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# Properties of hydroxypropylmethylcellulose granules produced by water spraying

Cheng-Hsiung Liu [a], Shou-Chiung Chen [a], Yuh-Horng Kao [a], Ching-Cheng Kao [a], Theodore D. Sokoloski [b] and Ming-Thau Sheu [a]

[a] *Graduate Institute of Pharmaceutical Sciences, Taipei Medical College, Taipei (Taiwan, ROC) and* [b] *Pharmaceutical Sciences, UW2820, SmithKline Beecham, P.O. Box 1539, King of Prussia, PA 19406-0939 (USA)*

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## Summary

Granulation of powdered HPMCs stirred in a planetary mixer was induced by simple spraying with water. The influence of nozzle size, the amount of water added, and grade of HPMC on particle size, density, angle of repose, and compressibility was determined for the several granules produced. The properties of tablets made from them were also evaluated. It was found that the effect of process variables on the physical properties of neat HPMC granules is the same in the presence the drug, diclofenac sodium. Using a smaller sized nozzle results in a narrower granule size distribution. The amount of water needed to optimize granule size for tabletting is in the range of 90–120 ml per 200 g of powder mixture. The release of diclofenac sodium from such matrix tablets follows a non-Fickian mechanism; release is affected primarily by the grade of HPMC and the rate at which it hydrates.

## Introduction

Various types of swellable polymers have been used as matrix materials for controlled release formulations. Among these, hydroxypropylmethylcelluloses (HPMCs) are widely used for controlled release oral delivery as demonstrated in the review by Hogan (1989). Several factors can affect drug release from HPMC matrices. These include drug loading (Lapidus et al., 1966; Ford et al., 1985), drug particle size (Ford et al., 1985); drug solubility (Ranga Rao et al., 1990); the presence of surfactant (Feely et al., 1988; Ford et al., 1991a); temperature (Ford et al., 1991b); compressional force (Huber et al., 1968; Ford et al., 1985); HPMC viscosity grade (Shah et al., 1989), particle size (Dahl et al., 1990), and source (Lucisano et al., 1989); formulation additives (Ford et al., 1987; Feely et al., 1988; Mitchell et al., 1990) and tablet shape (Ford et al., 1987).

In many cases drug-HPMC mixtures do not have adequate flow properties for tabletting and it is common to use less desirable methods such as direct die filling or double compression. Wet granulation with water as a simple binding aid

*Correspondence to:* M.-T. Sheu, Graduate Institute of Pharmaceutical Sciences, Taipei Medical College, Taipei, Taiwan, R.O.C.

has not been employed probably because of the tendency of HPMC to gel and form lumps in the presence of water. It was thought that if water were added by spraying onto a stirred powder, agglomeration would be avoided; an important part of the present study deals with the aqueous spraying of HPMC stirred in a planetary mixer. The physical properties of granules and tablets that result using different starting materials and processes were compared. The results found in these studies identified a set of formulation and process variables that could be used to formulate a matrix release product for a model drug, diclofenac sodium. The in vitro release of diclofenac sodium from such HPMC matrix tablets was measured.

## Materials and Methods

### *Materials*

Diclofenac sodium (lot no. 0100951) was obtained from Yung-Shin Pharm. Co. (Taiwan, R.O.C.). Three viscosity grades of hydroxypropylmethylcellulose were used as supplied by Shin-Etsu Chem. Co. (Tokyo, Japan): Metolose 60-SH, 50 cps (type 2910, methoxyl 29.3%, hydroxypropoxyl 9.0%); Metolose 60-SH, 4000 cps (type 2910, methoxyl 29.3%, hydroxypropoxyl 9.0%); and Metolose 90-SH, 100 cps (type 2208, methoxyl 23.3%, hydroxypropoxyl 7.5%). All other reagents were analytical or pharmaceutical grade.

### *Methods*

#### *Granulation*

A total of 200 g of HPMC with or without diclofenac sodium (1 : 1) was placed in a planetary mixer (KitchenAid model K45SS, KitchenAid Inc., St. Joseph, MI, U.S.A.). Three different amounts of water were sprayed onto the powders using a sprayer, squeezing by hand. The powders were mixed at a constant speed of approx. 50 rpm. Two nozzle diameters, 0.012 inch (output 0.14 ml/s) and 0.025 inch (output 0.7 ml/s), were used to produce different sized water droplets. The spraying process took approx. 20–25 min depending upon the size of nozzle used and the amount of the water added. After the measured amount of water had been added, the wetted granules were discharged and tray-dried for 12 h at 50°C in a hot air oven. Three batches were prepared for a given formulation.

#### *Granule characterization*

The size distribution of the granules was measured by sieve analysis (Tyler Analysensieb, no. 12–115 mesh, Haver & Boecker, Westfalen). The bulk and tap density of the granules were measured in a 100 ml graduated cylinder via a mechanical tapping device (Erweka, SVM) actuated for 10 min. The values obtained were used to calculate the compressibility index. The angle of repose was measured using a fixed funnel and cone. The moisture content of each batch of granules was determined using an IR moisture analyzer (Kett, Japan) with a 20 min drying time at 80°C.

#### *Preparation and characterization of matrix tablets*

Dried HPMC/diclofenac sodium granules for each formulation were passed through a no. 20 mesh sieve and then mixed with 1% Aerosil-200. Tablets were manufactured using a rotary press (Jenn-Chiang Machinery Co.) with 9 mm flat round punches. Weight variation was determined using 20 tablets and an electronic balance (Sartorius, Type 1801, Germany). Tablet hardness was evaluated for 10 tablets using an Erweka TBH 28 tester. Friability was determined for a batch of 10 tablets (Roche Friabilator Model AE-20, Aikho Engineering, R.OC.); 5 min and a speed of 25 rpm were used. The thickness of 10 tablets was averaged as measured with a Vernier Caliper (Mitutoyo, Tokyo, Japan).

#### *Dissolution studies*

The USP paddle method was used to measure release of diclofenac sodium from HPMC matrix tablets at 37°C. At predetermined time intervals, 5 ml of bathing medium was withdrawn and replaced with fresh solution. A medium of changing pH was used; initially 900 ml of 0.1 N HCl solution was used for 2 h. Then trisodium phosphate was added to change the pH to 6.8 and the

study continued for 24 h. The stirring speed was 100 rpm. Diclofenac sodium content was determined from the UV absorbance at 276 nm after appropriate dilution. The average for three to six tablets was used to calculate a cumulative fraction of drug released at each sampling time.

## Results and Discussion

*HPMC granules*

Spraying water onto a stirred HPMC powder proved to be a successful process for the preparation of granules with minimized clumping. It was found that all of the granulations that were manufactured, with and without added drug, had moisture levels of 1–2% after drying. Using sieves of 12–115 mesh, the cumulative percent oversize was determined for each batch of granules manufactured. When these values were plotted in the form of probability vs the logarithm of screen size, reasonable linearity was seen as typified in Fig. 1 for granules formed using 1 : 1 mixtures of the several polymers with diclofenac sodium; A and B represent results using different nozzle sizes. Granules made using polymer alone gave similar results. Linearity in such plots supports the likelihood that the granules are log-normally distributed and, based on this finding, mean sizes and distributions were determined for each of the different materials and methods used. The last column in Tables 1–4 lists the sizes found. The geometric mean diameter among the granulations ranges from 412 to 6260 $\mu$m and depends on the amount of water used, the type of HPMC employed, and the nozzle size. Particle size distributions ($s$ values) among the different granulations produced are also significantly different. Some trends are evident: geometric mean diameter increases with an increase in the amount of water used for all viscosity grades of HPMC tested with or without diclofenac sodium; because of the hydrophilicity of the HPMC polymers this result was expected. The geometric mean diameter also increases with increasing nozzle diameter at the same amount of water added; this result was also true for all grades of HPMC tested with or without diclofenac sodium. Not only are the particles smaller but also their distribution is narrower using a smaller nozzle. Although these trends with increasing amounts of water or nozzle size are general, it should be noted that, in comparison with neat polymer, the presence of drug results in granules of larger mean diameter and wider distribution for all types of HPMC and with either nozzle.

It does not appear that the granule size correlates with the viscosity grade of HPMC; greater geometric mean diameters resulted for granules prepared using 100 cps viscosity grade (90-SH) compared to those of the 50 cps (60-SH) or 4000 cps grades. According to the manufacturer's tech-

TABLE 1

*Physical properties of drug-free HPMC granules produced with a nozzle size of 0.012 inch*

| HPMC grade (cps) | Total water added (ml) | Density (g/ml) | | Compressibility index (%) | Angle of repose (°) | Moisture content (%) | Geometric mean ($\mu$m) $\pm \ln \sigma_g$ |
|---|---|---|---|---|---|---|---|
| | | Bulk | Tap | | | | |
| 50 | 90 | 0.22 (0.01) [a] | 0.27 (0.01) | 19.3 (0.5) | 35.2 (0.7) | 1.0 (0.2) | 445 ± 0.68 |
| | 120 | 0.21 (0.01) | 0.26 (0.01) | 17.4 (0.6) | 35.2 (0.4) | 1.4 (0.1) | 551 ± 0.64 |
| | 150 | 0.23 (0.01) | 0.27 (0.02) | 16.0 (0.1) | 34.9 (0.3) | 1.4 (0.2) | 647 ± 0.63 |
| 100 | 90 | 0.21 (0.01) | 0.26 (0.01) | 20.7 (0.7) | 40.0 (0.5) | 1.3 (0.1) | 568 ± 0.75 |
| | 120 | 0.24 (0.01) | 0.29 (0.01) | 18.6 (0.5) | 40.0 (0.7) | 1.3 (0.1) | 799 ± 0.69 |
| | 150 | 0.28 (0.01) | 0.33 (0.01) | 15.8 (0.5) | 40.4 (0.7) | 1.4 (0.1) | 959 ± 0.67 |
| 4000 | 90 | 0.15 (0.01) | 0.20 (0.01) | 23.0 (0.8) | 45.1 (0.6) | 1.2 (0.1) | 441 ± 0.66 |
| | 120 | 0.15 (0.01) | 0.18 (0.01) | 18.5 (0.5) | 45.1 (0.3) | 1.3 (0.1) | 587 ± 0.67 |
| | 150 | 0.16 (0.01) | 0.20 (0.01) | 18.4 (0.6) | 45.1 (0.3) | 1.5 (0.1) | 734 ± 0.68 |

[a] Mean of three batches measured three times each (S.D.).

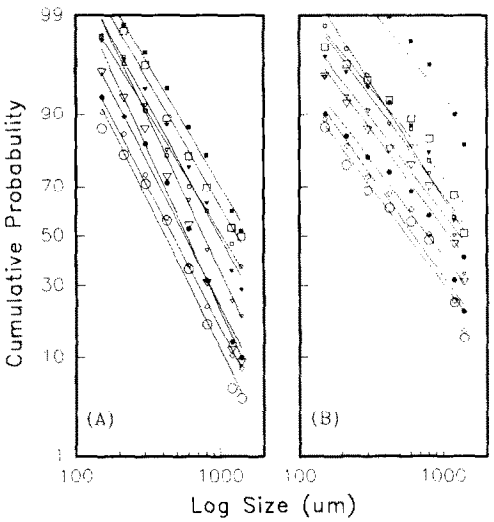


Fig. 1. Plot of cumulative probability vs logarithm of screen size for HPMC/diclofenac sodium granules manufactured with a nozzle size of 0.012 inch (A) or 0.025 inch (B). (Open symbols) HPMC 50 cps; (closed symbols) HPMC 100 cps; (open symbols, with dot) HPMC 4000 cps; (squares) 150 ml; (triangles) 120 ml; (circles) 90 ml).

nical data, the hydration rate for the 90-SH grade is faster than that for the 60-SH grade. Thus, the size results obtained may be related to the rate of hydration.

HPMC granules formed in the absence of other ingredients were irregularly shaped and open in structure. As shown in Tables 1 and 2, both bulk and tap density increase and compressibility index decreases with increasing amount of water when sprayed using a small nozzle. The effect of the amount of water that is used on granule bulk and tap density is ambiguous when using the larger nozzle. There is no significant effect on the compressibility index when different sized nozzles are used to spray the same amount of water. However, both bulk and tap density increased using the larger nozzle for the same viscosity grade HPMC and the same amount of water. Tables 1 and 2 also indicate that, although no significant change occurs in the angle of repose using the same HPMC viscosity grade with increasing amount of water and different nozzles, there appears to be a trend toward increasing angle of repose with increasing HPMC viscosity grade when the smaller diameter nozzle is used. Although the influence of the amount of water applied on the angle of repose is very small for the same HPMC for either nozzle size, compared to the results with the small nozzle, the angle of repose for granules is less with all HPMC grades when the larger nozzle is used. Granules produced using the 50 cps grade HPMC would appear to have suitable flow properties based on their angle of repose. The other two viscosity grades apparently have fair to poor flow; angle of repose 35–40°.

TABLE 2

*Physical properties of drug-free HPMC granules produced with a nozzle size of 0.025 inch*

| HPMC grade (cps) | Total water added (ml) | Density (g/ml) | | Compressibility index (%) | Angle of repose (°) | Moisture content (%) | Geometric mean ($\mu$m) $\pm \ln \sigma_g$ |
|---|---|---|---|---|---|---|---|
| | | Bulk | Tap | | | | |
| 50 | 90 | 0.35 (0.01) [a] | 0.44 (0.01) | 20.6 (0.9) | 28.8 (0.8) | 1.1 (0.2) | 504 ± 1.05 |
| | 120 | 0.36 (0.01) | 0.44 (0.01) | 19.3 (0.5) | 31.7 (1.0) | 1.4 (0.1) | 828 ± 0.99 |
| | 150 | 0.34 (0.02) | 0.41 (0.02) | 16.6 (0.5) | 31.8 (1.1) | 1.5 (0.2) | 1 280 ± 0.96 |
| 100 | 90 | 0.31 (0.01) | 0.39 (0.01) | 21.8 (0.4) | 39.9 (0.3) | 1.1 (0.1) | 822 ± 1.02 |
| | 120 | 0.31 (0.01) | 0.35 (0.01) | 15.7 (0.5) | 39.3 (0.9) | 1.3 (0.1) | 1 202 ± 0.99 |
| | 150 | 0.34 (0.02) | 0.40 (0.02) | 15.3 (0.5) | 40.1 (0.3) | 1.5 (0.1) | 1 367 ± 0.87 |
| 4 000 | 90 | 0.28 (0.01) | 0.40 (0.02) | 29.4 (0.8) | 40.1 (0.3) | 1.3 (0.1) | 617 ± 1.16 |
| | 120 | 0.26 (0.02) | 0.35 (0.03) | 24.5 (0.5) | 35.2 (0.4) | 1.3 (0.1) | 921 ± 1.03 |
| | 150 | 0.23 (0.03) | 0.28 (0.03) | 16.2 (0.8) | 35.1 (0.3) | 1.6 (0.1) | 1 292 ± 1.05 |

[a] Mean of three batches measured three times each (S.D.).

TABLE 3

*Physical properties of HPMC / diclofenac sodium granules produced with a nozzle size of 0.012 inch*

| Composition | Total water added (ml) | Density (g/ml) | | Compressibility index (%) | Angle of repose (°) | Moisture content (%) | Geometric mean ($\mu$m) $\pm \ln \sigma_g$ |
|---|---|---|---|---|---|---|---|
| | | Bulk | Tap | | | | |
| HPMC 50 cps | 90 | 0.29 (0.01) [a] | 0.38 (0.01) | 24.0 (0.7) | 37.7 (0.5) | 1.4 (0.1) | 469 ± 0.78 |
| diclofenac | 120 | 0.32 (0.02) | 0.40 (0.02) | 20.0 (0.8) | 32.8 (1.0) | 1.4 (0.2) | 765 ± 0.71 |
| sodium (1 : 1) | 150 | 0.52 (0.02) | 0.62 (0.02) | 15.3 (0.7) | 30.6 (0.9) | 1.6 (0.1) | 1 031 ± 0.91 |
| HPMC 100 cps | 90 | 0.30 (0.01) | 0.34 (0.04) | 19.9 (0.3) | 35.4 (0.5) | 1.2 (0.1) | 566 ± 0.76 |
| diclofenac | 120 | 0.36 (0.01) | 0.45 (0.01) | 19.0 (0.5) | 34.4 (0.9) | 1.4 (0.1) | 983 ± 0.82 |
| sodium (1 : 1) | 150 | 0.39 (0.02) | 0.47 (0.03) | 16.2 (0.5) | 34.7 (0.7) | 1.5 (0.1) | 1 597 ± 0.89 |
| HPMC 4 000 cps | 90 | 0.23 (0.02) | 0.32 (0.02) | 28.3 (0.5) | 39.1 (0.9) | 1.3 (0.2) | 412 ± 0.74 |
| diclofenac | 120 | 0.25 (0.01) | 0.32 (0.01) | 23.0 (0.9) | 39.0 (0.9) | 1.3 (0.1) | 583 ± 0.68 |
| sodium (1 : 1) | 150 | 0.35 (0.08) | 0.45 (0.10) | 18.2 (0.4) | 34.9 (0.3) | 1.5 (0.1) | 1 311 ± 0.87 |

[a] Mean of three batches measured three times each (S.D.).

*HPMC / diclofenac sodium (1 : 1) granules*

The physical properties of HPMC/ diclofenac sodium (1 : 1) granules prepared under various spraying conditions are listed in Tables 3 and 4. The effects of HPMC type, the amount of water applied and spray nozzle size were similar to those seen when granules were made from HPMC alone. One noteworthy difference was that with drug present granules show an increase in both bulk and tap density and a decrease in the angle of repose. The calculated values for compressibility show no significant change but the decreased angle of repose indicates an increase in flowability of the drug-containing granules.

An optimal granulation process should produce granules with good flowability and a high size fraction of granules within the range suitable for tabletting. The optimal amount of water needed to achieve this was found to be between 90 and 120 ml per 200 g of the HPMC/ diclofenac sodium mixture. As the amount of binding liquid increased to 150 ml, granules aggregated which resulted in an increase in the mean size necessitating a crushing step prior to tabletting. Further-

TABLE 4

*Physical properties of HPMC / diclofenac sodium granules produced with a nozzle size of 0.025 inch*

| Composition | Total water added (ml) | Density (g/ml) | | Compressibility index (%) | Angle of repose (°) | Moisture content (%) | Geometric mean ($\mu$m) $\pm \ln \sigma_g$ |
|---|---|---|---|---|---|---|---|
| | | Bulk | Tap | | | | |
| HPMC 50 cps | 90 | 0.42 (0.01) [a] | 0.54 (0.01) | 21.4 (1.0) | 34.8 (0.4) | 1.3 (0.2) | 632 ± 1.08 |
| diclofenac | 120 | 0.42 (0.02) | 0.51 (0.02) | 16.2 (0.4) | 32.3 (0.9) | 1.3 (0.2) | 1 316 ± 1.15 |
| sodium (1 : 1) | 150 | 0.50 (0.03) | 0.59 (0.04) | 15.1 (1.1) | 33.1 (0.6) | 1.6 (0.1) | 1 472 ± 0.96 |
| HPMC 100 | 90 | 0.43 (0.01) | 0.55 (0.01) | 21.5 (0.5) | 35.4 (0.5) | 1.2 (0.1) | 787 ± 1.15 |
| diclofenac | 120 | 0.46 (0.01) | 0.55 (0.01) | 16.5 (0.5) | 34.7 (0.7) | 1.3 (0.1) | 1 619 ± 1.11 |
| sodium (1 : 1) | 150 | 0.60 (0.02) | 0.71 (0.03) | 15.3 (0.5) | 34.1 (1.1) | 1.6 (0.1) | 6 259 ± 1.24 |
| HPMC 4 000 cps | 90 | 0.39 (0.02) | 0.53 (0.02) | 26.3 (0.5) | 37.3 (1.0) | 1.0 (0.2) | 566 ± 1.13 |
| diclofenac | 120 | 0.38 (0.02) | 0.49 (0.02) | 21.6 (0.5) | 35.3 (0.5) | 1.0 (0.2) | 1 114 ± 1.13 |
| sodium (1 : 1) | 150 | 0.41 (0.01) | 0.49 (0.01) | 16.0 (0.5) | 39.1 (1.1) | 1.5 (0.1) | 2 131 ± 1.22 |

[a] Mean of three batches measured three times each (S.D.).

more, the smaller spraying nozzle produced a greater percentage of granules suitable for tabletting.

*Evaluation of matrix tablets*

The physical properties of matrix tablets prepared from granules containing drug using the three viscosity grades of HPMC are listed in Table 5. The weight variation for most tablets is within acceptable limits, reflecting the favorable flow property conferred by the granulation procedure. Friability is extremely low and hardness ranges from $3.46 \pm 0.47$ to $8.26 \pm 0.38$ Kp; tablets made from the granules prepared with 150 ml of water give the lowest hardness values. The significant differences found in hardness can be attributed to many factors including size distribution, deformability, compressibility and compression force. In fact, it was observed that granules produced with the greater amount of water (150 ml) are large granules that are intrinsically hard which must be crushed prior to tabletting. It may be that the increase in number of fine particles produced during comminution together with the intrinsic hardness of the primary granule leads to insufficient bonding, resulting in a decreased tablet hardness.

The results relating to the release of diclofenac sodium from tablets using granules produced under different conditions and different viscosity grades of HPMC are represented by plots of percent delivered vs time as shown in Fig. 2, each panel (A–C) corresponding to the use of a particular HPMC grade. Diclofenac sodium is a salt whose conjugate acid has a $pK_a$ of 4. The solubility of such a drug is markedly affected by the pH of the release medium. Because of the nature of the drug and in order to simulate pH variations along the GI tract, release studies were conducted using a changing pH medium. As shown in Fig. 2, a lag phase persists well beyond neutralization of the release medium. The similarity in the release patterns within each segment (A–C) shows that the amount of water applied

TABLE 5

*Physical properties of HPMC / diclofenac sodium matrix tablets*

| Formula | Nozzle size (inch) | Total water added (ml) | Average weight (mg) (S.D., $n = 20$) | Hardness (Kp) (S.D., $n = 10$) | Friability (%) (S.D., $n = 3$) | Thickness (mm) (S.D., $n = 20$) |
|---|---|---|---|---|---|---|
| HPMC 50 cps diclofenac sodium (1 : 1) | 0.012 | 90 | 205.1 (6.7) | 6.6 (0.8) | 0.17 (0.01) | 2.98 (0.06) |
| | | 120 | 212.5 (8.0) | 6.9 (0.8) | 0.10 (0.01) | 2.96 (0.04) |
| | | 150 | 222.6 (5.9) | 5.0 (0.5) | 0.13 (0.02) | 2.87 (0.02) |
| | 0.025 | 90 | 195.5 (5.2) | 5.9 (0.6) | 0.25 (0.02) | 2.72 (0.07) |
| | | 120 | 205.3 (7.5) | 5.7 (0.7) | 0.11 (0.02) | 2.93 (0.04) |
| | | 150 | 201.7 (4.0) | 4.8 (0.5) | 0.17 (0.03) | 2.86 (0.02) |
| HPMC 100 cps diclofenac sodium (1 : 1) | 0.012 | 90 | 201.6 (9.2) | 7.2 (0.4) | 0.16 (0.02) | 2.83 (0.05) |
| | | 120 | 209.6 (6.2) | 7.0 (0.8) | 0.12 (0.01) | 3.11 (0.05) |
| | | 150 | 209.7 (5.3) | 4.9 (0.5) | 0.11 (0.02) | 2.96 (0.05) |
| | 0.025 | 90 | 220.2 (4.8) | 7.4 (0.9) | 0.13 (0.03) | 3.01 (0.05) |
| | | 120 | 213.0 (5.2) | 5.8 (0.7) | 0.13 (0.03) | 3.00 (0.06) |
| | | 150 | 206.9 (5.3) | 4.9 (0.5) | 0.11 (0.02) | 2.96 (0.05) |
| HPMC 4 000 cps diclofenac sodium (1 : 1) | 0.012 | 90 | 206.0 (8.4) | 8.3 (0.4) | 0.14 (0.02) | 3.15 (0.07) |
| | | 120 | 216.5 (16.1) | 7.3 (1.4) | 0.17 (0.02) | 3.12 (0.04) |
| | | 150 | 212.4 (10.1) | 6.4 (0.5) | 0.10 (0.02) | 2.98 (0.04) |
| | 0.025 | 90 | 204.2 (4.3) | 7.0 (0.6) | 0.16 (0.02) | 2.89 (0.03) |
| | | 120 | 207.0 (7.3) | 6.4 (0.9) | 0.19 (0.06) | 2.91 (0.04) |
| | | 150 | 194.6 (8.9) | 3.5 (0.5) | 0.16 (0.04) | 2.80 (0.05) |

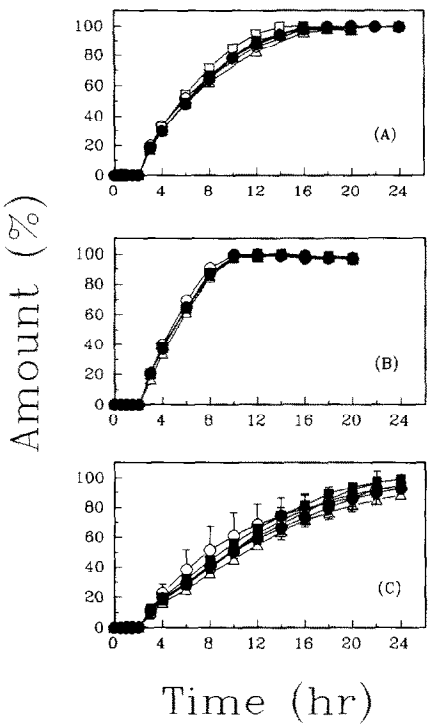


Fig. 2. Percent release of diclofenac sodium from HPMC matrix tablets as a function of time. (A) 50 cps viscosity grade: (open symbols) nozzle size, 0.012 inch; (closed symbols) nozzle size, 0.025 inch; (squares) 150 ml; (triangles) 120 ml; (circles) 90 ml. (B) 100 cps viscosity grade (symbol designations as in panel A). (C) 4000 cps viscosity grade (symbol designations as in A above).

and the nozzle size used to produce granules have no effect on tablet performance in vitro. The type of HPMC used appears to be the dominant factor in controlling the release rate of drug; 90-SH/100 cps > 60-SH/50 cps > 60-SH/4000 cps. The rate of hydration of the polymer may be quite important; the 90-SH/100 cps grade, which has the most rapid rate of hydration (greater than that of the 60-SH/50 cps grade), results in the faster release rate.

To characterize relative release rate, a rate constant $K$ was calculated for the data in Fig. 2 by fitting the release data from 3 to 8 h (i.e., beyond the lag phase) to the logarithmic form of the equation:

$$M_t/M_0 = K \cdot t^n$$

where $M_t/M_0$ is the fraction of drug released at time $t$, $K$ denotes a release rate constant incorporating structural and geometric characteristics, and $n$ is a diffusional release exponent indicative of the type of release (Retgers et al., 1987). The values of $K$, $n$ and the coefficient of correlation, $r$, obtained for all matrix tablets are given in Table 6. The values of $n$ for all cases ranged from 0.6442 to 0.8471, indicating a non-Fickian release mechanism for diclofenac sodium.

TABLE 6

*Release rate constant (K), release exponent (n) and correlation coefficient (r) for the release of diclofenac sodium from HPMC matrix tablets*

| Formula | Total water added (ml) | $K$ | | $n$ | | $r$ | |
|---|---|---|---|---|---|---|---|
| | | S [a] | L | S | L | S | L |
| HPMC 50 cps | 90 | 20.46 | 18.03 | 0.666 | 0.710 | 0.999 | 1.000 |
| diclofenac sodium | 120 | 18.97 | 17.44 | 0.655 | 0.728 | 1.000 | 0.999 |
| (1:1) | 150 | 19.25 | 17.64 | 0.727 | 0.730 | 0.999 | 0.999 |
| HPMC 100 cps | 90 | 22.28 | 22.20 | 0.794 | 0.778 | 0.998 | 0.999 |
| diclofenac sodium | 120 | 17.90 | 19.76 | 0.874 | 0.820 | 0.999 | 0.999 |
| (1:1) | 150 | 21.65 | 19.20 | 0.769 | 0.846 | 0.999 | 0.997 |
| HPMC 4000 cps | 90 | 10.77 | 12.34 | 0.644 | 0.698 | 0.999 | 0.999 |
| diclofenac sodium | 120 | 11.11 | 12.26 | 0.664 | 0.682 | 0.999 | 0.999 |
| (1:1) | 150 | 13.60 | 14.29 | 0.691 | 0.662 | 1.000 | 0.999 |

[a] Nozzle size: S, 0.012 inch; L, 0.025 inch.

## Conclusion

Granulation of HPMC by spraying water on the powder while it is stirred in a planetary mixer is achievable with minimized agglomeration. The resulting granules have improved flowability. In order to obtain a higher percentage of granules in a size range suitable for tabletting, a small sized nozzle should be used to spray an optimal amount of water per dry weight of polymer. Tablets containing diclofenac sodium made from such granules show that the rate of release is predominantly controlled by the grade of HPMC and very likely its hydration rate.

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