Influence of Formulation Variables and Manufacturing Process on Propranolol Extended Release Profile from HPMC Matrices Tablets

Yaw-Bin Huang, Yi-Hung Tsai, Wan-Chiech Yang, Jui-Sheng Chang, Pao-Chu Wu

School of Pharmacy, Kaohsiung Medical University, Kaohsiung City 80708, Taiwan

Received 28 May 2003; accepted 18 February 2004
DOI 10.1002/app.20655
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: The influences of some formulation variables and manufacturing processes of the release rates of propranolol from gelation of hydroxypropylmethylcellulose (HPMC) matrices tablets were investigated. The amount of propranolol was determined by UV–Vis spectroscopy at 290 nm. The effects of extended release of matrices tablets were evaluated by the *in vitro* dissolution test and were compared to the United States Pharmacopoeia (USP) monograph specifications. The results showed that the lowest viscosity grade of HPMC (Metolose 4000) used gave the least burst effect in the earlier stage. The drug/Metolose ratio was an important influence on the drug release; increasing the polymer content decreased the dissolution rate of the drug. The release rate was increased with increase in the tablet content of avicel. The release curve of experimental formulation with 17% avicel was optimal compared with the USP monograph specification; there was no burst effect in the earlier stage (the release percent at 1.5 h was 26.6%) and almost total drug was released from matrices tablet after 24 h (97.4%). The other factors such as lubricant level (0.5 to 2.0%), compaction pressure (100 to 200 kPa), brand of HPMC (HPMC 4000 from Shin Etsu or Methocel K4MP from Dow Chemical Co.), and manufacturing process (tabletted from wet-massed granules or by direct compression) appeared not to modify release rates. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 93: 1886–1890, 2004

Key words: propranolol; hydroxypropylmethylcellulose (HPMC); viscosity; gelation; extended release; UV–Vis spectroscopy

INTRODUCTION

Propranolol, a nonselective β-adrenergic blocking agent, was widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders, but its bioavailability is very limited (30%). Its elimination half-life is also relatively short (about 2–6 h). Therefore, it is a suitable candidate for extended release formulation.[1–3]

The hydrophilic gel-forming matrices tablets are extensively used for oral extended release dosage forms because of their simplicity, cost effectiveness, and reduction of the risk of systemic toxicity due to dose dumping.[4–7] Furthermore, pH-independent drug release is preferable for oral extended release formulations, so as not to be affected largely by their drug release in the gastrointestinal (GI) tracts by intra- and intersubject variations of both gastric pH and GI transit time. Hydroxypropylmethylcellulose (HPMC) is a pH-independent material and can form hydrogels in GI; hence, HPMC was used as a retardant to prepare the propranolol extended release matrices tablets in this study. The effects of type and additional amount of HPMC on the drug release were evaluated.

Previous studies[8–11] report insufficient drug absorption from controlled release products in an *in vivo* study because of the suppression of drug release due to the environment of colon (small volume of GI fluid and viscous colonic content) in the later stage. Some excipients such as polyethylene glycol, lactose, and surfactants incorporated into the gel-forming matrices can improve the phenomenon *in vitro* and/or *in vivo* because these excipients can stimulate the water penetration into the inner parts of the matrices, thus resulting in the drug release from matrix.[12–18] Microcrystalline cellulose (Avicel) is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulation. It also has some lubricant and disintegrant properties; consequently, it can improve the manufacturing process and adjust the drug release.[19–20] Therefore, in this study, the different amounts of avicel were used to modify the drug release rate and manufacturing process in this study. In addition, other factors that might affect the drug release including lubricant content, tabletted from wet-massed granules or by direct compression, and compaction pressure, were also investigated.

The purpose of the present work was to prepare the propranolol extended release dosage form by using HPMC and to evaluate the influence of formulation in-

Correspondence to: P.-C. Wu (pachwu@kmu.edu.tw).

TABLE I
The Release Percent of Propranolol from Different Types HPMC Matrices Tablets with Drug/Metolose Ratio of 1/5

Time	Dissolved (%)		
	Metolose 4000	Metolose 15,000	Metolose 30,000
0.5	4.97 ± 0.53	30.86 ± 8.74	32.96 ± 8.19
1.0	18.36 ± 1.46	51.76 ± 11.97	45.79 ± 9.28
1.5	19.09 ± 1.21	64.36 ± 11.94	55.53 ± 10.14
2.0	73.87 ± 17.50	74.97 ± 12.84	57.88 ± 10.14
3.0	90.18 ± 16.51	89.67 ± 11.81	62.94 ± 12.07
4.0	97.41 ± 13.12	100.07 ± 9.87	73.42 ± 7.80
5.0	99.99 ± 15.51	108.17 ± 5.42	75.34 ± 4.54

gredients and preparation process on the drug release from matrices tablets. The effects of extended-release of these experimental formulations were determined by dissolution test and compared with the specified United States Pharmacopoeia (USP) monographs.

EXPERIMENTAL

Materials

The following reagents were used: propranolol hydrochloride, *p*-hydroxybenzoate-butyl ester (TCI, Tokyo, Japan), Metolose (HPMC; viscosity 4000, 15000, 30000 grade; Shin Etsu Chemical Co., Tokyo, Japan), methocel (HPMC; K4MP; Dow Chemical Co., USA), and microcrystalline cellulose (Avicel; Asahi, Tokyo, Japan). All other chemicals and solvents were of analytical reagent grade and were obtained from ECHO Chemical Co., Kaosuing, Taiwan.

Preparation of propranolol HPMC matrices tablet

In matrices tablet systems, the tablet is in the form of a compressed compact containing an active ingredient, HPMC, lubricant, and avicel. The matrices may be tabletted from wet-massed granules or by direct compression. In brief, the drug and additives were weighted and mixed well. Water was added to make a wet mass. Then, the wet component was granulated through a 40-mesh sieve. The granules were dried in an oven for 3 h at 40°C and then blended with 0.5–2% of magnesium stearate. The mixture containing 100 mg propranolol was weighted and fed manually into the die of an instrumented single-punch tabletting machine to produce tablets by using flat-faced punches. The upper punch compaction pressure was set at 100–200 kPa.

Determination of the release of propranolol from HPMC matrices tablet

The USP[21] basket method was used for all the *in vitro* dissolution studies. Simulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) without enzymes were used as a dissolution medium. The rate of stirring was 100 rpm. The propranolol tablets were placed in 900 mL gastric fluid and maintained at 37°C. Five millili-

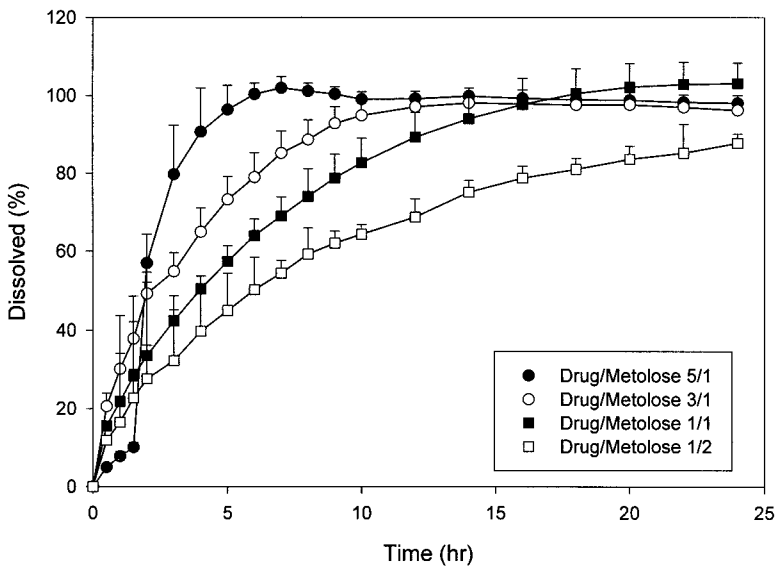

Figure 1 Dissolution profiles of propranolol matrices tablets with different drug/Metolose 4000 ratio.

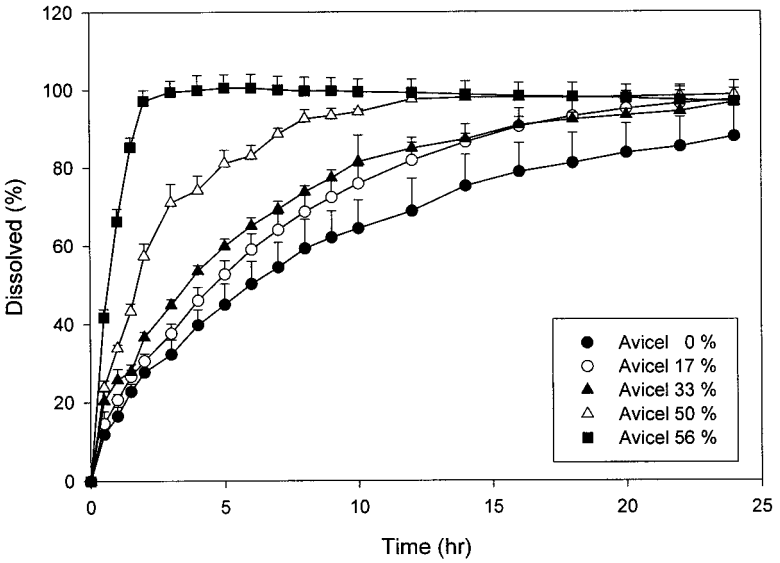

Figure 2 Dissolution profiles of propranolol matrices tablets containing different amounts of avicel.

ters of samples was taken at appropriate intervals. After 1.5 h, the dissolution medium pH was changed from 1.2 to 6.8 by adding concentrated phosphate buffer to simulate intestinal fluid and was then run for the time specified. The samples were analyzed by UV–Vis spectroscopy at 290 nm.

Data analysis

To propose the possible release mechanism, the drug released from HPMC matrices tablet was fitted to the following simple exponential model[22]

$$M_t/M_\infty = kt^n$$

where M_t/M_∞ is the fractional drug release percentage at time t, k is a constant related to the properties of the drug delivery system, and n is the diffusional exponent, which characterizes the drug transport mechanism. When $n = 0.5$, the drug diffuses through and is released from the polymeric matrices with a quasi-Fickian diffusion mechanism. For $n > 0.5$, an anomalous, non-Fickian drug diffusion occurs. When $n = 1$, a non-Fickian, case II or zero-order release kinetic could be observed. The dissolution profiles were com-

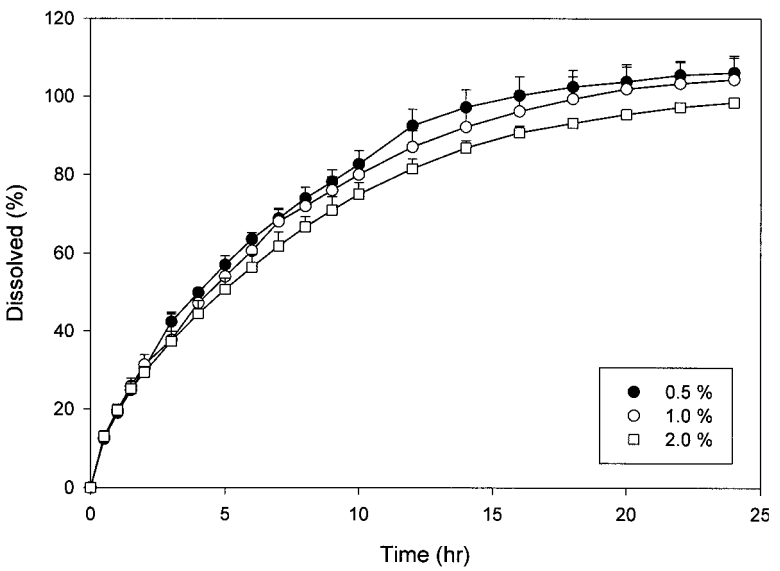

Figure 3 Dissolution profiles of propranolol matrices tablets containing different amounts of magnesium stearate as lubricant.

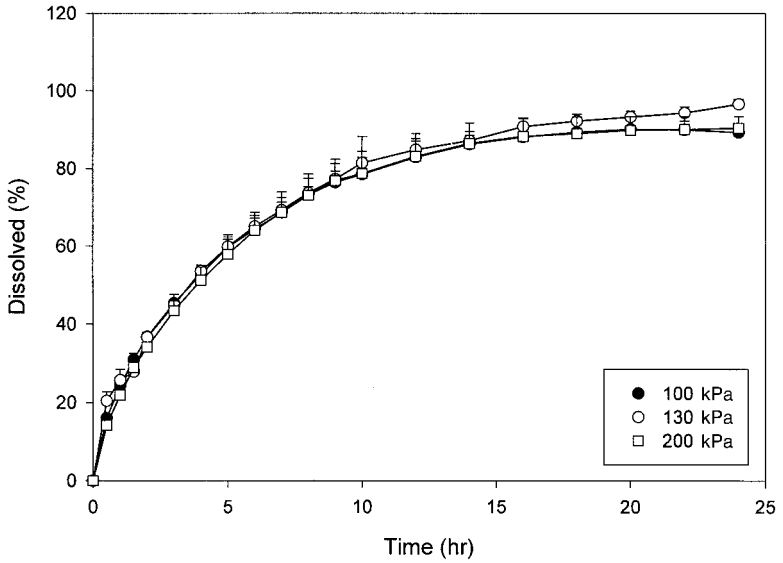

Figure 4 Dissolution profiles of propranolol matrices tablets compressed with different compaction pressures.

pared by using the similarity factor f_2 defined by the following equation and recently adopted by the FDA,[23] where an f_2 value > 50 (50–100) indicates that the two profiles are similar.

RESULTS AND DISCUSSION

Three different types of HPMC, including Metolose 4000, Metolose 15000, and Metolose 30000, were used to prepare propranolol extended release dosage form. The release percent of propranolol from these Metolose matrices tablets at different time are listed in Table I. In the earlier stage, the significant burst effect was observed in the Metolose 15000 and Metolose 30000 of tablets. The least burst effect was obtained from the Metolose 4000 tablet. This result might be due to the gel formed from low viscosity Metolose, which easily spreads over the surface of a matrices tablet to reduce excess dissolution of the drug in the earlier stage. In the later stage, as expected, the slower drug released from higher viscosity Metolose was observed. This can be attributed to the stronger hydrogel strength structure formed from the higher viscosity polymer.[24] To diminish the burst effect of formulation, the low-viscosity polymer (Metolose 4000) was selected as the retardant thereafter. The effect of varying the drug/Metolose 4000 ratio on the drug release was evaluated. As expected, the drug release rate decreased with an increase in the tablet content of Metolose (Fig. 1). These results could be attributed to an increase in thickness of gel layer resulting in the reduction of drug release. According to the USP 23[21] monograph for propranolol extended release dosage form, the percentage of drug release at 1.5, 4, 8, 14, and 24 h were not more than 30, 35–60, 55–80, 70–95, and 81–110%, respectively. It could be seen that the dissolution profiles of drug/Metolose 1/1 and 1/2 of matrices tablets almost met the demand of USP. Despite considerable comparison of the release patterns, the formulation with a drug/Metolose ratio of 1/1 had a slight burst effect and the release percentages at 8 and 14 h were on the brink of the upper limit. In the drug/Metolose 1/2 tablet, there was no burst effect in the earlier stage but the release percentage in the later stage was on the edge of the lower limit. Therefore, the optimal formulation can possibly be obtained while the drug/Metolose ratio is within 1/1 to 1/2. To obtain the optimal formulation that had the least burst effect, most of the drug was released after 24 h, and insufficient drug absorption from controlled release products in the *in vivo* study was avoided because of suppression of drug release[8–11]; the different amounts of avicel were incorporated into the matrices tablet, of which the drug/Metolose ratio was 1/2. Figure 2 obviously showed that the drug release rate was increased as the tablet content of avicel increased. Comparing these dissolution profiles with USP monograph specifications, the release curve of formulation with 17% avicel was most suitable; there was no burst effect in the earlier stage (the release percentage at 1.5 h was 26.6%), and almost total drug was released from matrices tablet after 24 h (97.4%). The release mechanism of propranolol from Metolose matrices tablet was evaluated on the basis of a simple exponential model.[22] The correlation coefficiencies, release rate constant (k), and exponent constant (n) were 0.9918 ($P < 0.01$), 21.9, and 0.51, respectively. It showed that the mechanism of drug release from HMPC matrices tablet was a quasi-Fickian diffusion.

TABLE II
The Similarity Factor (f_2) Test for Comparing the Dissolution Profiles

Time (h)	Metolose 4000	Methocel K4MP	f_2	Wet-massed granule	Direct compression	f_2
1.5	25.84	25.65	100	25.84	22.78	78
4.0	44.01	49.41	79	44.01	40.63	71
8.0	67.46	73.38	70	67.46	61.77	68
14.0	86.51	90.17	68	86.51	79.51	65
24.0	98.91	98.86	70	98.91	92.31	63

The influence of magnesium stearate on drug release rate was shown in Figure 3. These dissolution patterns were similar and indicated that the level of lubricant from 0.5 to 2% did not significantly modify the release rate. In general, increases in compaction pressure may alter the tortuosity or porosity of a tablet, resulting in a variation of the release rate of drug.[24–25] As shown in Figure 4, variation of compaction pressure from 100 to 200 kPa did not cause a noticeable change in the dissolution profiles. Two brands of HPMC, Metolose 4000 (viscosity 4000; Shin Etsu) and Methocel K4MP (viscosity 4000; Dow Chemical Co.), were used to prepare the propranolol matrices tablets. Both dissolution profiles were compared by using the FDA[23] recommended similarity factor (f_2). The results of the comparison are shown in Table II. The values of f_2 were higher than the criteria value (50), indicating that the equal viscosity of HPMC can produce similar dissolution profiles. The effect of preparation process, tabletted from wet-massed granule or by direct compression, was also studied. As shown in Table II, the values of f_2 of both dissolution profiles were higher than 50, indicating that the propranolol HPMC matrices tablet can be manufactured from wet-massed granule or by direct compression.

The above results showed that the drug/polymer ratio and avicel content were the main influencing factors on the drug release from matrices tablets. The optimal propranolol extended release formulation could be obtained by using HPMC as retardant. The mechanism of drug release form HMPC matrices tablet followed quasi-Fickian diffusion.

References

1. Rekhi, S. G.; Porter, S. C.; Jambhekar, S. S. Drug Dev Ind Pharm 1995, 221, 709.
2. Taylan, B.; Capan, Y.; Guven, O.; Kes, S.; Hincal, A. J Controlled Release 1996, 38, 11.
3. Eddington, N. D.; Ashraf, M.; Augsburger, L. L.; Leslie, J. L.; Fossler, M. J.; Lesko, L. J.; Shah, V. P.; Rekhi, G. S. Pharm Dev Tech 1998, 3, 535.
4. Gao, P.; Meury, R. H. J Pharm Sci 1996, 85, 725.
5. Gohel, M. C.; Amin, A. F. J Controlled Release 1998, 51, 115.
6. Huang, Y. B.; Tsai, Y. H.; Yang, W. C. Y. H.; Chang, J. S.; Wu, P. C. Eur J Pharm Biopharm, to appear.
7. Huang, Y. B.; Tsai, Y. H.; Yang, W. C. Y. H.; Chang, J. S.; Wu, P. C. Biol Pharm Bull to appear.
8. Cressman, W. A.; Summer, D. J Pharm Sci 1971, 60, 132.
9. Uchida, T.; Kawata, M.; Goto, S. J Pharmacobio-Dyn 1986, 9, 631.
10. Katori, N.; Okudaria, K.; Aoyagi, N.; Takeda, Y.; Uchiyama, M. J Pharmacobio-Dyn 1991, 14, 567.
11. Ford, J. L.; Rubinstein, M., II; IIogan, J. E. Int J Pharm 1985, 24, 339.
12. Feely, L. C.; Davis, S. S. Int J Pharm 1988, 41, 83.
13. Efentakis, M.; Al-Hmound, H.; Choulis, N. N. Acta Pharm Technol 1990, 36, 237.
14. Vlachou, M.; Hani, N.; Efentakis, M.; Tarantili, P. A.; Andreopoulos, A. G. J Biomater Appl 2000, 15, 65.
15. Nokhodchi, A.; Norouzi-Sani, S.; Siahi-Shadbad, M. R.; Lotfipoor, F.; Saeedi, M. Eur J Pharm Sci 2002, 54, 349.
16. Sako, K.; Sawada, T.; Nakashima, H.; Yokohama, S.; Sonobe, T. J Controlled Release 2002, 81, 165.
17. Gonza'lez, I. M.; Robles, L. V. Int J Pharm 2003, 251, 183.
18. Knan, G. M.; Zhu, J. B. J Controlled Release 1999, 57, 197.
19. Li, J. Z.; Rekhi, G. S.; Augsburger, L. L.; Shangraw, R. F. Pharm Dev Tech 1996, 1, 343.
20. Nazzal, S.; Nutan, M.; Palamakula, A.; Shah, R.; Zaghloul, A. A.; Khan, M. A. Int J Pharm 2002, 240, 103.
21. USP XXIII. United States Pharmacopeial Convention, Inc., Rockville, MD, 1995; p. 1328.
22. Ritger, P. L.; Peppas, N. S. J Controlled Release 1987, 5, 37.
23. United States Food and Drug Administration (FDA). Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, Rockville, MD, August 1997; http://www.fda.gov/oder/guidance.htm.
24. Zuleger, S.; Lippold, B. C. Int J Pharm 2001, 217, 139.
25. Garzon, M. L.; Villafuerte, L. Int J Pharm 2002, 231, 33.