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Pharmaceutical overview of spherical crystallization

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Abstract

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability, compactability and bioavailability of crystalline drugs. General methods of spherical crystallization are spherical agglomeration, emulsion solvent diffusion and ammonia diffusion method. The principle steps involved in the process of spherical crystallization are flocculation zone, zero growth zone, fast growth zone and constant size zone. Factors controlling the process of agglomeration are solubility profile, mode and intensity of agitation, temperature of the system and residence time. Spherical crystallization is having wide applications in pharmaceuticals like improvement of flowability and compressibility of poorly compressible drugs, masking bitter taste of drugs and improving the solubility and dissolution rate of poorly soluble drug.

Keywords: spherical crystallization, flowability, compactability, bioavailability.

Introduction

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs. [1]. 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, flowability), packability (bulk density), wettability (contact angle) and compressibility. It was revealed from the studies that spherical agglomerates exhibited improved flowability, wettability, compaction behavior and bioavailability.

Methods of spherical crystallization

I. Spherical agglomeration

A near saturated solution of the drug in the good solvent is poured into the poor solvent. Provided that the poor and good solvents are freely miscible and the affinity between the solvents is stronger than the affinity between the drug and the good solvent, crystals will precipitate immediately. In the spherical agglomeration method also a third solvent called the bridging liquid is added in a smaller amount to promote the formation of agglomerates. [2]. Under agitation, the bridging liquid (the wetting agent) is added. The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid act to adhere the crystals to one another. [3]. The SA method has been applied to several drugs, and it has been found that the product properties are quite sensitive to the amount of the bridging liquid. [4]. Less than the optimum amount of bridging liquid produces plenty of fines and more than optimum produces very coarse particles. [5] Also the choice of bridging liquid, the stirring speed and the concentration of solids (or of the solute) are of importance. In the case of lactose, the agglomerate size distribution was affected by both the size of raw particles and the amount of bridging liquid used. At increasing stirring rate the agglomeration was reduced because of increasing disruptive forces. [6]. Higher stirring rate produce agglomerates that are less porous and more resistant to mechanical stress, and the porosity decreases when the concentration of solid increases [7]. The viscosity of the continuous phase has an effect on the size distribution of the agglomerates. The choice of bridging liquid has an influence on the rate of agglomeration and on the strength of the agglomerates.

II. Emulsion solvent diffusion

In the emulsion solvent diffusion the affinity between the drug and the good solvent is stronger than that of the good solvent and the poor solvent. [8] The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets. The method is considered to be simpler than the SA method, but it can be difficult to find a suitable additive to keep the system emulsified and to improve the diffusion of the poor solute into the dispersed phase.

III. Ammonia diffusion method

In this method, the mixture of three partially immiscible solvent i.e. acetone, ammonia water, dichloromethane was used as a crystallization system. In this system ammonia water acted as bridging liquid as well as good solvent, Acetone was the water miscible but a poor solvent, thus Drug precipitated by solvent change without forming ammonium salt. Water immiscible solvent such as hydrocarbons or halogenated hydrocarbons e.g. dichloromethane induced liberation of ammonia water. [9].

The principle steps involved in the process of spherical crystallization

Bermer and Zuider Wag proposed four steps in the growth of agglomeration. [10].

1. Flocculation Zone:

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

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

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

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

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

Factors controlling the process of agglomeration: [11]

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

2. Mode and intensity of agitation: High speed agitation is necessary to disperse the bridging liquid throughout the system. Any change in agitation pattern or fluid flow would be reflected as change in force acting on agglomerate, which ultimately affects the shape of agglomerate. The extent of mechanical agitation in conjugation with the amount of bridging liquid determines the rate of formation of agglomerate and their final size.

3. Temperature of the system: Study revealed that the temperature has a significant influence on the shape, size and texture of the agglomerates. The effect of temperature on

spherical crystallization is probably due to the effect of temperature on the solubility of drug substance in the ternary system.

4. Residence time: The time for which agglomerates remain suspended in reaction mixture affect their strength.

Applications of spherical crystallization in pharmaceuticals

1. To improve the flowability and compressibility:

Today the tablet is the most popular dosage form of all pharmaceutical preparations produced. From the manufacturing point of view tablets can be produced at much higher rate than any other dosage form. Tablet is the most stable readily portable and consumed dosage form. The formulation of tablet is optimized to achieve goals. The focus today in the business is better drug delivery concepts, but also makes the simple standard formulations as economical as possible to produce. One of the most economical solutions is to find directly compressible formulations and this is especially at interest for large volume products.

Table 1: List of drugs on various spherical agglomeration techniques have been tried for improving physicochemical properties

Drug	Method	Property improved	Reference
Roxythromycin	SA	Flowability and Compressibility	17
Aminophylline	SA	Flowability and Compressibility	18
Naproxen	SA	Flowability and Compressibility	19
Aspirin	SA	Flowability and Compressibility	20
Salicylic acid	SA	Flowability and Compressibility	21
Aspartic acid	SA	Flowability and Compressibility	22
Ibuprofen	SA	Flowability and Compressibility	23
Acetyl salicylic acid	SA	Flowability and Compressibility	24
Ascorbic acid	SA	Flowability and Compressibility	25
Tranilast	SA	Solubility and Bioavailability	26
Celecoxib	SA	Flowability and Compressibility	27
Mefenamic acid	SA	Flowability and Compressibility	28
Nabumetone	SA	Flowability and Compressibility	28
Aceclofenac	SA	Solubility and Bioavailability	29
Fenbufen	SA	Solubility and Bioavailability	30
Flurbiprofen	SA	Solubility and Bioavailability	31
Ibuprofen	ESD	Flowability and Compressibility	32
Acebutalol HCl	ESD	Flowability and Compressibility	33
Mefenamic acid	ESD	Flowability and Compressibility	34
Carbamazepine	SA	Flowability and Compressibility	35
ATH	ADM	Taste masking	36
Norfloxacin	ADM	Flowability and Compressibility	37
Enoxacin	ADM	Taste masking	38

SA: Spherical agglomeration, ESD: Emulsion solvent diffusion, ADM: Ammonia diffusion method, HCl: Hydrochloride, ATH: Ampicilin trihydrate.

These have been renewed interest in examining the potential of direct compression tabletting over recent years since in comparison to the used at the more traditional granulation process. Such manufacturing of the tablets involves simple mixing and compression of powders which

gives benefits like time and cost saving [12]. An interesting alternative is to manufacture larger particles in situ by agglomeration of the small crystals during the crystallization. In addition, it has been revealed that agglomerates have properties that make suitable for direct compression tabletting. Crystals could be generated employing any of the available techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding [13]. Thus the novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during crystallization process has been desired [14]. The use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression [15, 16]. Due to different crystal habit many drugs show inconvenient flowability and compressibility. So these problems can be solved by converting them into a agglomerated crystals by changing the crystal habit and spheronization so as to increase the flowability and compressibility. Various drugs of which flow and compressibility are improved were listed in table 1.

2. For masking bitter taste of drug:

Microcapsules are prepared to mask the bitter taste of the drug. They are suitable for coating granules, since spherical material can be uniformly coated with a relatively small amount of polymer. Microcapsules of following drugs were prepared for masking of bitter taste. Various drugs of which taste masking has done were listed in table 1.

3. For increasing solubility and dissolution rate of poorly soluble drug:

Spherical crystallization has been described as a very effective technique in improving the dissolution behavior of some drugs having low water solubility and a slow dissolution profile. Various drugs of solubility and bioavailability is improved were listed in table 1.

References

[1] A.R. Paradkar, A.P. Pawar, K.R. Mahadik, S.S. Kadam. *Indian Drugs* **1994**; 6: 229–233.
[2] Y. Kawashima. New processes—application of spherical crystallization to particulate design of pharmaceuticals for direct tabletting and coating and new drug delivery systems. In: Powder Technology and Pharmaceutical Processes. Handbook of Powder Technology, **1994**; 9: 493–512.
[3] Y. Kawashima, M. Okumura, H. Takenaka. *Powder Technol*. **1984**; 39: 41–47.
[4] Y. Kawashima, M. Imai, H. Takeuchi, H. Yamamoto, K. Kamiya, T Hino. *Powder Technol*. **2003**; 130: 283–289.
[5] A. Bausch, H. Leuenberger. *Int J Pharm*. **1994**; 101: 63–70.
[6] A.S. Bos, F.J. Zuiderweg. *Chem Eng Res Des*. **1987**; 65a: 187.
[7] A.F. Blandin, D. Mangin, A. Rivoire, J.P. Klein, JM Bossoutrot. *Powder Technol*. **2003**; 130: 316–323.
[8] A. Sano, T. Kuriki, Y. Kawashima, H. Takeuchi, T. Hino, T. Niwa. *Chem Pharm Bull*. **1992**; 40: 3030–3035.
[9] Y. Kawashima, F. Cui, H. Takeuchi, T. Hino, T. Niwa, K. Kiuchi. *Int J Pharm*. **1995**; 119: 139-147.
[10] M.K. Chouracia, A. Jain, S. Valdya, S.K .Jain. *Indian Drugs*. **2004**; 41 (6), 319-29.
[11] P.K. Kulkarni, B.G. Nagavi. *Ind. Jr. Pharm. Eudc*. **2002**; 36(2), 66-73.
[12] R.F. Shangraw. Compressed tablets by direct compression. In: Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: Tablets, vol. 1. Marcel Dekker, New York, **1989**; 195–246.

[13] J.K. Guillory. Polymorphism in pharmaceutical solids. Marcel Dekker, New York, **1989**; 183-226.
[14] Y. Kawashima. *Arch Pharm. Res*. **1984**; 7(2): 145-151.
[15] Y. Kawashima, H. Ohno, H. Takenaka. *J. Pharm. Sci.* **1981**; 70(8): 913-916.
[16] Y. Kawashima, K. Furukawa, H. Takenaka. *Powder Technol.* **1981**; 30: 211.
[17] G.G. Bermer, F.G. Zuiderweg. Proceedings of international symposium of fine particles. AIME, New York. **1992**; 1524-46.
[18] Y. Kawashima, S. Aoki, H Takenaka, Y. Miyake. *J Pharm Sci*. **1984**; 73 (10): 1407-10.
[19] M.S. Gordon , Z.T. Chowhan. *Drug Dev Ind Pharm*. **1990**; 16 (8): 1279-1290.
[20] M.C. Deshpande, KR Mahadik, AP Pawar, AR Paradkar. *Ind J Pharm Sci*. **1997**; 59 (1): 32-34.
[21] Y. Kawashima, M. Okumura, H. Takenaka. *Science*. **1982**; 216(4): 1127-28.
[22] P. Szabo-Revesz, H. Goczo, K. Pintye-Hodi, P. Kasa, I.M. Eros. M. Hasznos-Nezdei, B. Farkas. *Powder Technol*. **2001**; 114: 118–124.
[23] M. Jbilou, A. Ettabia, A.M. Guyot-Hermann, J.S. Guyot. *Drug Dev Ind Pharm*. **1990**; 25(3): 297-305.
[24] H. Goczo, R.P. Szabo, M. HasznosNezdei, et al. *Chem Pharm Bull*. **2000**; 48(12): 1877-81.
[25] Y. Kawashim, M. Imai, H. Takeuchi, H. Yamamoto, K. Kamiya. *KONA*. **2002**; 20(3): 251-261.
[26] Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino, Y. Itoh, S Furuyama. *J Pharm Sci*. **1991**; 80(5): 472-78.
[27] V.R. Gupta, M. Srinivas, M.M. Patel, G.K. Jani. *Acta Pharm*. **2007**; 57: 173-184.
[28] C.L. Viswanathan, S.K. Kulkarni, D.R. Kolwankar. *AAPS Pharm Sci Tech* **2006**; 7 (2): Article 48.
[29] A.N. Usha, S. Mutalik, M.S. Reddy, A.K. Ranjith, P. Kushtagi, N. Udupa. *Eur J Pharm Biopharm.* **2008**: 70: 674-683.
[30] P.D. Martino, C. Barthelemy, F. Piva, E. Joiris, C. Marthelemy. *Drug Dev.Ind.Pharm*. **1999**; 25 (10), 1073-1081.
[31] M.K. Chourasia, S.K. Jain, N.K. Jain. *Ind.Jr.Pharm.Sci*. **2003**; May-June, 287-291.
[32] Y. Kawashima, T. Niwa, T. Handa, H. Takeuchi, T. Iwamoto. *J Pharm Sci*. **1989**; 78(1); 68-72.
[33] Y. Kawashima, F. Cui, H. Takeuchi, T. Hino, T. Niwa, K. Kiuchi. **1995**; *Int J Pharm.*119: 139-147.
[34] S. Bhadra, M. Kumar, S. jain, S. Agrawal, G.P. Agrawal. *Pharm Tech.* Feb. **2004**; 66-76.
[35] A.Y. Yadav, V.B. Yadav. *Asian Journal of Pharmaceutics*; **2009**, 1, 18-25.
[36] M.C. Gohle, R.K. Parikh, H. Shen, R.R. Rubey. *Ind J Pharm Sci*. **2003**; 634-37.
[37] G.P. Hector, B. Jorge, A. Carlo. *J Pharm Sci.* **1998**; 87(4): 519-23.
[38] M. Ueda, Y. Nakamura, H. Makita, Y. Imasato, Y. Kawashima. *Chem Pharm Bull*. **1991**; 39(5):1277-1281.