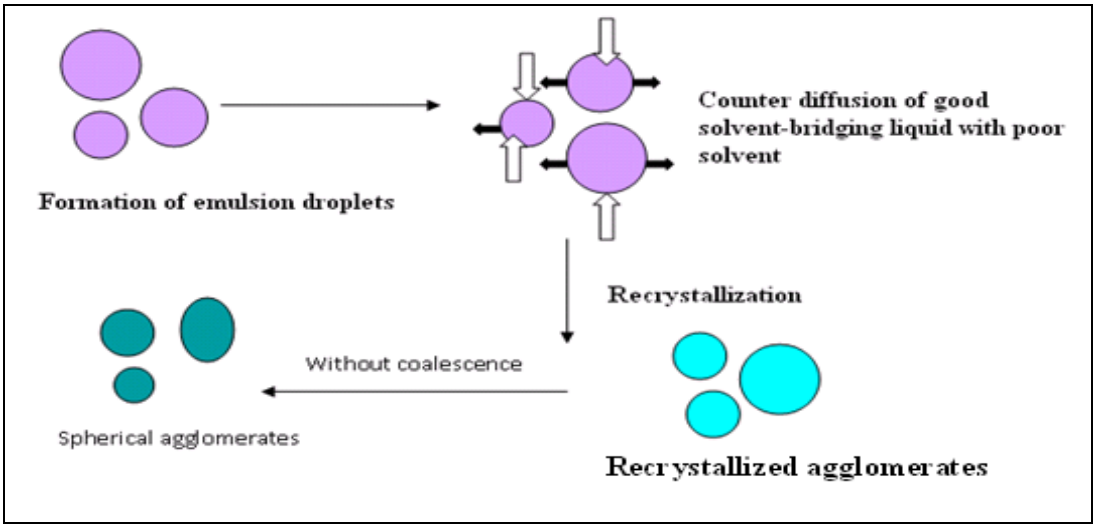

Figure no 3: Mechanism of recrystallized agglomerates formation by Quasi emulsion solvent diffusion method.

3. Ammonia Diffusion Method (ADM)

In the ammonia diffusion method, a solvent solution consisting of three immiscible solvents such as acetone, ammonia water, and dichloromethane was employed to crystallize. This approach is appropriate for active medicinal compounds that are soluble in both acid and basic environments. The ammonia diffusion technique works by a) allowing acetone to invade ammonia water droplets. b) Ammonia diffusion from the agglomerates to the outside solvent, c) agglomeration formation [15, 16].

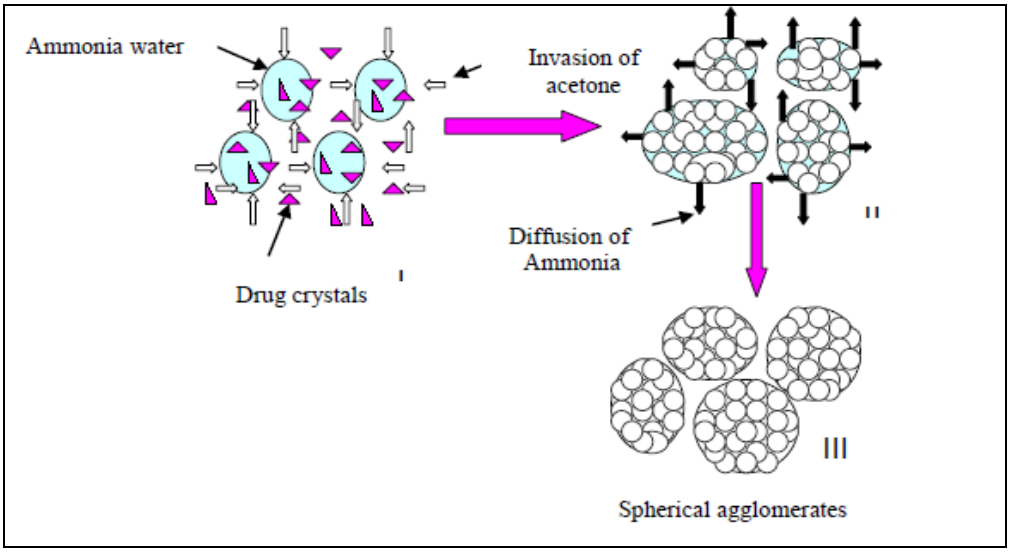

Figure no 3: Mechanism of recrystallized agglomerates formation by ammonia diffusion method.

4. Neutralization Technique (NT):

In this method, API is recrystallized using a basic solvent as a good solvent (ex. Sodium Hydroxide solution) and an acidic solution as a poor solvent (ex. Hydrochloric acid). A neutralization of NaOH solution by diluting HCL leads to crystallization where ether as an organic solvent acts as a solvent to form agglomerates. The agglomerates with acceptable PSD and good flowability were formed with the subsequent addition of water-soluble polymer [17].

5. Crystallo-co-agglomeration (CAA):

In the crystal-co-agglomeration technique crystallization and agglomeration takes place simultaneously. By crystal-co-agglomerates, we can prepare agglomerates of fixed-dose combinations. And can make agglomerates with the excipients also [18]. This method is novel as all the spherical crystallization methods are generally used for high-dose drugs but by using crystalloid-co-agglomerates we can prepare agglomerates of low-dose drugs also [19, 20]. By using the crystal-co-agglomerates technique low dose drugs can be agglomerated to give extended-release formulation [21]. crystalloid-co-agglomerates to be prepared by preparing a homogeneous mixture of drugs, diluents, polymers, or disintegrants in a good solvent with bridging liquid and stirring well to get homogeneous mass and poured simultaneously the homogeneous mass and bad solvent (we can prepare a slurry of polymers in bad solvents also) in a vessel with constant stirring which leads to the formation of agglomerates. Then do the filtration and decantation of agglomerates and dry the agglomerate.

EVALUATION OF SPHERICAL CRYSTALS

Spherical crystals are evaluated for their physicochemical characterization. Different analytical techniques are used for evaluation.

1. Drug content:

The drug content in Spherical crystals is to be carried out to evaluate the losses of API during processing and the final drug content in the agglomerate [22].

2. Saturation Solubility:

Solubility of the agglomerates may change drastically as this is a recrystallization technique there may be chances of change in polymorphism and formation of solvates or hydrate. Saturation solubility is performed by selecting a suitable method to determine the solubility of agglomerates and to compare the solubility of agglomerates with the intrinsic solubility of API [23].

3. Particle size and distribution:

Due to the agglomeration process particle size changes drastically and the agitation force imparts the sphericity to the agglomerates. A sieve analysis technique can be employed [24].

4. Particle Shape and morphology:

Particle shape and morphology play important role in the flow property of the material so particle shape and morphology are to be evaluated by using an optical microscope and scanning electron microscope (SEM)[25].

5. Melting point:

The melting point of the crystallized drug is to be measured using the capillary method and to be compared with such a drug.

6. Flow properties [26]

Flow property is dependent on the surface of the particle, the shape of the particle, particle distribution, and the flow properties of the spherical crystals or agglomerates to be measured by the below methods.

a) Density:

The density of the spherical crystals is to be calculated and compared with such a drug. And the density means the mass per unit volume. Density will be derived from the below formula.

$$\text{Density} = M/V$$

Where, M = Mass

V = Volume

b) Angle of Repose

The angle of repose can be measured by reprogramming and calculating the value following the formula to be used.

$$\text{Tan } \theta = h/0.5d$$

Where, h=height of the pile, d= diameter of the pile

As per USP General chapter <1174> powder flow, the scale of the angle of repose is as follows **(Table 1):**

Table 1: Flow properties and corresponding angles of repose

Flow Properties	The angle of repose (Degrees)
Excellent	25 – 30
Good	31 – 35
Fair-aid not needed	36 – 40
Passable-may hang up	41 – 45
Poor-must agitate, vibrate	46 – 55
Very poor	56 – 65
Very, very poor	> 66

c) Compressibility or Carr's index:

The ease of powder flow is given by Carr's index, the formula for the calculation is as below.

$$I = (1-V/Vo) \text{ X } 100$$

Where V = volume after tapping

Vo = volume before tapping.

d) Hausner Ratio:

To calculate the Hausner ratio data is to be generated for bulk and tapped density and to be calculated from the below equation.

$$\text{Hausner ratio} = \text{Tapped density/Bulk density}$$

As per USP General chapter <1174> powder flow, the scale of Carr's index and Hausner ratio is as follows (Table 2).

Table 2: Scale of flowability

Compressibility Index (%)	Flow Character	Hausner Ratio
≤ 10	Excellent	1.00 – 1.11
10 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
> 38	Very, very poor	> 1.60

e) Porosity:

To have good compressibility to the agglomerates, there are two types of porosity intergranular porosity and intergranular porosity, and can be depicted with help of true and granular densities. Below is the equation for porosity determination.

Intra granular porosity = 1-Granular density/True density.

Intergranular porosity = 1-Bulk density/Granular density

Total Porosity = 1-Bulk density/True density.

f) Packability:

Packability has been improved by the spherical crystal formation. The friction, cohesive stress, and shear indexes are less when compared to one crystal, resulting in improved packing characteristics of the agglomerates.

5. XRD analysis:

During spherical crystallization change in crystal, habit takes place to access the change in habitat of crystal the XRPD study to be performed.

6. Differential scanning calorimetry (DSC) [27]

While preparing the spherical crystals we need to add a stabilizer to stabilize the agglomerate. We use several polymers during the process. To monitor the effect of polymer on the melting points and the effect of the crystal habit of agglomerate.

7. Compression behavior of the formulation prepared by using spherical crystals

To process the direct compression, process the desired characteristics of the raw material is it should be free-flowing, having good compactibility and compressibility. The parameters to be evaluated for tablets manufactured by using spherical crystals are friability, hardness, disintegration, plastic deformation during the compression-like expansion of tablets, etc.

8. Drug Release.

The drug release and in-term bioavailability are based on different characteristics like surface area, density, and the specific surface area of crystals. The formulation prepared by spherical crystallization is to be evaluated for drug release by performing a validated dissolution method.

Factors influencing the process of spherical crystallization

Spherical crystallization technologies improve drug physicochemical properties like particle size and shape, density, stability, flowability, packability, agglomerated crystal compaction behavior, wettability, solubility, dissolution rate, and bioavailability are all factors to consider [28]. Characterization of spherical agglomerates in terms of physicochemical properties. The material's flow properties are influenced by the force generated between the particles, particle size, particle size distribution, particle shape, surface texture or roughness, and surface area. Because agglomerates have a shorter angle of repose than single crystals, their flowability is much improved. The following are a few factors discussed which affect the process of spherical crystallization [29].

Solvents:

The kind of solvent, quantity, and composition of the bridging liquid has an impact on the sphericity of the agglomerates that are produced [30]. As a general rule, in a normal SA procedure, the size of the agglomeration grows along with the amount of bridging liquid.

Observation shows that, as much bridging liquid is added to the system, there is no discernible difference in the size of the agglomerates after that point [31].

Agitation:

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. Higher agitation rates cause shearing of the agglomerates resulting in smaller agglomerates with fines or no agglomerates at all. Lower rates of agitation will produce the irregular size of spheres, which does not resolve the objectives of the method. Optimization of the agitation speed is a necessity for the production of agreeable products [32].

Temperature:

In the process of agglomeration, the optimum temperature is fundamentally important. The crystals contained a significant percentage of particles and did not aggregate at higher temperatures than room temperature. Compared to agglomerates created at room temperature, larger agglomerates were generated at lower temperatures, which unquestionably lowers the solubility and mechanical strength [33, 34].

Additives:

Polymers like polyethylene glycol, polyvinyl pyrrolidone, and hydroxypropyl methylcellulose slow down the nucleation process. These polymers stop crystals from spontaneously aggregating, giving adequate time for the development of spherical agglomerates. The polymers' altered crystal habits cause them to interfere with sphericity and particle size [35].

CONCLUSION:

In recent years due to an increase in the popularity of directly compressible formulation due to cost efficiency and reduced regulatory burden and non-compliance by reducing the no of steps during tablet manufacturing. Spherical crystallization has evolved as a major technique to prepare directly compressible raw materials. It has been observed that by spherical crystallization we can improve the Physicochemical properties of the Raw material such as flow property, density, and solubility. Due to improved flow properties and compaction behavior, spherical agglomerates demonstrated higher micrometric qualities in this work,

which may be useful in increasing the dissolve rate of poorly soluble tableting by direct compression. The use of spherical crystallization as the final step in bulk drug production can improve tablet manufacturing efficiency.

REFERENCES

1. Ribardiere A, Tchoreloff P, Couarraze G, Puisieux F. Modification of ketoprofen bead structure produced by the spherical crystallization technique with a two-solvent system. Int. J. Pharm. 1996;144(2):195-207.
2. Kawashima Y. -New Process-Application of Spherical Crystallization to Particulate Design of Pharmaceuticals for Direct Tabletting and Coating, and New Drug Delivery Systems. Powder Technol. 1994:493-512.
3. Keshwani BH, Jaimini MA, Sharma DI. Spherical crystallization: a revolution in the field of particle engineering. Int J Curr Pharm Res. 2015;7(4):19-25.
4. Ranpise AA, Chaudhari SP, Phatak AA, Kadam PM. A review on spherical crystallization-the novel agglomeration technique. Res J Pharm Technol 2012;5(10):1275-80.
5. Chatterjee A, Gupta MM, Srivastava B. Spherical crystallization: A technique use to reform solubility and flow property of active pharmaceutical ingredients. Int. J. Pharm. Investig.2017 Jan;7(1):4.
6. Patil SV, Sahoo SK. Spherical Crystallization: a method to improve tabletability. Res J Pharm Technol 2009;2(2):234-7.
7. Ghosh B, Patel J, Bose P, Roy D. Crystallo Coagglomeration-A Review. Int. J. Recent Sci. Res.. 2018;9(2):24226-30.
8. Kumar S, Chawla G, Bansal AK. Spherical crystallization of mebendazole to improve processability. Pharm. Dev. Technol.2008 Jan 1;13(6):559-68.
9. Bos AS, Heerens JJ. Light backscattering as a technique to measure solids particle size and concentration in suspension. Chem Eng Commun. 1982 Aug 1;16(1-6):301-11.
10. Thenge RR, Chandak MP, Adhao VS. Spherical Crystallization: A Tool to Improve the Physicochemical Properties of APIs. Asian j. pharm. res. dev. 2020 Jun 15;8(3):104-10.
11. Kawashima Y, Okumura M, Takenaka H. Spherical crystallization: direct spherical agglomeration of salicylic acid crystals during crystallization. Science. 1982 Jun 4;216(4550):1127-8.
12. Kawashima Y, Okumura M, Takenaka H. The effects of temperature on the spherical crystallization of salicylic acid. Powder technol. 1984 Aug 1;39(1):41-7.
13. Di Martino P, Di Cristofaro R, Barthelemy C, Joiris E, Filippo GP, Sante M. Improved compression properties of propyphenazone spherical crystals. Int. J. Pharm. 2000 Mar 20;197(1-2):95-106.
14. Chen H. Improve the Manufacturability and Dissolution Performance of Drugs Through Spherical Crystallization (Doctoral dissertation, University of Minnesota).
15. Ueda M, Nakamura Y, Makita H, Imasato Y, Kawashima Y. Particle Design of Enoxacin by Spherical Crystallization Technique. I.: Principle of Ammonia Diffusion System (ADS). Chem. Pharm. Bull.1990 Sep 25;38(9):2537-41.
16. Puechagut HG, Bianchotti J, Chiale CA. Preparation of norfloxacin spherical agglomerates using the ammonia diffusion system J. Pharm. Sci.1998 Apr 1;87(4):519-23.
17. Gadhave MV, Banerjee SK. Preparation and characterization of spherical crystals of embelin to improve the solubility and micromeritic properties. Int. J. Pharm. Clin. Res. 2014;6:363-9.
18. Ghosh B, Patel J, Bose P, Roy D. Crystallo Coagglomeration-A Review. Int. J. Recent Sci. Res. 2018;9(2):24226-30.
19. Paradkar AR, Pawar AP. Crystallo-co-agglomeration: A novel particle engineering technique. Asian J. Pharm. (AJP): Free full text articles from Asian J Pharm. 2014;4(1).
20. Pawar AP, Paradkar AR, Kadam SS, Mahadik KR. Crystallo-co-agglomeration: A novel technique to obtain ibuprofen-paracetamol agglomerates. AAPS PharmSciTech. 2004; (3):57-64.

21. Maghsoodi M, Taghizadeh O, Martin GP, Nokhodchi A. Particle design of naproxen-disintegrant agglomerates for direct compression by a crystallo-co-agglomeration technique. Int. J. Pharm. 2008;351(1-2):45-54.
22. Nokhodchi A., Maghsoodi M.J:, Preparation of spherical crystal agglomerates of naproxen containing disintegrant for direct tablet making by spherical crystallization technique. AAPS PharmSciTech. 2008;9:54-59.
23. Yadav AV, Yadav VB. Designing of pharmaceuticals to improve physicochemical properties by spherical crystallization technique. J. Pharm. Res. 2008;1(2):105-112.
24. Honmane S, Kadam A, Choudhari S, Patil R, Ansari SA, Gaikwad V. Effect of polymers and process parameters in augmenting the compactability and dissolution behaviour of oxcarbazepine spherical agglomerates. J Drug Deliv Sci Technol. 2021;11:102578.
25. Fadke J, Desai J, Thakkar H. Formulation development of spherical crystal agglomerates of itraconazole for preparation of directly compressible tablets with enhanced bioavailability. Aaps Pharmscitech. 2015;16(6):1434-1444.
26. Hareeja MM, Al-Khedairy EB. Formulation and in-vitro evaluation of spherical crystal agglomerates of ebastine by quasi emulsion solvent diffusion method. Iraqi J. Pharm. Sci. (P-ISSN: 1683-3597, E-ISSN: 2521-3512). 2018;6:77-92.
27. Singh MC, Loharkar RR, "Spherical crystallization of sitagliptine phosphate monohydrate for formulation of directly compressible tablets," Int. J. Pharm. Sci. Res., 2020; 11 (5): 2082-2092.
28. Thenge RR, Chandak MP, Adhao VS. Spherical Crystallization: A Tool to Improve the Physicochemical Properties of APIs. AJPRD. 2020; 8:104-110.
29. Sinha B, Müller RH, Möschwitzer JP. Bottom-up approaches for preparing drug nanocrystals: formulations and factors affecting particle size. Int. J. Pharm. 2013; 453:126-141.
30. Maghsoodi M. Role of solvents in improvement of dissolution rate of drugs: Crystal habit and crystal agglomeration. Adv Pharm Bull. 2015;5:13-18.
31. Katta J, Rasmuson AC. Spherical crystallization of benzoic acid. Int J Pharm. 2008; 348: 61-69.
32. 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: 32-34.
33. Velivela S, Pati NB, Gupta VR. Spherical crystallization: a novel technique in drug particle designing. World J. Pharm. Pharm. Sci. 2018; 25:363-376.
34. Wolbert F, Fahrig IK, Gottschalk T, Luebbert C, Thommes M, Sadowski G. Factors Influencing the Crystallization-Onset Time of Metastable ASDs. Pharmaceutics. 2022; 14: 269-276.
35. Patil S, Pawar A, Kumar S. Effect of additives on the physicochemical and drug release properties of pioglitazone hydrochloride spherical agglomerates. Trop. J. Pharm. Res. 2012; 11:18-27.