Spherical Agglomeration of Mefenamic Acid and Nabumetone to Improve Micromeritics and Solubility: A Technical Note

Submitted: October 14, 2005; Accepted: April 9, 2006; Published: May 26, 2006

Chelakara L. Viswanathan,[1] Sushrut K. Kulkarni,[1] and Dhanashri R. Kolwankar[1]

[1]Bombay College of Pharmacy, Kalina, Santacruz (East), Mumbai 400 098, India.

KEYWORDS: spherical crystallization, mefenamic acid, nabumetone, micromeritics, spherical agglomeration.

INTRODUCTION

Developing novel methods to increase the bioavailability of drugs that inherently have poor aqueous solubility is a great challenge to solid dosage form formulators. Mechanical micronization of crystalline drugs and incorporation of surfactants during the crystallization process are the techniques commonly used to improve the bioavailability of poorly soluble drugs.[1,2] The micronization process was found to alter the flow and compressibility of crystalline powders and cause formulation problems. Incorporation of surfactants generally led to less significant increase in aqueous solubility. To overcome this problem, Kawashima et al[3,4] developed a spherical crystallization technique that led to improving the flow and direct compressibility of number of microcrystalline drugs.[5] Improvement of dissolution profile was also achieved in some cases.[6]

In the present work, mefenamic acid and nabumetone were chosen for development as their microcrystalline forms exhibited poor micromeritic properties and they also had poor aqueous solubility. Novel spherical agglomeration procedures were developed by modifying the Kawashima technique by incorporating polymers during the agglomeration process and choosing different agglomerating solvents. The agglomerates were evaluated by x-ray diffraction, differential scanning calorimetry (DSC), and scanning electron microscopy for flow and direct compressibility and finally for solubility.

MATERIALS AND METHODS

The glass apparatus used for spherical agglomeration was as per the specifications given by Kawashima et al[3] and was locally procured. An efficient mechanical stirrer with an RQ-124 speed regulator was used for stirring and the speed recorded in revolutions per minute (rpm). The glass apparatus was placed in a thermostatically controlled water bath and the temperature was maintained at 25 ± 1°C during agglomeration. The agglomerates formed were isolated by filtration under vacuum and dried in a vacuum dryer.

Microcrystalline mefenamic acid and nabumetone were procured from Sekhsaria Chemicals Pvt Ltd (Thane, India), and the solvents used were from Qualigens India Pvt Ltd (Mumbai, India).

Spherical Agglomeration of Mefenamic Acid

Method 1

Mefenamic acid (2.5 g) was dissolved in 40 mL dimethylformamide (DMF) by gentle warming and the solution was added with stirring to 400 mL distilled water contained in the agglomerating vessel. Chloroform, 10.5 mL (agglomerating solvent), was then added drop wise and the contents simultaneously stirred for 30 minutes at a speed of 900 rpm.

Similarly 2.5 g of mefenamic acid was agglomerated using 2.29 mL carbon tetrachloride (CCl_4) as the agglomerating solvent at an agitation speed of 650 rpm.

Method 2

Mefenamic acid (2.5 g) was dissolved in 40 mL DMF by gentle warming and then cooled to 25°C. A solution of 0.1% wt/vol of hydroxypropylmethyl cellulose (HPMC) in distilled water (30 mL) was then added to it with stirring. The precipitated solid was dissolved by further addition of 30 mL DMF and gentle warming. This solution was added with stirring to 400 mL distilled water contained in the agglomerating vessel. Chloroform (18 mL) was added drop wise and contents stirred for 30 minutes at agitation speed of 900 rpm.

Similarly, 2.5 g of mefenamic acid was agglomerated using 2.8 mL CCl_4 at agitation speed of 600 rpm.

Spherical Agglomeration of Nabumetone

Method 1

Nabumetone (2.0 g) was dissolved in 30 mL ethanol by gentle warming and the solution added to 400 mL distilled

Corresponding Author: Chelakara L. Viswanathan, Bombay College of Pharmacy, Kalina, Santacruz (East), Mumbai 400 098, India. Tel: +91-22-26670871; Fax: +91-22-26670816; E-mail: chelakara_viswanathan@yahoo.com

water and agglomerated using 6.4 mL cyclohexane at an agitation speed of 400 rpm for 30 minutes.

Similarly, 2.0 g of nabumetone was agglomerated using 7.0 mL n-hexane at an agitation speed of 400 rpm for 30 minutes.

Method 2

Nabumetone (2.0 g) was dissolved in 30 mL ethanol by gentle warming and then the solution was added with stirring to 400 mL distilled water. A solution of 2% wt/vol lecithin in cyclohexane (6.4 mL) was then added drop wise and stirred for 15 minutes at a speed of 400 rpm.

Similarly, 2.0 g of nabumetone was agglomerated using 2% wt/vol lecithin in n-hexane (6.4 mL) at an agitation speed of 400 rpm for 15 minutes.

Evaluation of Agglomerates

Angle of Repose and Bulk Density

Angle of repose and bulk density were determined for microcrystalline/agglomerates of both mefenamic acid and nabumetone by following standard methods.

Compressibility Studies

Microcrystalline/agglomerates (250 mg) of mefenamic acid and nabumetone were compressed using a hydraulic press (Lawrence and Mayo-India Pvt Ltd [Mumbai, India]) at various pressures (500, 1000, 1500, 2000, 2500, and 3000 lb/sq in) and the hardness determined using Monsanto hardness tester (Mumbai, India).

Dissolution Studies

Microcrystalline/agglomerates (25 mg) of mefenamic acid were placed in muslin in a rotating basket (USP XXII) and then placed in 250 mL phosphate buffer and stirred at a speed of 100 rpm with temperature maintained at 37 ± 1°C. Aliquots of 5 mL were withdrawn at appropriate time intervals and an equal volume of water was replaced in the vessel. Mefenamic acid in the aliquot was assayed spectrophotometrically at 285 nm.

Solubility Studies

In the case of nabumetone, solubility study was done by shaking 100 mg of nabumetone microcrystalline/agglomerates with 20 mL of buffers of pH 1.2, 6.0, and 7.4 for 24 hours and then filtering and determining the amount of undissolved solid.

Results and Discussion

Spherical agglomeration procedure was used to improve micromeritics and solubility of commercially procured microcrystalline samples of mefenamic acid and nabumetone. Solvents in which the drug has poor solubility (<5 mg/mL) were chosen as agglomerating solvents. Additional criteria used in the selection of solvents was their ability to wet the microcrystals and produce uniform spherical agglomerates in a desired size range. The technique used during the agglomeration process is called solvent change (SC).

Agglomeration of Mefenamic Acid

Mefenamic acid was dissolved in DMF and added with stirring into a large amount of water to get microcrystals that were then agglomerated using chloroform and CCl_4 as solvents. Agglomeration at 10 ± 1°C and at 500 rpm led to ready formation of lumps, whereas no agglomerates were formed at 900 rpm. At 40 ± 1°C, a 2-phase system was obtained. At 25 ± 1°C using chloroform, big and irregular agglomerates were formed at 500 rpm, whereas spherical agglomerates were obtained at 900 rpm. With CCl_4, spherical agglomerates were formed at 650 rpm. The size of the agglomerates formed differed (with chloroform 250-500 μm and with CCl_4 100-250 μm). Recovery of agglomerates was in the range of 75% to 80%. Mefenamic acid and HPMC were brought into solution to disperse the drug in the polymer and then agglomerated as before.

Agglomeration of Nabumetone

Nabumetone was dissolved in ethanol and added with stirring into a large amount of water to get microcrystals that were then agglomerated using cyclohexane and n-hexane as solvents. Temperature, agitation speed, and amount of solvent used were optimized. Thus, no agglomeration occurred at 10 ± 1°C, at 50 ± 1°C large agglomerates were formed, and at 25 ± 1°C spherical agglomerates of desired size range were formed. The size of the agglomerates formed differed (with cyclohexane 250-800 μm and n-hexane 200-500 μm). Recovery of agglomerates was in the range of 75% to 80%. Lecithin was used to enhance solubility. Microcrystals dispersed in water were agglomerated using lecithin containing cyclohexane and n-hexane. Preliminary study by incorporating polymers polyethylene glycol (PEG) 6000, PEG 4000, and sodium lauryl sulfate did not improve solubility.

Evaluation of Agglomerates

The x-ray diffraction patterns for agglomerates were similar to those of microcrystalline drugs, confirming absence of polymorphic changes. DSC study shows thermograms with

Table 1. Angle of Repose and Apparent Density of Mefenamic Acid and Nabumetone*

Serial No.	Sample	Angle of Repose, Degrees	Apparent Density, g/cm^3
	Mefenamic Acid		
1.	Microcrystalline	51	0.43
2.	DWC	40	0.61
3.	DWCP	39	0.64
4.	DWCC	43	0.53
5.	DWCCP	45	0.55
	Nabumetone		
6.	Microcrystalline	16	0.18
7.	EWCH	27	0.28
8.	EWCHL	25	0.27
9.	EWH	28	0.31
10.	EWHL	26	0.30

*DWC indicates DMF-water-chloroform; DWCP, DMF-water-chloroform-HPMC; DWCC, DMF-water-carbon tetrachloride; DWCCP, DMF-water-carbon tetrachloride-HPMC; EWCH, ethanol-water-cyclohexane; EWCHL, ethanol-water-cyclohexane-lecithin; EWH, ethanol-water-n-hexane; EWHL, ethanol-water-n-hexane-lecithin.

sharp melting at 230°C and 80°C for mefenamic acid and nabumetone respectively. Scanning electron microscopy showed microcrystalline mefenamic acid, with particle size of 8 to 10 µm, agglomerates DWC (DMF-water-chloroform) and DWCP (DMF-water-chloroform-HPMC) (250-500 µm), and DWCC (DMF-water-carbon tetrachloride) and DWCCP (DMF-water-carbon tetrachloride-HPMC) (100-250 µm). Lenticular structures of HPMC wee observed in agglomerates DWCP and DWCCP. Microcrystalline nabumetone, with a particle size of 12 µm, agglomerates EWCH (ethanol-water-cyclohexane) and EWCHL (ethanol-water-cyclohexane-lecithin) (250-800 µm), and EWH (ethanol-water-n-hexane) and EWHL (ethanol-water-n-hexane-lecithin) (200-500 µm).

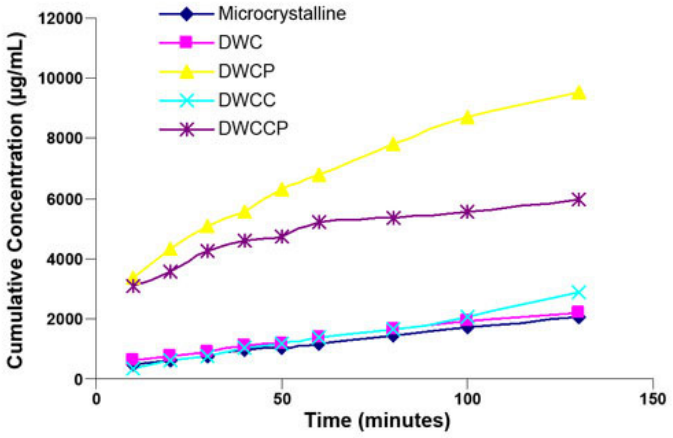

Figure 1. Dissolution study of agglomerates of mefenamic acid.

Lecithin was observed on the surface of EWHL agglomerates. Angle of repose for agglomerates of mefenamic acid was 39° to 45° and their apparent density was 0.53 to 0.64 g/cm^{-3} (Table 1) showing improved flow property. Angle of repose for agglomerates of nabumetone was 25° too 28° and their apparent density was 0.27 to 0.31 g/cm^{-3} (Table 1) showing improved flow property. Compressibility studies show significantly higher compressibility for agglomerates compared with microcrystalline mefenamic acid. Incorporation of HPMC further enhanced compressibility. In the case of nabumetone, compressibility increased on agglomeration. Incorporation of lecithin, however, reduced the compressibility (Table 2). When the compression pressure was increased to 3000 lb/sq in, a drastic reduction of hardness was noted for both microcrystalline drug and the agglomerates and hence may be attributed to be a characteristic of the powder. Similar observations were reported during spherical agglomeration of naproxen.[5,7] Dissolution rate Mefenamic acid increased with agglomeration and with addition

Table 2. Hardness versus Compressibility of Tablets of Mefenamic Acid and Nabumetone*

		Hardness (kg/cm^2) at Compression Pressure (lb/sq in)					
Serial No.	Sample	500	1000	1500	2000	2500	3000
	Mefenamic acid						
1.	Microcrystalline	—	—	0.75	0.8	0.8	1.0
2.	DWC	0.75	1.1	1.25	1.8	2.0	3.2
3.	DWCP	4.25	4.5	5.75	5.8	6.7	6.8
4.	DWCC	—	0.75	0.75	1.8	2.2	3.1
5.	DWCCP	3.21	3.30	4.20	4.5	5.3	5.8
	Nabumetone						
6.	Microcrystalline	2.25	2.75	3.0	3.25	4.0	2.5
7.	EWCH	5.00	6.50	7.0	7.0	7.25	3.0
8.	EWCHL	2.50	3.0	3.5	3.75	4.00	3.0
9.	EWH	4.25	4.50	5.0	6.0	6.25	2.5
10.	EWHL	2.50	2.75	3.0	3.25	3.50	2.5

*DWC indicates DMF-water-chloroform; DWCP, DMF-water-chloroform-HPMC; DWCC, DMF-water-carbon tetrachloride; DWCCP, DMF-water-carbon tetrachloride-HPMC; EWCH, ethanol-water-cyclohexane; EWCHL, ethanol-water-cyclohexane-lecithin; EWH, ethanol-water-n-hexane; EWHL, ethanol-water-n-hexane-lecithin.

Table 3. Solubility Studies for Nabumetone*

Serial No.	Medium	Solubility (mg/100 mL)				
		Microcrystalline	EWCH	EWCHL	EWH	EWHL
1.	Buffer (pH 1.2)	1.50	1.61	3.4	1.70	3.46
2.	Buffer (pH 6.0)	2.60	2.80	5.4	2.87	5.50
3.	Buffer (pH 7.4)	1.85	1.92	4.1	1.98	4.25

*EWCH, ethanol-water-cyclohexane; EWCHL, ethanol-water-cyclohexane-lecithin; EWH, ethanol-water-n-hexane; EWHL, ethanol-water-n-hexane-lecithin.

of HPMC (eg, DWCP showed dissolution of 95.5% at the end of 130 minutes, Figure 1). Because of the very poor aqueous solubility of nabumetone, a solubility study was undertaken instead of a dissolution study. Buffers of pH 1.2, 6.0, and 7.4 were used to study their effects on solubility. Solubility behavior with pH was 6.0 > 7.4 > 1.2 (Table 3). Agglomerates with lecithin incorporation showed significantly higher solubility. As significant change in the solubility was not observed when nabumetone or its agglomerates were shaken with buffers for short periods (1, 2, and 4 hours), the study was extended to 24-hour shaking.

SUMMARY AND CONCLUSIONS

Spherical agglomeration techniques were developed for improving the flow and compressibility characteristics of microcrystalline mefenamic acid and nabumetone. The process involved agglomerating microcrystals using agglomerating solvents. Temperature and speed of agitation were optimized to obtain spherical agglomerates in a desired range, which was found to be essential to enhance compressibility. Incorporation of polymer HPMC during agglomeration significantly enhanced the dissolution rate of mefenamic acid while incorporation of solubilizing agent lecithin improved the solubility of nabumetone. Thus, spherical agglomeration is an important technique for improving direct compressibility of pharmaceutical powders and is especially useful when the drug dosage is high.

ACKNOWLEDGMENTS

The authors acknowledge the financial support from All India Council of Technical Education (AICTE) for this project.

REFERENCES

1. Atkinson RM, Belford C, Tomich EG. Effect of particle size on blood Griseofulvin levels in man. *Nature.* 1962;193:588–589.

2. Prescott LF, Steel RF, Ferrier WR. The effect of particle size on the absorption of Phenacetin in man. A correlation between plasma concentration of phenacetin and effects on the central nervous system. *Clin Pharmacol Ther.* 1970;11:496–504.

3. Kawashima Y, Okumara M, Takenaka H. A novel agglomeration technique to transform a microcrystalline drug into an agglomerated form during crystallization. *Science.* 1982;216:1127–1128.

4. Kawashima Y, Okumara M, Takenaka H, Kojwa A. Direct preparation of spherically agglomerated salicylic acid crystals during crystallization. *J Pharm Sci.* 1984;73:1535–1538.

5. Gordon MS, Chowhan LT. Manipulation of naproxen particle morphology via the spherical crystallization technique to achieve a directly compressible raw material. *Drug Dev Ind Pharm.* 1990;16:1279–1290.

6. Sano A, Kuriki T, Handa T, Takeuchi H, Kawashima Y. Particle design of Tolbutamide in the presence of soluble polymer or surfactant by the spherical crystallization technique: improvement of dissolution rate. *J Pharm Sci.* 1987;76:471–474.

7. Kotteke MK, Rudnic EM. Tablet Dosage forms. In: Banker GS, Rhodes CT, eds. *Modern Pharmaceutics.* 4th ed. New York, NY: Marcel Dekker; 2002:291–333.