We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,600
Open access books available

178,000
International authors and editors

195M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Preparation of Carvedilol Spherical Crystals Having Solid Dispersion Structure by the Emulsion Solvent Diffusion Method and Evaluation of Its in vitro Characteristics

Amit R. Tapas, Pravin S. Kawtikwar and Dinesh M. Sakarkar
Sudhakarrao Naik Institute of Pharmacy, Pusad, Dist Yavatmal, Maharashtra India

1. Introduction

Solid dispersion is one of the most efficient techniques to improve the dissolution rate of poorly water-soluble drugs, leading to an improvement in the relative bioavailability of their formulations. At present, the solvent method and the melting method are widely used in the preparation of solid dispersions. In general, subsequent grinding, sieving, mixing and granulation are necessary to produce the different desired formulations.

The spherical agglomeration technique has been used as an efficient particle preparation technique developed by Kawashima in the 1980s (Kawashima et al., 1994). Initially, spherical agglomeration technique was used to improve powder flowability, packability, and compressibility (Usha et al. 2008; Yadav and Yadav, 2008; Bodmeier and Paeratakul et al., 1989). Then polymers were introduced in this system to modify their release (Di Martino et al., 1999). Currently, this technique is used more frequently for the solid dispersion preparation of water-insoluble drugs in order to improve their solubility, dissolution rate and simplify the manufacturing process (Cui et al., 2003, Tapas et al. 2009, 2010). Spherical crystallization has been developed by Yoshiaki Kawashima and co-workers as a novel particulate design technique to improve processibility such as mixing, filling, tableting characteristics and dissolution rate of pharmaceuticals (Kawashima et al., 1974, 1976, 1981, 1982, 1983, 1984, 1985, 1989, 1991, 1994, 1995, 2002, 2003). The resultant crystals can be designated as spherical agglomerates (Kulkarni and Nagavi, 2002). Spherical crystallization is an effective alternative to improve dissolution rate of drugs (Sano et al., 1992). Now days functional drug devices such as microspheres, microcapsules, microballoons and biodegradable nanospheres were developed using the emulsion solvent diffusion techniques involving the introduction of a functional polymer into the system (Di Martino et al., 1999; Marshall and York, 1991; Garekani and Ford, 1999). This can be achieved by various methods such as

1. Spherical Agglomeration (SA)
2. Quasi Emulsion Solvent Diffusion (QESD)
3. Ammonia Diffusion System (ADS)
4. Neutralization (NT)
Out of which first two are the most common methods in practice.

In the spherical crystallization process, crystal formation, growth and agglomeration occur simultaneously within the same system. In this method, a third solvent called the bridging liquid is added in a smaller amount to purposely induce and promote the formation of agglomerates. Crystals are agglomerated during the crystallization process and large spherical agglomerates are produced. A near saturated solution of the drug in a good solvent is poured into a poor solvent. The poor and good solvents are freely miscible and the "affinity" between the solvents is stronger than the affinity between drug and good solvent, leading to precipitation of crystals immediately. Under agitation, the bridging liquid (the wetting agent) is added, which is immiscible with the poor solvent and preferentially wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid acts to adhere the crystals to one another and facilitates them to agglomerate (Fig. 1).

![Fig. 1. Two sample particles joined together by a liquid bridge](image)

In spherical agglomeration method, when a drug solution (in good solvent) was poured into a poor solvent under agitation, the drug crystals were formed immediately and agglomerated with a bridging liquid dispersed in the poor solvent, because the bridging liquid has a preference for wetting the drug crystals.

Quasi emulsion solvent diffusion method is also known as transient emulsion method. Firstly the drug was dissolved in a mixed solvent of good solvent and bridging liquid. Because of the increased interfacial tension between the two solvents, 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. Especially hydrophilic/hydrophobic additives are used to improve the diffusion remarkably. In this method the shape and the structure of the agglomerate depend strongly on the good solvent to poor solvent ratio and the temperature difference between the two
solvents when the drug solution was introduced into the poor solvent under certain temperature and stirring, the drug solution was dispersed immediately to form quasi o/w emulsion droplets, the emulsion droplets were gradually solidified, forming spherical agglomerates along with the diffusion of the good solvent from the droplets into the poor solvent.

Spherical agglomeration has got more importance than other methods because it is easy to operate and the selection of the solvents is easier than in the other methods. Quasi emulsion solvent diffusion method has the second importance.

An ammonia diffusion system is applicable to amphoteric drug substances. In this method, the mixture of three partially immiscible solvent i.e. acetone, ammonia water, dichloromethane was used as crystallization system. In this system ammonia water acted as bridging liquid as well as good solvent, acetone as the water miscible but poor solvent, thus drug precipitated by solvent change without forming ammonium salt. Water immiscible solvent such as hydrocarbon or halogenated hydrocarbons e.g. dichloromethane induced liberation of ammonia water.

In neutralization method sodium hydroxide acts as a good solvent and hydrochloric acid as a poor solvent or vice-versa. These solutions were added to each other in order to get neutralization. The bridging liquid was added drop wise under agitation to form spherical agglomerates.

In this study special attention was given to improving the solubility and dissolution rate of poorly water soluble drug carvedilol using quasi emulsion solvent diffusion method. Carvedilol (CAR) (fig. 2), (+)-1-(carbazol-4yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol is an α, β and β adrenergic receptor antagonist (Sweetman, 2002). It is used to treat mild to moderate essential hypertension, mild to severe heart failure, and patients with systolic dysfunction after myocardial infraction. Carvedilol is practically insoluble in water and exhibits pH dependent solubility. Its solubility is <1µg/ml above pH 9.0, 23 µg/ml at pH 7, and about 100 µg/ml at pH 5 at room temperature. It’s extremely low solubility at alkaline pH levels may prevent the drug from being available for absorption in the small intestine and colon, thus making it poor candidate for an extended release dosage form. In the present study, to overcome the problems related to solubility, dissolution rate, flowability, and compressibility, the microspheres having solid dispersions structure of Carvedilol were prepared by emulsion solvent diffusion method by using a poloxamer (poloxamer F68 and poloxamer F127) as a hydrophilic polymer.

![Chemical structure of Carvedilol (CAR)](https://www.intechopen.com)
2. Materials and methods

2.1 Materials
Carvedilol was supplied by Dr. Reddy’s Laboratory, Hyderabad, India as a gift sample. Poloxamer F68 and F127 were supplied by Lupin Research Park, Pune, India. All other chemicals used were of analytical grade.

2.2 Methods
Carvedilol (1.0 g) with poloxamer was dissolved in good solvent methanol (12.0 mL). The bridging liquid dichloromethane (2.0 mL) was added to it. The resulting solution was then poured dropwise into the poor solvent distilled water (100 mL) containing Aerosil 200 Pharma (0.1 g). The mixture was stirred continuously for a period of 0.5 h using a controlled speed mechanical stirrer (Remi motors, India) at 1000 rpm. As the good solvent diffused into the poor solvent, droplets gradually solidified. Finally the coprecipitated microspheres of the drug-polymer were filtered through Whatman filter paper (No.1) and dried in desiccator at room temperature. The amount of poloxamers was altered to get desired microspheres. The composition is given in Table 1.

| Composition/Parameters | CP681 | CP682 | CP1271 | CP1272 |
|------------------------|-------|-------|--------|--------|
| CAR (g)                | 1.0   | 1.0   | 1.0    | 1.0    |
| Methanol (ml)          | 12.0  | 12.0  | 12.0   | 12.0   |
| DCM (ml)               | 2.0   | 2.0   | 2.0    | 2.0    |
| Water (ml)             | 100   | 100   | 100    | 100    |
| Poloxamer F68 (g)      | 1.5   | 3.0   | --     | --     |
| Poloxamer F127 (g)     | --    | --    | 1.5    | 3.0    |
| Aerosil 200 pharma (g) | 0.1   | 0.1   | 0.1    | 0.1    |
| Stirring speed (rpm)   | 1000  | 1000  | 1000   | 1000   |

Table 1. Composition of spherical crystals

2.2.1 Drug content study
The drug content study of agglomerates was determined by dissolving 100 mg of crystals in 3 ml methanol and diluting further with distilled water (100 ml) followed by measuring the absorbance of appropriately diluted solution spectrophotometrically (PharmaSpec UV-1700, UV-Vis spectrophotometer, Shimadzu) at 286 nm.

2.2.2 Fourier Transform Infrared Spectroscopy (FTIR)
The FTIR spectra of powder CAR, and their agglomerates were recorded on an FTIR spectrophotometer (JASCO, FTIR V-430 Plus).

2.2.3 Differential Scanning Calorimetry (DSC)
DSC analysis was performed using a DSC 823 calorimeter (Mettler Toledo model) operated by STARE software. Samples of CAR and its agglomerates were sealed in an aluminium
crucible and heated at the rate of 10 °C/min up to 300 °C under a nitrogen atmosphere (40 ml/min).

2.2.4 Powder X-ray diffraction studies
Powder X-ray diffraction patterns (XRD) of the CAR and its spherical agglomerates were monitored with an x-ray diffractometer (Philips Analytical XRD) using copper as x-ray target, a voltage of 40 KV, a current of 25 mA and with 2.28970 Å wavelength. The samples were analyzed over 2θ range of 10.01–99.99° with scanning step size of 0.02° (2θ) and scan step time of 0.8 second.

2.2.5 Scanning electron microscopy
The surface morphology of the agglomerates was accessed by SEM. The crystals were sputter coated with gold before scanning.

2.2.6 Micromeric properties
The size of agglomerates was determined by microscopic method using stage and eyepiece micrometers. The shape of the agglomerates was observed under an optical microscope (×60 magnification) attached to a computer. Flowability of untreated carvedilol and agglomerates was assessed by determination of angle of repose, Carr’s index (CI) and Hausner’s ratio (HR) (Wells, 2002). Angle of repose was determined by fixed funnel method (Martin et al., 2002). The mean of three determinations was reported. The CI and HR were calculated from the loose and tapped densities. Tapped density was determined by tapping the samples into a 10 ml measuring cylinder. The CI and HR were calculated according to the following equation 1 and 2.

\[
C.I. = \frac{Tapped \ density – Bulk \ density}{Tapped \ density} \times 100 \quad (1)
\]

\[
H.R. = \frac{Tapped \ density}{Bulk \ density} \quad (2)
\]

2.2.7 Solubility studies
A quantity of crystals (about 100 mg) was shaken with 10 mL distilled water in stoppered conical flask at incubator shaker for 24 h at room temperature. The solution was then passed through a whatmann filter paper (No. 42) and amount of drug dissolved was analyzed spectrophotometrically.

2.2.8 Dissolution rate studies
The dissolution rate studies of carvedilol alone and its spherical agglomerates were performed in triplicate in a dissolution apparatus (Electrolab, India) using the paddle method (USP Type II). Dissolution studies were carried out using 900 ml of 0.1N HCl (pH 1.2) at 37 ± 0.5 °C at 50 rpm as per US FDA guidelines (U.S. Food and drug administration [USFDA], 2010 and Bhutani et al., 2007.). 12.5 mg of carvedilol or its equivalent amount of...
spherical agglomerates were added to 900 ml of 0.1N HCl (pH 1.2). Samples (5 ml) were withdrawn at time intervals of 10, 20, 30, and 60 min. The volume of dissolution medium was adjusted to 900 ml by replacing each 5 ml aliquot withdrawn with 5 ml of fresh 0.1N HCl (pH 1.2). The solution was immediately filtered, suitably diluted and the concentrations of carvedilol in samples were determined spectrophotometrically at 286 nm. The results obtained from the dissolution studies were statistically validated using ANOVA.

2.2.9 Dissolution efficiency studies

The dissolution efficiency (DE) of the batches was calculated by the method mentioned by Khan (Khan, 1975). It is defined as the area under the dissolution curve between time points \( t_1 \) and \( t_2 \) expressed as a percentage of the curve at maximum dissolution, \( y_{100} \), over the same time period or the area under the dissolution curve up to a certain time, \( t \), (measured using trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. \( \text{DE}_{60} \) values were calculated from dissolution data and used to evaluate the dissolution rate (Anderson et al., 1998).

\[
\text{Dissolution Efficiency} = \frac{\int_0^t y(t)\,dt}{y_{100}(t_2 - t_1)} \times 100
\]

3. Result and discussion

3.1 Preparation of spherical crystals

A typical spherical crystallization system involved a good solvent, a poor solvent for a drug and a bridging liquid. The selection of these solvent depends on miscibility of the solvents and solubility of drug in individual solvents. Accordingly acetone, dichloromethane, water were selected as a good solvent, bridging liquid, and poor solvent, respectively. CAR is soluble in methanol, but poorly soluble in water. Also it is soluble in dichloromethane which is immiscible in water. Hence, this solvent system was used in the present study. When drug polymer solution was poured into the poor solvent under agitation at selected temperature, the drug polymer solution became immediately semitransparent due to the presence of small sized emulsion droplets. Gradually emulsion droplets solidified along with diffusion of the good solvents, as bridging liquid dichloromethane was commixed with good solvent, when the good solvent in the droplets diffused into the poor solvent, the residual dichloromethane in the droplets bridged the Aerosil, coprecipitated drug, and polymer to form spherical crystals. The Aerosil acts as a dispering agent and mass compactor, because coacervation droplets formed from the drug-polymer droplets during the solidifying period were sticky and readily coalesced, while the introduction of Aerosil efficiently prevented coalescence and produced compact spherical crystals.

3.2 Optimization of process variables for preparation of spherical crystals

To optimize the Carvedilol spherical crystallization by methanol, water, dichloromethane solvent system following parameters considered amount and mode of addition of bridging liquid, stirring speed and temperature. (Table 2).
Preparation of Carvedilol Spherical Crystals Having Solid Dispersion Structure by the Emulsion Solvent Diffusion Method and Evaluation of Its in vitro Characteristics

### Table 2. Parameters affecting spherical agglomeration

| S.No. | Parameter                              | Variables | Observation                        |
|-------|----------------------------------------|-----------|------------------------------------|
| 1     | Conc. of Bridging Liquid (Dichloromethane) | 1 ml      | No agglomeration                   |
|       |                                        | 2 ml      | Agglomeration                      |
|       |                                        | 3 ml      | No agglomeration                   |
| 2     | Agitation speed                        | 800 rpm   | Spherical but large                |
|       |                                        | 1000 rpm  | Spherical                          |
|       |                                        | 1200 rpm  | Irregular shape and small          |
| 3     | Agitation time                         | 15 min    | Incomplete agglomerates            |
|       |                                        | 30 min    | Spherical agglomerates             |
| 4     | Mode of addition of bridging liquid     | Whole at a time | Crystals of irregular geometry     |
|       |                                        | Drop wise | Spherical agglomerates             |

### 3.3 Drug content study

Percent drug content was found to be in the range of 92.12±1.60 to 94.4±2.37 (Table 3).

### 3.4 Micromeritic properties

Pure CAR could not pass through the funnel during the angle of repose experiment which could be due to the irregular shape and high fineness of the powder, which posed hurdles in the uniform flow from the funnel. It exhibited poor flowability and packability as indicated by Hausner ratio (1.52) and Carr’s Index (34.37%). All agglomerates showed excellent flowability and packability (Angle of repose: 23-28°; Carr’s Index: 15-18%; Hausner ratio: 1.13-1.17) when compared to pure CAR. The improved flowability of agglomerates may be due to good sphericity and larger size of agglomerates. During the tapping process, smaller agglomerates might have infiltrated into the voids between larger particles, which could result improved packability (lower CI). The results of micromeritic properties are shown in Table 3.

### Table 3. Micromeritics, Drug Content, Particle size, aqueous solubility data of carvedilol and its spherical crystals

| S.No. | Samples  | Drug Content | Carr’s Index | Hausner Ratio | Angle of Repose | Particle Size (µm) | Aqueous Solubility (µgmL⁻¹) |
|-------|----------|--------------|--------------|---------------|-----------------|-------------------|---------------------------|
| 1     | CAR      | 100.0±0.0    | 34.37±1.79   | 1.52±1.26     | ---             | 71.55±5.37        | 21.0 ± 0.51               |
| 2     | CP681    | 94.4±2.37    | 17.53±1.49   | 1.15±2.67     | 27.12±2.43      | 112.7±31.26       | 32.20 ± 1.32              |
| 3     | CP682    | 92.3±2.02    | 15.64±1.43   | 1.13±2.21     | 25.36±0.67      | 136.4±18.57       | 39.04 ± 1.65              |
| 4     | CP1271   | 94.19±1.15   | 18.63±2.90   | 1.17±1.82     | 28.42±0.23      | 88.92±25.38       | 58.08 ± 1.28              |
| 5     | CP1272   | 92.12±1.60   | 17.24±1.87   | 1.14±1.53     | 23.05±0.89      | 102.03±20.11      | 64.25 ± 1.31              |

*Mean ± SD, n = 3; bSignificantly different compared to pure CAR (p<0.05).

### 3.5 FTIR, DSC and powder X-ray studies

The FTIR spectra of CAR as well as its spherical crystals are presented in Figure 3. FTIR of CAR showed a characteristic peaks at 3343.96 (N-H str. Aromatic Amines), 3062.41 (C-H str.
Fig. 3. FTIR spectra of (A) – Carvedilol, (B) – CP682, (C) – CP1272

Aromatic Hydrocarbon), 2923.56 (C-H str. in –CH$_3$ / –CH$_2$), 1592.91 (C=C str. Aromatic), 1253.5, 1214.93, 1099.23 (C-O str. in Ar C=C-O-C) cm$^{-1}$. There was no considerable change in the IR peaks of the spherical agglomerates when compared with pure CAR, which revealed that no chemical interaction had occurred between drug and polymer during agglomeration process.

Figure 4 shows the DSC thermogram of pure CAR and its spherical crystals. DSC thermogram of CAR showed endothermic peak at 120.47°C, which represented melting of carvedilol. There was negligible change in the melting point endotherms of prepared spherical crystals compared to pure drug (CP682 = 115.47°C, CP1272 = 118.67°C). The endotherms at 57.05°C and 59.07°C ascribed to the melting of Poloxamer F68 and Poloxamer F127 respectively. This observation further supports the IR spectroscopy results, which indicated the absence of any interactions between the drug and additives used in the preparation. However, there was a decrease, although very small, in the melting point of the drug in the spherical crystals compared to that of pure carvedilol. This indicates the little amorphization of carvedilol when prepared in the form of spherical crystals.
Fig. 4. DSC thermogram of (A) – Carvedilol, (B) – CP682, (C) – CP1272.

The XRD patterns of CAR shown in figure 5. The intense peaks at 2θ of 26.16°, 27.48°, 36.47° and 39.34° with peak intensities (counts) 310, 256, 228 and 135 respectively obtained from CAR confirmed the crystalline form of CAR. The PXRD patterns of CAR spherical crystals could be distinguished from the pure CAR. Peaks at around 8.4, 17, 22° 2θ confirms the change in crystal arrangements of CAR in its spherical crystal form.
Fig. 5. XRD patterns of (A) – Carvedilol, (B) – CP682, (C) – CP1272.
3.6 Scanning electron microscopy

The results of surface morphology studies are shown in Figure 6. The SEM results revealed the spherical structure of agglomerates. The surface morphology studies also revealed that the agglomerates were formed by very small crystals, which were closely compacted into spherical form. These photo-micrographs show that the prepared agglomerates were spherical in shape which enabled them to flow very easily.
3.7 Dissolution rate studies

The dissolution curves of pure carvedilol and its spherical crystals in 0.1 N HCl (pH 1.2) are shown in fig. 7. The release rate profiles were expressed as the percentage drug released vs. time. Table 4 shows % drug dissolved in 1h (DP$_{60}$) and dissolution efficiency values at 30 min (DE$_{30}$) for carvedilol and its spherical crystals. These values are tested statistically through one way ANOVA and are found significantly different (p<0.05) from pure carvedilol. As indicated carvedilol was dissolved more than 80% from spherical crystals CP681, CP1271 and CP1272 after 1h and more than 90% from spherical crystal CP682 while the pure CAR powder was just dissolved 34.37% at comparable time. The results revealed that the spherical crystals caused significant increase (P<0.05) in drug release compared to the pure drug. Enhancement in dissolution rate of spherical agglomerates as compared to pure drug may be due the presence of hydrophilic polymer, Poloxamer. The mechanism

| Sample  | Carvedilol Release after 1h | Dissolution Efficiency at 30 min |
|---------|-----------------------------|---------------------------------|
| CAR     | 34.37±0.19                  | 20.56±0.09                      |
| CP681   | 83.42±0.25$^b$              | 66.12±0.31$^b$                  |
| CP682   | 95.52±0.25$^b$              | 70.63±1.38$^b$                  |
| CP1271  | 82.26±0.96$^b$              | 65.90±0.14$^b$                  |
| CP1272  | 84.42±0.07$^b$              | 67.39±0.39$^b$                  |

$^a$Mean ± SD, n = 3

$^b$Significantly different compared to carvedilol (p < 0.05).

Table 4. Drug Release and Dissolution Efficiency

www.intechopen.com
behind the greater solubility and dissolution of CAR from its agglomerated form may resemble the solid dispersion mechanism despite the larger particle size of agglomerates. This effect may be due to improved wettability of the surface of agglomerates by the adsorption of poloxamer onto the surfaces of crystals. These results confirm that the dissolution rate of carvedilol was increased in form of spherical crystals when compared to its pure form.

4. Conclusion

CAR-poloxamer spherical crystals were prepared successfully by ESD method. The resultant crystals have the desired micromeritic properties, such as flowability and packability. In the present investigation Poloxamer F68 and Poloxamer F127 has significantly improved dissolution rate of carvedilol. However in vivo bioavailability studies are required to ensure whether, the results obtain in this investigation can be extrapolated to the in vivo conditions.

5. Acknowledgments

The authors gratefully acknowledge Dr. Reddy’s Laboratory, Hyderabad, India for the gift sample of Carvedilol. The authors are thankful to AISSMS college of Pharmacy, Pune, India for providing FTIR and DSC facilities. Also the authors would like to thank Shivaji University, Kolhapur, India for providing PXRD facility.
6. References

Anderson, N.H., Bauer, M., Boussac, N., Khan-Malek, R., Munden, P., Sardaro, M. (1998). An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. *Journal of Pharmaceutical and Biomedical Analysis*, 17, 811-822.

Bhutani, S., Hiremath, S.N., Swamy, P.V., Raju, S.A. (2001). Preparation and evaluation of inclusion complexes of carvedilol. *Journal of Scientific and Industrial Research*, 66, 830-834.

Bodmeier R., Paeratakul R. (1989). Spherical agglomerates of water-insoluble drugs. *Journal of Pharmaceutical Sciences*, 78, 964-967.

Cui F., Yang M., Jiang Y., Cun D., Lin W., Fan Y., Kawashima Y (2003). Design of sustained-release nitrendipine microspheres having solid dispersion structure by quasi-emulsion solvent diffusion method. *Journal of Controlled Release*, 91, 375-384.

Di Martino, P., Barthelemy, C., Piva, F., Joiris, E., Palmieri, G.F., Martelli, S. (1999). Improved dissolution behavior of fenbufen by spherical crystallization. *Drug Delivery and Industrial Pharmacy*, 25, 1073-1081.

Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R. (1999). Formation and Compression Properties of Prismatic Polyhedral and Thin Plate-like Crystals of Paracetamol. *International Journal of Pharmaceutics*, 187, 77-89.

Kawashima Y, Aoki S, Takenaka H. Spherical agglomeration of aminophylline crystals during reaction in liquid by the spherical crystallization technique. *Chem. Pharm. Bull.* 1982; 30, 1900-2.

Kawashima Y, Capes CE. Experimental study of the kinetics of spherical agglomeration in as stirred vessel. *Powder Technol.* 1974; 10, 85-92.

Kawashima Y, Capes CE. Further studies of the kinetics of spherical agglomeration in a stirred vessel. *Powder Technol.* 1976; 13, 279-288.

Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K. Improvements in flowability and compressibility of pharmaceutical crystals for direct tabletting by spherical crystallization with a 2 solvent system. *Powder Technol.* 1994; 78, 151-157.

Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K. Improved static compression behaviors and tablettabilities of spherically agglomerated crystals produced by the spherical crystallization technique with a two-solvent system. *Pharma. Res.* 1995; 12, 1040-4.

Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K. Parameters determining the agglomeration behavior and the micromeritic properties of spherically agglomerated crystals prepared by the spherical crystallization technique with miscible solvent systems. *Int. J. Pharm.* 1995; 119, 139-47.

Kawashima Y, Furukawa K, Takenaka H. The physicochemical parameters determining the size of agglomerate prepared by the wet spherical agglomeration technique. *Powder Technol.* 1981; 30, 211-16.

Kawashima Y, Imai M, Takeuchi H, Yamamoto H, Kamiya K, Hino T. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tabletting designed by spherical crystallization process. *Powder Technol.* 2003; 130, 283-289.

Kawashima Y, Imai M, Takeuchi H, Yamamoto H, and Kamiya, K. Development of Agglomerated Crystals of Ascorbic acid by the Spherical Crystallization Technique for Direct Tabletting, and Evaluation of their Compactibilities, *Kona*. 2002; 20, 251-261.
Kawashima Y, Lin SY, Ogawa M, Handa T, Takenaka H. Preparations of agglomerated crystals of polymorphic mixtures and a new complex of indomethacin-epirizole by the spherical crystallization technique. *J. Pharm. Sci.* 1985; 74, 1152-6.

Kawashima Y, Morishima K, Takeuchi H, Niwa T, Hino T, Kawashima Y. Crystal design for direct tablettng and coating by the spherical crystallization technique. *AIChE Symposium Series.* 1991; 284, 26-32.

Kawashima Y, Naito M, Lin SY, Takenaka H. An experimental study of the kinetics of the spherical crystallization of sodium theophylline monohydrate. *Powder Technol.* 1983; 34, 255-60.

Kawashima Y, Okumura M, Takenaka H. Spherical crystallization: direct spherical agglomeration of salicylic acid crystals during crystallization. *Science.* 1982; 4550(216), 1127-8.

Kawashima Y, Okumura M, Takenaka H. The effects of temperature on the spherical crystallization of salicylic acid. *Powder Technol.* 1984; 39, 41-47.

Kawashima Y, Takeuchi H, Niwa T, Hino T, Yamakoshi M, Kihara K. Preparation of spherically agglomerated crystals of an antibacterial drug for direct tablettng by a novel spherical crystallization technique. *Congr. Int. Technol. Pharm.* 1989; 5, 228-34.

Kulkarni, P.K. and Nagavi B.G. (2002). Spherical crystallization. *Indian Journal of Pharmaceutical Education*, 36, 66-71.

Khan, K.A. (1975). The concept of dissolution efficiency. *Journal Pharmacy and Pharmacology*, 27, 48-49.

Marshall, P.V., York, P. (1991). Compaction Properties of Nitrofurantoin Samples Crystallised from Different Solvents. *International Journal of Pharmaceutics*, 67, 59-65.

Martin, A., Bustamante, P., Chun, A. (2002). Micromeritics, In: *Physical Pharmacy- physical chemical principles in the pharmaceutical sciences*, 4th ed., pp. 423-452, Lippincott Williams and Wilkins, Baltimore.

Sano, A., Kuriki T., Kawashima Y., Takeuchi H., Hino T., and Niwa T. (1992). Particle design of tolbutamide by spherical crystallization technique. V. Improvement of dissolution and bioavailability of direct compressed tablets prepared using tolbutamide agglomerated crystals. *Chemical and Pharmaceutical. Bulletin*, 40, 3030-3035.

Sweetman, S.C. (Ed(s)). (2002). *Martindale The Complete Drug Reference.* 33rd ed., Pharmaceutical Press, London, 2002, pp. 855-856.

Tapas, A.R., Kawtikwar, P.S., Sakarkar, D.M. (2009). Enhanced dissolution rate of felodipine using spherical agglomeration with Inutec SP1 by quasi emulsion solvent diffusion method. *Research in Pharmaceutical Sciences*, 4, 77-84.

Tapas, A.R., Kawtikwar, P.S., Sakarkar, D.M. (2010). Spherically agglomerated solid dispersions of valsartan to improve solubility, dissolution rate and micromeritic properties. *International Journal of Drug Delivery*, 2, 304-313.

Usha, A.N., Mutalik, S., Reddy, M.S., Rajith, A.K., Kushaghi, P., Udupa, N. (2008). Preparation and in vitro, preclinical and clinical studies of aceclofenac spherical agglomerates. *European Journal of Pharmaceutics and Biopharmaceutics*, 70, 674-683.

U.S. Food and drug administration [Internet]. Dissolution methods for drug products; 2010. Available from: http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Disolutions.cfm?PrintAll=1.

www.intechopen.com
Wells, J. (2002). Pharmaceutical preformulation, the physicochemical properties of drug substances, In: Pharmaceutics- the science of dosage form design, M.E. Aulton (Ed), pp. 113-138, Churchill Livingstone, London.
Crystallization is used at some stage in nearly all process industries as a method of production, purification or recovery of solid materials. In recent years, a number of new applications have also come to rely on crystallization processes such as the crystallization of nano and amorphous materials. The articles for this book have been contributed by the most respected researchers in this area and cover the frontier areas of research and developments in crystallization processes. Divided into five parts this book provides the latest research developments in many aspects of crystallization including: chiral crystallization, crystallization of nanomaterials and the crystallization of amorphous and glassy materials. This book is of interest to both fundamental research and also to practicing scientists and will prove invaluable to all chemical engineers and industrial chemists in the process industries as well as crystallization workers and students in industry and academia.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Amit R. Tapas, Pravin S. Kautikwar and Dinesh M. Sakarkar (2012). Preparation of Carvedilol Spherical Crystals Having Solid Dispersion Structure by the Emulsion Solvent Diffusion Method and Evaluation of Its in vitro Characteristics, Advances in Crystallization Processes, Dr. Yitzhak Mastai (Ed.), ISBN: 978-953-51-0581-7, InTech, Available from: http://www.intechopen.com/books/advances-in-crystallization-processes/preparation-of-carvedilol-spherical-crystals-having-solid-dispersion-structure-by-the-emulsion-solve
