Indomethacin Controlled Release Matrix Tablet Prepared by Wet Granulation Procedure[1)]

Guojie XU,[a] Hisakazu SUNADA,*[,b] and Ruhua ZHANG[c]

Bejing Institute of Pharmacology and Toxicology,[a] 27 Taiping Road, Bejing, 100850, China, Faculty of Pharmacy, Meijo University,[b] Yagotoyama, Tempaku-ku, Nagoya 468, Japan, and Shenyang Pharmaceutical University,[c] 103 Wenhua Road, Shenhe district, Shenyang 110015, China. Received June 10, 1996; accepted September 24, 1996

Hydroxypropyl methylcellulose has been used as a rate-controlling polymer in indomethacin controlled release tablet formulations. Examination was made of the feasibility of manufacturing indomethacin-controlled matrix tablets using an agitating fluid bed and extrusion granulators. The results indicated that l) the agitating fluid bed granulator gave porous granules; 2) geometric median diameter and granule hardness were directly correlated with the concentration of the binder solution (at the range of 0.75—1.50% of HPMC) sprayed on the powder bed when using the agitating fluid bed; 3) granule flowability for the two granulators was essentially the same; 4) extrusion granulation led to high granule hardness; 5) parameters determined using Kawakita's equation indicated granules made by the agitating fluid bed were compressible, while those by extrusion showed good filling; 6) tablet diametrical tensile strength was related to granule hardness and geometric median diameter. High granule hardness and small geometric median diameter resulted in high tablet diametrical tensile strength.

Key words hydroxypropyl methylcellulose; indomethacin; controlled release matrix tablet; wet granulation; agitating fluid bed; extrusion

Granulation is very important in the pharmaceutical industry. However owing to the high viscosity and swellable ability of hydroxypropyl methylcellose (HPMC), preparation of a granulation hydrogel of sustained release formulations containing HPMC as a retarding agent is difficult. Indomethacin (IMN) was used in the present study as a hydrophobic model drug, and HPMC as the sustained release agent, to assess the feasibility of granulating hydrogel matrix tablets.

Experimental

Materials Indomethacin (Sumitomo Pharmaceutical Co., Osaka, Japan), hydroxypropyl methylcellulose 90SH4000SR(Shin-Etsu Chemical Co., Tokyo, Japan), anhydrous lactose (Pharmlatose 200M, DMV BA. Veghel, Holland), corn starch (Nihon Shokuhin, Co., Kurashiki, Japan) and magnesium stearate (Wako Pure Chemical Industries, Ltd., Osaka, Japan) were used for this study.

Agitating Fluid Bed Granulation Procedure The granulating solution was prepared by heating distilled water to more than 80 °C, followed by the addition of 10% of the total amount of HPMC. The solution was then allowed to cool and stand overnight and the evaporated water was replaced. IMN, anhydrous lactose, corn starch and the remaining HPMC for preparing a 500 g batch were placed in the agitating fluid bed granulator (Powrex Co., Itami, Japan). The powder bed was agitated for 5 min and then fluidized until the inlet air temperature reached 85 °C. The binder solution (Table l) was sprayed at two different times to facilitate granule formation: 15 g/ml for l0 min, and then l0 g/ml until it was used up completely. The product was dried until the outlet temperature was 35 °C.The granule batches were designated as lots ♯A, ♯B and ♯C (Table 1).

Procedure for Extrusion Granulation Appropriate amounts of HPMC, IMN, anhydrous lactose and corn starch to prepare a 300 g batch were placed in the mixer, and after being pre-mixed for 15 min, 90% (v/v) ethanol was then added and the system was mixed for l0 min. The wet mass was placed in basket-type extruders, then passed through a 24 mesh screen. The granules were then dried at 60 °C for 2 h and this batch was designated as lot ♯D.

Granule Preparation All granules were milled through a 24 mesh screen using a New Speed Mill (Okada Seiko Co., Ltd., Tokyo, Japan), and followed by blending 0.5% magnesium stearate with the milled granules for l0 min in a plastic bag by hand.

Characterization of Granules All granules were evaluated with respect to aerated bulk density, packed bulk density, angle of repose, uniformity, angle of spatula and particle size distribution using a Powder Tester (Hosokawa Micron Co., Osaka, Japan). Compressibility, uniformity and flowability index were determined based on the data of Carr's report.[2)] Geometric median diameter was expressed as the median of the logarithm of the particle size distribution curve.

Granule Hardness This parameter was determined based on the crushing force of granules 355 to 500 μm in diameter using the particle hardness tester, Grano (Okada Seiko Co.,Tokyo, Japan). According to the equation of Hiramatsu, granule hardness (St) is expressed as[3)]:

$$St = 0.7P/A \quad (1)$$

$$A = \pi D^2/4 \quad (2)$$

where P is the maximum crushing load (kg), A the sectional area and D the granule diameter. The result of St is the average of 30 determinations.

Granule Compression Behavior This behavior was examined using a Universal Tension and Compression Tester (Shimadzu Autograph AG 5000G, Shimadzu Seisakusho Co., Kyoto, Japan). A one-gram sample l80—355 μm in diameter was compressed to a tablet l6 mm in diameter at a compression speed of 1000 mm/min.

Tablet Preparation Lubricated granules were compressed into tablets 8.0 mm in diameter using a rotary tablet machine with a tableting pressure recording unit (Kikusui Seisakusho Co., Kyoto, Japan). The tableting force was 800, 1000 and 1200 kg.

Tablet Diametrical Tensile Strength This parameter was determined after the tablets had been stored in a sealed glass bottle for one month at room temperature. Tablet diametrical crushing strength (S_d) was calculated as[4)]:

$$S_d = 2P/\pi DT \quad (3)$$

Table 1. Parameters for Granulating IMN Controlled Release Matrix Tablet by Fluid Bed Granulating Method

Granulation lot ♯	Variables of granulation		
	Spray solution concentration (%)	Spray solution total amount (g)	Spray time (min)
A	0.75	667	62
B	1.00	500	45
C	1.50	333	28

Granulating conditions: Inlet air temperature, 85°C; outlet air temperature, 30°C; fluidization air flow, 36 m^3/h; spray air pressure, 3.0 kg/cm^2; disk impeller agitating speed, 350 rpm.

* To whom correspondence should be addressed.

where P is the maximum load causing tablet diametrical crushing failure, D the tablet diameter, T the tablet thickness, and S_d the diametrical crushing strength.

Dissolution Test IMN dissolution from tablets was made to take place using a dissolution tester (Tianjin Medical Electronic Apparatus Co., Tianjin, China). Nine hundred milliliters of pH 7.2 phosphate buffer solution maintained at 37 ± 0.5 °C served as the dissolution medium. A USP paddle was used at a rotational speed of 100 rpm. Five-milliliter aliquots were withdrawn at certain intervals, and to each an equal volume of fresh dissolution medium was added. The amount of IMN released was monitored at 318 nm. All procedures were performed in triplicate for each tablet batch.

Results and Discussion

The geometric median diameter of granules produced by the agitating fluid bed ranged from 214 to 359 μm, and was directly related to binder concentrations of 0.75—1.5%. The denser the binder solution, the larger the granule median diameter. Particle size distribution also differed significantly according to batches (Fig. 1). The characteristic features of the four batches of granules are specified in Table 2. Granulation #C has a large geometric diameter and a high percentage of large particles. The theory of Newitt *et al.*,[5] whose mechanism for binding to particles in the wet state involves pendular, funicular, capillary and droplet or suspension[6] aspects, would explain this. The quicker the binder was sprayed, the greater was the amount of liquid between particles. The greater the binder solution concentration, the more viscous was the liquid in the wet state. Agglomeration thus increased progressively. Granules #A showed a rather uniform particle size distribution and small geometric diameter, due to increased spraying time that permitted more uniform polymer application and prolonged attrition time between particles.

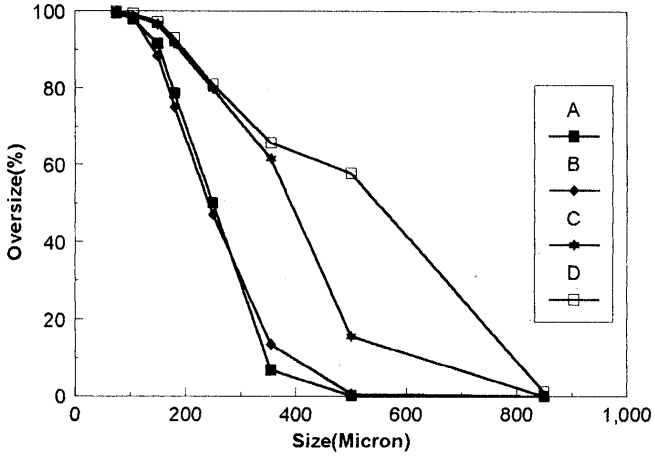

Fig. 1. Particle Size Distributions of the Four Batches of Granulations

Table 2. The Physical Properties of Granulation

	Agitating fluid bed method Lot#			Extrusion
	A unmil/mil	B unmil/mil	C unmil/mil	D unmil/mil
Median diameter (μm)	214/217	225/233	359/296	385
Aer. bulk density (g/ml)	0.32/0.32	0.28/0.29	0.31/0.33	0.56
Pack. bulk density (g/ml)	0.41/0.43	0.33/0.37	0.36/0.40	0.66
Compressibility (%)	22.0/25.6	15.2/21.6	16.7/17.5	15.2
Repose angle (deg.)	40/39	43/41	44/39	46
Spatula angle (deg.)	48/47	49.0/42.5	48.5/48.5	52.5
Uniformity	1.64/1.60	1.78/1.83	2.28/2.00	2.15
Flowability index	72/71	75/74	76/75	74
Granule hardness (g/mm^2)	1289 ± 688	1257 ± 793	919 ± 611	1377 ± 1068
Kawakita equation's a	0.754	0.807	0.772	0.716
Kawakita equation's b	2.32	3.52	2.88	1.86

Mil. and unmil. refer to granulations with and without granulation preparation process (Before magnesium stearate was added).

The fluid bed has been shown to be capable of producing porous granules, and agitating fluid bed granulation may be widely applicable for densifying granules.[7] Unfortunately, in this study, granulations #A, #B and #C showed low and essentially identical bulk densities which retard granulor flow. In addition to particle size and compressibility, particle shape and surface characteristics are also very important determinants of particle flowability. Porous granules produced by the fluid bed or agitating fluid bed may have irregular surfaces which would lessen flowability due to the interlocking of granules. Such a situation would be expected for granulations #A, #B and #C, with virtually the same angle of repose, angle of spatula and flowability index. Granulation #A showed very great particle hardness and granulation, #C showed slight particle hardness, thus demonstrating that large granules are porous and fragile.

The size of particles made by extrusion depends primarily on orifice size and extrudate length. During size adjustment, particle shape and size also changed and many fine particles were produced, thus showing that #D granules have a large geometric median diameter and wide size distribution. Owing to the granulating pressure, the #D granules were very highly aerated with packed bulk density and high hardness. Their small compressibility promotes their flow, but because of the wide particle size distribution and cylinder-like shape, the angles of repose and spatula are large, with consequent moderate flowability.

High bulk density is an essential feature of tablets since the amount of filling is limited by die length. Granulation #D appears to present no problem during tableting, while #A, #B and #C with small bulk density may encounter this trouble during die filling. #A, #B and #C granules were passed through a 24 mesh screen with the hope of augmenting thier bulk density, but thier bulk density and flowability remained essentially the same.

Granule compression behavior was evaluated by the equations of Kawakita[8]:

$$C = \frac{V_0 - V}{V} \tag{4}$$

$$P/C = 1/ab + P/a \tag{5}$$

where C is the decreased fraction of the relative granule volume; V_0 and V, the initial granule bed volume and volume at pressure P respectively; and a and b, constants: a is equal to the initial porosity of the powder bed and b is the compression coefficient or, at unit pressure, the decreased porosity fraction of the powder bed. The constant, b is related to powder plasticity.[9]

Plots of P/C *versus* P gave a line, and a and b calculated from the slope and intercept of this line are indicated in Table 2.

Granulation #D, with the smallest a, showed that a

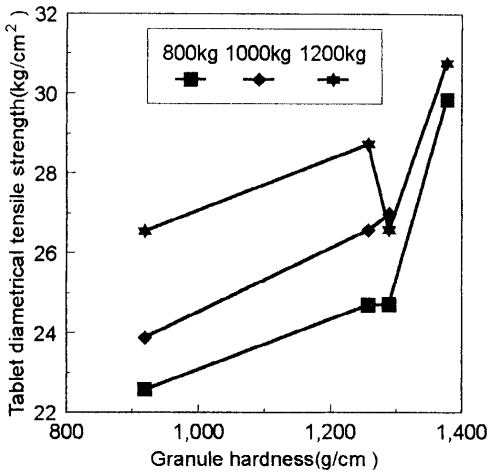

Fig. 2. The Relation between the Diametrical Tensile Strength of a Tablet and Granule Hardness

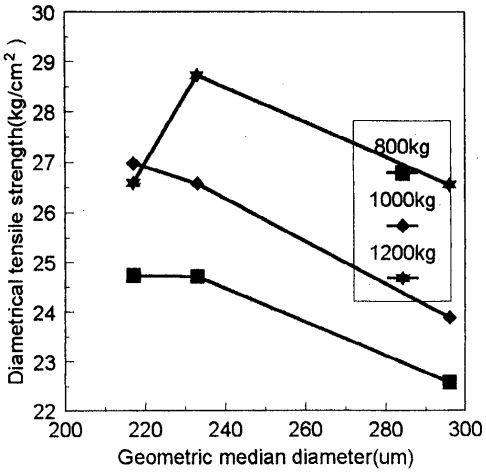

Fig. 3. The Relation between Tablet Diametrical Tensile Strength and Geometric Median Diameter

larger initial filling fraction is more possible by extrusion than by the agitating fluid bed owing to the very large particle size anticipated for the few contact points per unit aera, and also to the small interparticular cohesive force at zero pressure which resists dense packing. Granulations #A, #B and #C showed large *b*, and thus agitating fluid bed granules would appear more compressible than those obtained by extrusion. This means that plastic flow occurs easily in granulations #A, #B and #C.

With an increase in tableting force, the diametrical crushing strength increased very little prior to crushing.

The diametrical tensile strength of tablets in granulations #A, #B and #C was much the same, but harder and smaller granules appeared to be produced preferentially (Figs. 2 and 3). Interparticulate bonds would thus appear strong, and tablet fracture may occure across grains according to the theory of Orewan.[10]

Granulation #D, with the greatest granule hardness,

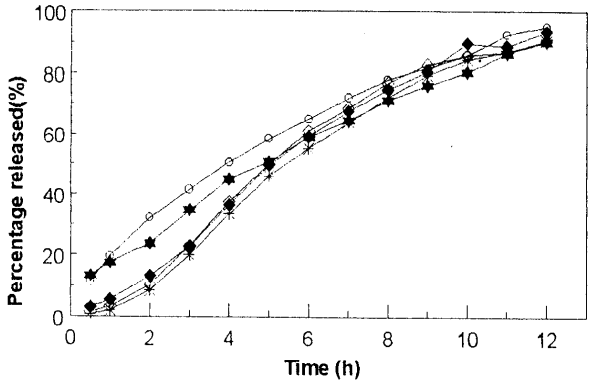

Fig. 4. Release Percentage *vs.* Time of Batches of #B and #D at Various Compression Pressures

—○— B, 800 kg; —■— B, 1000 kg; —◆— B, 1200 kg; —◇— D, 800 kg; —×— D, 1200 kg.

produced the hardest tablets and the largest geometric median diameter, apparently contradicting Orewan. Large granule hardness due to extrusion may be the reason for this.

The dissolution of IMN from the tablets of batches #B and #D is shown graphically in Fig. 4. The two batches showed essentially the same mode of release, which was slightly faster for #B than #D. This was more apparent at the start of dissolution. With batch #B, compression force affected drug release; as compression force increased, the rate of release decreased. Surface disintegration of the tablets made in granulation #B would thus appear to occur to a greater extent than in granulation #D, and the surface disintegration of tablets produced *a* at low pressure may be greater than that at high pressure.

Conclusions

Agitating fluid bed and extrusion granulations were examined in this study. Granule flowability, hardness and compressibility were satisfactory, as were also dissolution and diametrical crushing strength. Either method should prove adequate for producing HPMC hydrogel matrix tablets.

References

1) Part 1, Xu G., Sunada H., *Chem. Pharm. Bull.*, **43**, 483—487 (1995).
2) Carr R. L., Jr., *Chemical Engineering, Jan.*, **18**, 163—168 (1965).
3) Hiramatsu Y., Seki Y., Motoyama H., *Nippon Kogyo Kaishi*, **81**, 1024—1028 (1965).
4) Fell J. T., Newton J. M., *J. Pharm. Sci.*, **59**, 688—691 (1970).
5) Newitt D. M., Conway-Janes J. M., *Trans. Instn. Chem. Engrs.*, **36**, 422—425 (1956).
6) Record P. C., *Int. J. Pharm. Tech. Prod. Mfr.*, **1**(2), 32—35 (1980).
7) Dahl T. C., Bormeth A. P., *Drug Dev. Ind. Pharm.*, **16**(4), 581—590 (1990).
8) Ramberger R., Burger A., *Powder Technology*, **43**, 1—9 (1985).
9) James P. J., *Powder Metall. Int.*, **4**(2), 82—85 (1972).
10) Shotton E., Ganderton D., *J. Pharm. Pharmacol.*, Suppl., 144T, (1961).