puerarin in its phospholipid solid dispersion was enhanced.

REFERENCES

1. Zhu, Q.L. and Lu, X.R., **Chin. Trad. Herbal Drugs,** 1997, 28, 693.
2. Wang, C., Liu, X.L. and Gu, S.J., **Chin. Pharma. J.,** 1993, 28, 294.
3. Liu, X.L., Wang, S.J. and Yan, J.J., **J. Shenyang Pharm. Uni.,** 1990, 43, 123.
4. Bombardelli, E. and Magistretti, M.J., **European Patent No.,** EP 209 037, 1987.
5. Venkataram, S. and Rogers, J.A., **J. Pharm. Sci.,** 1984, 73, 757.
6. Wu, J.M., Chen, D.W. and Zhang, R.H., **Biomed. Chromatogr.,** 1999, 13, 493.
7. Suni, P., Dion, R.B. and Guru, V.B., **Drug Develop. Ind. Pharm.,** 2001, 27, 413.
8. Jin, X.L., Cheng, G.F., and Zhu, X.Y., **Chin. J. Clin. Pharmacol.,** 1991, 2, 115.
9. Jin, X.L. and Zhu, X.Y, **Acta Pharmacol. Sin.,** 1992, 3, 284.
10. Jin, X.L., Cheng, G.F. and Zhu, X.Y, **Acta Pharma. Sin.,** 1997, 10, 782.
11. Zhang, Z.R., Xu, X.J. and Wei, Z.P., **Chin. Pharm. J.,** 1997, 4, 224.
12. Xie, H.T., Huang, X.H. and Sun, R.Y, **Chin. J. Clin. Pharmacol. Ther.,** 2001, 4, 289.

Preparation and Characterization of Agglomerates of Flurbiprofen by Spherical Crystallization Technique

M. K. CHOURASIA, NITIN K. JAIN, S. JAIN[1], N. K. JAIN AND S. K. JAIN*

Pharmaceutics Research Projects Laboratory, Department of Pharmaceutical Sciences, Dr. Hari Singh Gour Vishwavidyalaya, Sagar-470 003.

[1]School of Pharmacy, University of London, Brunswik Square, London, WCIN 1AX, UK

Accepted 11 December 2002

Revised 18 November 2002

Received 2 July 2002

Flurbiprofen is an analgesic and antiinflammatory drug with poor water solubility and compressibility. Flurbiprofen conventional drug crystals were converted into spherical crystal agglomerates via the spherical crystallization technique using acetone-water-hexane solvent system. The various parameters optimized were type, amount and mode of addition of bridging liquid, temperature, and agitation speed to get maximum amount of spherical crystals. These were characterized for micromeritic properties (particle size and shape, flowability), packability (bulk density), wettability (contact angle) and compressibility. It was revealed from the study that spherical agglomerates exhibited improved flowability, wettability and compaction behaviour.

One of the most revolutionary technologies in the manufacture of solid dosage forms is tableting by direct compression. It is economical, facilitates processing without the need for moisture and heat and only few procedures are involved. In the direct compression method it is necessary to increase the flowability and compressibility of the bulk powder in order to have sufficient mechanical strength of the compacted tablets[1]. More recently, a modified crystalline technique has been adopted for the development of directly compressible drugs. This technique, also known as spherical crystallization, is a particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into a compacted spherical form[2]. This technique as the name indicates, provides crystalline agglomerates that are spherical in shape, which exhibit excellent micromeritic properties (flowability, packability, compressibility and wettability). This technique has been used to modify the properties of many drugs such as fenbufen[3], ibuprofen[4], furosemide[5], indomethacin[6], ami-

***For correspondence**

E-mail: drskjainin@yahoo.com

nophylline[7], enoxacin[8], tolbutamide[9,10], sulphamethoxazole[11], phenytoin[12] and norfloxacin[13]. There are four methods for preparing spherical crystals. These are; (i) simple spherical crystallization, (ii) emulsion solvent diffusion, (iii) ammonia diffusion, and (iv) neutralization[14]. In the present work spherical crystals of flurbiprofen (SC of FB) were prepared by simple spherical crystallization process and various *in vitro* parameters of these have been evaluated. Simple spherical crystallization process is easy, common and faster relative to other methods and hence this process was chosen for the preparation of spherical crystals. Initially SC were prepared with 80 mg of FB and the process was scaled up to 10 g.

Flurbiprofen was a generously gift from FDC Ltd. Mumbai. All reagents used in this investigation were of analytical grade and double distilled water was used. Flurbiprofen (80 mg) was dissolved in acetone (1ml) in a small test tube. Distilled water (10 ml) was added to precipitate the drug in fine crystals. The mixture was allowed to stand for 10 min. It was then stirred using a two-blade mechanical stirrer at 500 to 600 rpm and hexane (0.3 ml) was added drop wise as a bridging liquid while stirring. This system was agitated for 45 min at 25±2°. Spherical crystals were separated by filtration and dried in oven at 40°.

The effect of various parameters was investigated in order to achieve optimal conditions for spherical crystallization of flurbiprofen. The effect of type of bridging liquid on formulation of SC of FB was determined using hexane, chloroform, toluene and benzene. The effect of the volume (0.1 to 0.5 ml) of bridging liquid (hexane) on the formation SC of FB was investigated. The other parameters evaluated were agitation speed (300, 600 and 900 rpm), room temperature (RT) and drop-wise addition of bridging liquid. The effect of different temperatures on the formulation of SC of FB was investigated at 4±1°, room temperature (RT) and 50±1°. The other parameters kept constant i.e. amount of bridging liquid (0.3 ml), agitation speed (600 rpm) and drop-wise addition of bridging liquid (hexane). The effect of rate of addition of bridging liquid on formulation of SC of FB was also determined. The parameters maintained constant were, type of bridging liquid (hexane), amount of bridging liquid (0.3 ml), agitation speed (600 rpm), and temperature (RT).

The *in vitro* pharmaceutical and physiochemical attributes of the optimized formulation (SC of FB) and FB were evaluated. Particle size and shape was determined using optical microscopy. Bulk density was determined using a graduated measuring cylinder.

Flowability was determined in terms of angle of repose (fixed funnel method). A known amount of each formulation (FB, SC of FB) was allowed to flow through a funnel fixed at a constant height. Powder was allowed to drop on a graph paper placed on the smooth surface of a tile. Height and diameter of pile of powder were recorded.

A drop (50 μl) of saturated solution of FB and SC of FB in water was placed on the tablet surface and height of the drop was measured. The contact angle was determined using the equation[15]: $\text{Cos } \theta = 1 - Bh^2/\sqrt{3}\ (1-\varepsilon)\ (1 - Bh^2/2)$, where $B = P.g/2\gamma$ (γ=surface tension of saturated solution of formulation in water, dynes/cm, P=density of saturated solution of drug in water, g/cm^3, ε=porosity of tablet and h=height of liquid drop in cm.) The following parameters were determined

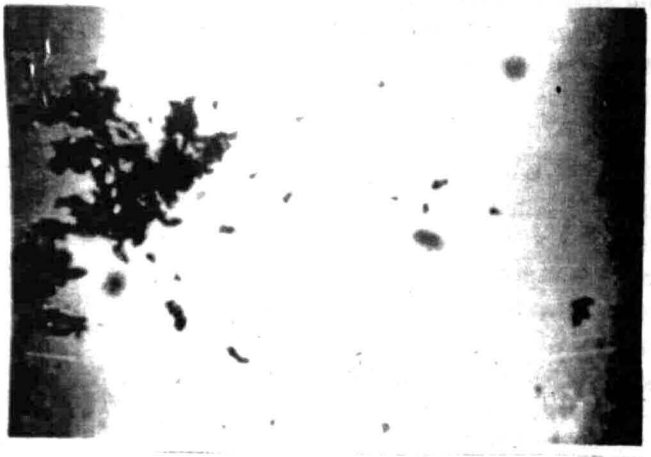

Fig. 1: Photomicrograph showing conventional drug crystals of flurbiprofen [X100].

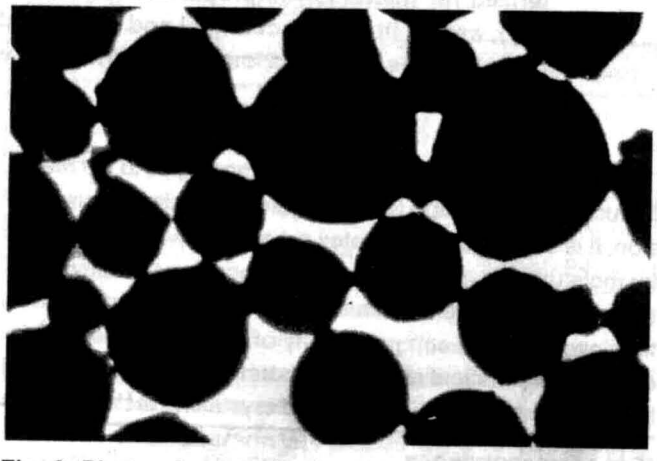

Fig. 2: Photomicrograph showing spherical crystals of flurbiprofen [X100].

for measuring wettability: Density of saturated solution of FB and SC of FB in water was determined using relative density bottle. Surface tension of saturated solution of FB and SC of FB in water was determined with the help of a stalagmometer.

Tablets of different FB and SC of FB were prepared. Thickness and diameter of tablets were determined with the help of a vernier calipers. Porosity was calculated from apparent density of the tablet. Compaction of agglomerates and conventional crystals was carried out using a compaction test apparatus (Autograph 5000D, Shimadzu, Japan), equipped with flat-faced punches. The die was lubricated with a very small amount of magnesium stearate. A weighed quantity of 300 mg was compressed with the upper punch moving down at 2 mm/min.

The conventional drug crystals of FB and spherical crystals of FB are shown in the figs. 1 and 2, respectively. The necessary requirement in spherical crystallization is that the bridging liquid should be immiscible in the dispersing medium i.e. water and the drug should have slight solubility in the bridging liquid. With reference to the above fact, toluene, benzene, chloroform, ether and hexane were tried as bridging liquids. Toluene, benzene, chloroform and ether resulted in the formation of clump instead of spherical crystals. This could be due to over solubilization of the drug, but when hexane was used as bridging liquid, small amounts of spherical crystals were formed and hence it was selected as the bridging liquid (Table 1).

Amount of bridging liquid is a critical process parameter in spherical crystallization process. Five batches were prepared. When 0.1 ml hexane was used no agglomeration occurred, which was due to the fact that very little amount of bridging liquid was available for solubilization necessary for agglomeration. When 0.5 ml hexane was used, large but soft agglomerates were produced and they coalesced during drying. A volume of 0.3 ml hexane resulted in the formation of good crystals with free flowing properties. Addition of whole amount of bridging liquid at a time, resulted in the localization of bridging liquid and hence formation of poor spherical crystals. Drop wise addition of bridging liquid with stirring, allowed proper distribution of bridging liquid, and resulted in efficient agglomeration.

Excellent spherical crystals were produced when agitated at 500 to 600 rpm. With increasing agitation speed, crystals with randomly broken edges were obtained, which was due to high shear force of blades of agitator. Under an agitation speeds slower than 250 rpm, the resultant agglomerates became more irregular and some of them adhered to shaft and vessel wall.

TABLE 1: EFFECT OF VARIOUS PARAMETERS ON FORMULATION OF SC OF FB.

Parameters	Observations
Type of bridging liquid	
Hexane	Spherical crystals
Toluene	Clump
Benzene	Clump
Chloroform	Clump
Amount of bridging Liquid	
0.1 ml	No agglomeration
0.2 ml	Partial agglomeration
0.3 ml	Spherical crystals
0.4 ml	Large agglomerates
0.5 ml	Clump
Agitation speed	
300 rpm	Irregular shape
600 rpm	Spherical crystals
900 rpm	Small agglomerates
Temperature	
4±2°	No agglomeration
RT	Spherical crystals
50±2°	Large agglomerates
Mode of addition of Bridging liquid	
Whole amount	Irregular spherical crystals
Drop wise	Spherical crystals

No agglomeration occurred on lowering the temperature of solvent and water mixture to 4±2° even on prolonged mixing. This was possibly due to decreased solubility of the drug in the agglomerating solvent at such a lower temperature. Less solubilization of the drug would cause reduced wetting (and hence tackiness) of the drug particles, and

TABLE 2: *IN VITRO* CHARACTERIZATION OF FORMULATIONS OF FB AND SC OF FB.

Parameter	Formulation	
	FB	SC of FB
Particle size	18.5 μm	499.7 μm
Bulk density	0.55 g/cm^3	0.94 g/cm^3
Angle of repose	46.7°	31.7°
Contact angle	88.6°	54.0°

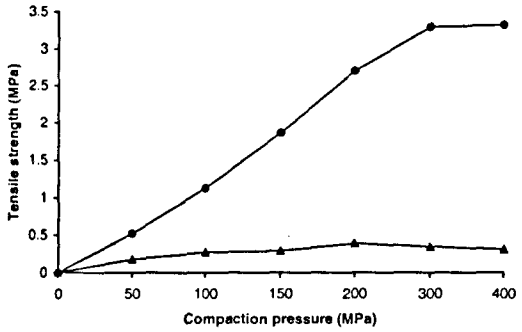

Fig. 3: Tensile strength of conventional crystals and agglomerates as a function of compaction pressure.

Compaction of spherical agglomerates (-●- SC of FB) and conventional crystals (-▲- FB) was carried out using a compaction test apparatus equipped with flat-faced punches.

therefore, decreased agglomeration. In another batch, very large agglomerates were formed on raising the temperature to 50±2°, which could be due to the increased solubility of the drug at this temperature. It is therefore apparent that temperature is an important process parameter.

The packing ability of FB and SC of FB were determined by tapping into a 25 ml-graduated cylinder[7]. Spherical crystals were found to have higher packability than flurbiprofen crystals. It was due to the lower surface and wider particle size distribution of spherical crystals. During the tapping process small particles might have infiltrated into the voids between the larger particles and resulted in improved packability (Table 2).

Flowability was determined in terms of angle of repose. FB crystals were found to have higher angle of repose in comparison to SC of FB, which could be due to the irregular shape of these crystals that is reflected from fig. 1, which hindered in the uniform flow of crystals from funnel. The reason for excellent flowability of spherical crystals is the perfect spherical shape and larger size of crystals (Table 2).

The wettability of crystals by water was investigated by measuring the contact angle of water to the compressed crystals. Spherical crystals were found to be more wettable than FB, which could be due to the lower crystallinity of, agglomerated crystals in comparison to the bulk drug (Table 2).

Compressibility of agglomerates was evaluated based on the tensile strength of the compact. Compaction of agglomerates and conventional crystals was carried out using a compaction test apparatus (Autograph 5000D, Shimadzu, Japan), equipped with flat-faced punches. Fig. 3 shows the tensile strength of the compact. Spherical agglomerates possessed superior strength characteristics in comparison to conventional drug crystals. It could be due to the fact that new surfaces freshly formed during compression. Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystal.

It is concluded that spherical crystallization is a potential approach to the manufacture of spherical agglomerates and these exhibit excellent micromeritic properties for direct tableting. The spherical agglomerates of flurbiprofen showed increased wettability, which may be helpful to increase the dissolution rate of poorly soluble drugs. Spherical agglomerates showed tableting by direct compression due to augmented flow properties and compaction behaviour. Utilizing spherical crystallization technique as the last step during bulk drug production can improve the efficiency of manufacturing of tablets.

ACKNOWLEDGEMENTS

The authors are grateful to FDC Ltd. Mumbai, India for supplying flurbiprofen gift sample and University Grant Commission, New Delhi, India for providing financial assistance to carry out this work.

REFERENCES

1. Szabone, R.P., Pintyene, H.K., Kasa, P.J., Eros, I., Hasznosne, N.M. and Farkas, B., **Acta Pharm. Hung.**, 1998, 68, 113.
2. Kawashima, Y., Okumura, M. and Takenaka, H., **Science**, 1982, 216, 1128.
3. Martino, D.P., Barthelemy, C., Piva, F., Joiris, E., Palmieri, G.F. and Martelli, S., **Drug Develop. Ind. Pharm.**, 1999, 25, 1073.
4. Jbilou, M., Ettabia, A., Guyot-Hermann, A.M. and Guyot, J.C., **Drug Develop. Ind. Pharm.**, 1999, 25, 297.

5. Akbuga, J., **Int. J. Pharm.**, 1991, 56, 193.
6. Kawashima, Y., Lin, S.Y. and Ogawa, M., **J. Pharm. Sci.**, 1985, 74, 1152.
7. Kawashima, Y., Aoki, S. and Takenaka, H., **J. Pharm. Sci.**, 1984, 73, 1407.
8. Kawashima, Y., Okumura, M. and Takenaka, H., **J. Pharm. Sci.**, 1984, 73, 1535.
9. Sano, T. Kuriki, and Handa, T., **J. Pharm. Sci.**, 1987, 76, 471.
10. Ma, X., Quan, Y., Li, S., Liu, Q. and Zhou, G., **Chem. Pharm. Bull.**, 1992, 40, 3030.
11. Kawashima, Y., Ohno, H. and Takenaka, H., **J. Pharm. Sci.**, 1981, 70, 913.
12. Kawashima, Y., Handa, T., Takenchi, H. and Okumaram, H., **Chem. Pharm. Bull.**, 1986, 34, 3376.
13. Puechagut, H.G., Bianchotti, J. and Chiale, C.A., **J. Pharm. Sci.**, 1998, 87, 519.
14. Paradkar, A.R., Pawar, A.P., Mahadik, K.R. and Kadam, S.S., **Indian Drugs**, 1993, 31, 229.
15. Lerk, C.R, Schoonin, A.J.M. and Fell, J.T. **J. Pharm. Sci.**, 1976, 65, 843.

Visible Spectrophotometric Methods for the Estimation of Loratadine from Tablets

I. SINGHVI
Department of Pharmacy, M. L. Sukhadia University, Udaipur-313 001.

Accepted 20 December 2002
Revised 12 November 2002
Received 18 March 2002

Two visible spectrophotometric methods have been developed for estimation of loratadine from tablet formulation. These visible spectrophotometric methods are based on formation of chloroform extractable coloured complex of drug with cobalt thiocynate and bromophenol blue. The coloured complex formed with cobalt thiocynate showed absorbance maxima at 624.5 nm and linearity in the concentration range of 1.2-3.6 mg/ml of loratadine while the coloured complex formed with bromophenol blue showed absorbance maxima at 413 nm and linearity in the concentration range of 0-120 μg/ml of loratadine. Results of analysis for both the methods were validated statistically.

Loratadine, chemically 4-(8-chloro-5,6-dihydro-11H-benzat-[5,6]cyclohepta [1, 2-b]pyridin-11-ylidene)-1-piperidinecarboxylic acid ethyl ester is an antihistaminic agent[1]. Few reported, analytical methods, for estimation of loratadine, include HPTLC[2-4], UV[5], colorimetric[6-7] and polorographic[8] methods. An attempt has been made in the present study to develop two simple visible spectrophotometric methods for analysis of loratadine from tablets.

A Jasco UV/vis recording spectrophotometer with 1 cm matched quartz cells was used for the preset study. All reagents used were of analytical grade. Cobalt thiocynate reagent was prepared as per IP. Bromophenol blue reagent 0.5 % was prepared in 0.2 M hydrochloric acid. Both the reagents were extracted several times with chloroform so as to remove chloroform soluble impurities.

***For correspondence**

For method I, standard drug solution in 0.2 M hydrochloric acid (6 mg/ml) was diluted with the same so as to give several dilutions in the concentration range of 1.2-3.6 mg/ml of loratadine. To 10 ml of each dilution taken in a separating funnel, 10 ml cobalt thiocynate reagent was added. Reaction mixture was shaken gently for 5 min. Then 10 ml of chloroform was added, shaken gently for 5 min and allowed to stand so as to separate the aqueous and chloroform layer. Coloured chloroform layer was separated out and the absorbance was measured at 624.5 nm against a reagent blank. Calibration curve was constructed from the absorbance values for several dilutions.

For analysis of sample solution, twenty tablets were accurately weighed and average weight of the tablet was