Department of Pharmacy, Zhejiang University City College, Hangzhou, P.R. China

Relationships between the release of soluble drugs from HPMC matrices and the physicochemical properties of drugs

X. C. Fu, W. Q. Liang, X. W. Ma

Received October 1, 2002, accepted October 12, 2002

Prof. Xuchun Fu, Department of Pharmacy, Zhejiang University City College, Hangzhou 310015, P.R. China
fuxuchun@mail.hz.zj.cn

Pharmazie 58: 221–222 (2003)

Hydroxypropyl methylcellulose (HPMC) is a semisynthetic ether derivative of cellulose. It has been the dominant hydrophilic vehicle used in controlled release dosage forms because of its non-toxic nature, ease of compression, and accommodation to high levels of drug loading. It is desirable to predict the drug release from HPMC matrices with sufficient accuracy in the design of drug-containing HPMC matrices.

Some studies have been reported to investigate the relationships between drug release rate and HPMC concentration or the size and shape of HPMC matrices [1–6]. However, these prediction models must be established for each drug. In this paper, relationships between the release of soluble drugs from HPMC matrices and the physicochemical properties of drugs were investigated whereby ranitidine hydrochloride, diltiazem hydrochloride, isoniazid, and ribavirin were selected as model drugs.

The volumes of drug molecules (V, nm^3) were calculated from the molecular geometries optimized using the semi-empirical self-consistent field molecular orbital calculation AM1 method [7]. The atomic radii used to calculate molecular volumes were those used by Clark [8]. The molecular volumes of ranitidine, diltiazem, isoniazid, and ribavirin are 0.3876 nm^3, 0.4996 nm^3, 0.1569 nm^3, and 0.2529 nm^3, respectively.

The following regression equations were obtained using stepwise multiple regression analysis for the fractions of these drugs released from HPMC matrices shown in the Table.

When HPMC concentration was 11% (w/w),

$$\log (M_t/M_\infty) = -0.3251 + 0.5164 \log t - 0.2258\ V$$

$$n = 21 \quad r = 0.9848 \quad s = 0.03377 \quad F = 288.8 \qquad (1)$$

$$\log (M_t/M_\infty) = -0.3249 + 0.5165 \log t + 2.297 \times 10^{-5}\ C_s - 0.2304\ V$$

$$n = 21 \quad r = 0.9848 \quad s = 0.03474 \quad F = 182.0 \qquad (2)$$

When HPMC concentration was 33%,

$$\log (M_t/M_\infty) = -0.3832 + 0.4973 \log t - 0.3047\ V$$

$$n = 25 \quad r = 0.9884 \quad s = 0.02822 \quad F = 464.5 \qquad (3)$$

$$\log (M_t/M_\infty) = -0.3805 + 0.4982 \log t + 2.036 \times 10^{-4}\ C_s - 0.3512\ V$$

$$n = 25 \quad r = 0.9892 \quad s = 0.02780 \quad F = 319.4 \qquad (4)$$

Table: Fractions (%) of drugs released from HPMC matrices

t (h)	Ranitidine hydrochloride		Diltiazem hydrochloride		Isoniazid		Ribavirin	
	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.
HPMC concentration 11% (eq. 1)								
0.5	26.24	27.04	22.40	25.51	31.56	30.48	30.40	29.00
1	36.84	38.67	33.63	36.48	45.65	43.60	45.62	41.48
2	56.40	55.31	52.63	52.19	63.52	62.36	65.14	59.33
3	70.66	68.20	71.43	64.34	74.03	76.89	70.85	73.15
4	81.74	79.12	82.80	74.65	86.18	89.20	75.46	84.86
5	ND	–	ND	–	ND	–	83.74	95.23
HPMC concentration is 33% (eq. 3)								
0.5	22.13	22.34	ND	–	26.30	26.26	26.97	24.55
1	31.75	31.53	24.15	29.15	39.37	37.07	35.42	34.65
2	41.63	44.51	39.73	41.14	54.10	52.32	48.59	48.92
3	58.75	54.45	51.74	50.33	63.99	64.01	57.07	59.84
4	67.27	62.82	60.67	58.07	71.03	73.86	66.44	69.05
5	73.15	70.19	ND	–	79.74	82.53	73.94	77.15
6	80.78	76.86	76.14	71.05	ND	–	77.59	84.47
HPMC concentration is 55% (eq. 6)								
0.5	21.57	20.49	ND	–	22.30	20.71	18.73	19.05
1	30.56	29.37	20.99	23.94	31.74	29.70	26.51	27.32
2	41.13	42.11	33.85	34.32	45.25	42.57	36.18	39.16
3	51.04	51.99	42.81	42.37	51.76	52.56	44.66	48.35
4	59.68	60.37	51.44	49.21	59.09	61.03	53.12	56.14
5	ND	–	ND	–	68.53	68.54	63.16	63.05
6	72.88	74.53	65.99	60.75	75.69	75.35	70.71	69.31
7	ND	–	ND	–	ND	–	77.76	75.09
8	82.27	86.55	77.09	70.55	ND	–	ND	–

ND: Not determined

When HPMC concentration was 55%,

$$\log (M_t/M_\infty) = -0.4952 + 0.5137 \log t - 0.1940 V$$
$$n = 28 \quad r = 0.9840 \quad s = 0.03592 \quad F = 382.2 \qquad (5)$$

$$\log (M_t/M_\infty) = -0.4878 + 0.5197 \log t + 7.415 \times 10^{-4} C_s - 0.3543 V$$
$$n = 28 \quad r = 0.9929 \quad s = 0.02443 \quad F = 560.9 \qquad (6)$$

In above equations, M_t is the amount of drug released at time t, M_∞ is the amount of drug released over a very long time, which corresponds in principle to the initial loading, t is the release time (h), C_s is drug solubility in distilled water at 37 °C (g/100 ml), V is the molecular volume of the drug (nm^3), n is the number of samples, r is the correlation coefficient, s is the standard deviation, F is the F-statistic.

Above equations show that the coefficients of their log t terms were very close to 0.5, meaning that diffusion was the predominant release mechanism in the release systems studied in this paper [9]. This was consistent with the conclusions reported by other researchers that water-soluble drugs were released primarily by diffusion of dissolved drug molecules across the HPMC gel layer [10–14].

Ritger and Peppas derived an equation for the Fickian release of soluble drugs from moderately swelling slabs [9], shown as eq. (7):

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi l^2}\right)^{1/2} \qquad (7)$$

Here, D is the drug diffusion coefficient, l is the initial slab thickness.

Eq. (7) indicates that the Fickian release of soluble drug was independent of its solubility in water. As shown in eqs. (1)–(6) the drug solubility parameter could not improve the statistical significance of the regression equations when HPMC concentration was less 33% and drug solubility displayed a week dependence on its release from HPMC when HPMC concentration was 55%.

According to the free volume theory [15], the diffusion coefficients of the diffusing molecules were exponentially dependent on their molecular volumes and smaller molecules had higher diffusion coefficients. As expected, the exponential dependence of drug diffusion coefficient on its molecular volume could be derived from eqs. (1)–(6) and eq. (7).

Experimental

1. Materials

Ranitidine hydrochloride, diltiazem hydrochloride, isoniazid, and ribavirin were selected as model drugs, due to their range of desirable solubilities in water. Ranitidine hydrochloride, diltiazem hydrochloride, isoniazid, and ribavirin have the solubilities of 125.5 g/100 ml, 59.25 g/100 ml, 21.67 g/100 ml, and 18.62 g/100 ml in distilled water at 37 °C, respectively.

2. Tablet preparation

Drug, HPMC (Methocel K4M), and dextrin were mixed and moistened with a 75% alcohol. The wet mass was forced through a 16 mesh sieve. The granules were dried at 60 °C until a constant weight was achieved, and then calibrated through the same sieve. Magnesium stearate was added to the dry granules. The final mixture was compressed by a single punch press. The obtained tablet was 11 mm in diameter and 2.7 mm in thickness. Total tablet mass was 300 mg containing 33% of drug, 1% of magnesium stearate, 66% of HPMC and dextrin. HPMC concentrations were varied by changing the relative amounts of HPMC and dextrin, in order to keep the matrix weight and surface area constant.

3. Drug release

All drug release experiments were carried out using a dissolution apparatus (rotating basket), rotating at 100 rpm in 1000 ml distilled water maintained at 37 °C. At predetermined time intervals, 5 ml samples (which were replaced with fresh medium) were withdrawn and the amount of drug released was determined spectrophotometrically at 314 nm for ranitidine hydrochloride, 235 nm for diltiazem hydrochloride, 263 nm for isoniazid, and 206 nm for ribavirin, respectively.

Reference

1 Ford, J. L.; Rubinstein, M. H.; Hogan, J. E.: Int. J. Pharm. **24**, 327 (1985)
2 Shah, N.; Zhang, G.; Apelian, V.; Zeng, F.; Infeld, M. H.; Malick, A. W.: Pharm. Res. **10**, 1693 (1993)
3 Gao, P.; Nixon, P. R.; Skoug, J. W.: Pharm. Res. **12**, 965 (1995)
4 Siepmann, J.; Podual, K.; Sriwongjanya, M.; Peppas, N. A.; Bodmeier, R.: J. Pharm. Sci. **88**, 65 (1999)
5 Siepmann, J.; Kranz, H.; Bodmeier, R.; Peppas, N. A.: Pharm. Res. **16**, 1748 (1999)
6 Siepmann, J.; Kranz, H.; Peppas, N. A.; Bodmeier, R.: Int. J. Pharm. **201**, 151 (2000)
7 Dewar, M. J. S.; Zoebisch, G. E.; Healy, E. F.; Stewart, J. J. P.: J. Am. Chem. Soc. **107**, 3902 (1985)
8 Clark, D. E.: J. Pharm. Sci. **88**, 807 (1999)
9 Ritger, P. L.; Peppas, N. A.: J. Controlled Rel. **5**, 37 (1987)
10 Skoug, J. W.; Borin, M. T.; Fleishaker, J. C.; Cooper, A. M.: Pharm. Res. **8**, 1482 (1991)
11 Skoug, J. W.; Mikelsons, M. V.; Vigneron, C. N.; Stemm, N. L.: **27**, 227 (1993)
12 Pham, A. T.; Lee, P. I.: Pharm. Res. **11**, 1379 (1994)
13 Colombo, P.; Bettini, R.; Massimo G.; Catellani, P. L.; Santi, P.; Peppas, N. A.: J. Pharm. Sci. **84**, 991 (1995)
14 Katzhendler, I.; Mader, K.; Friedman, M.: Int. J. Pharm. **200**, 161 (2000)
15 Cohen, M. H.; Turbull, D.: J. Chem. Phys. **31**, 1164 (1959)