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Influence of drug solubility on the release of slightly water-soluble drugs from HPMC matrices

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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 has been reported that the drug release rate from HPMC matrices is more or less relevant to various formulation variables such as drug loading, drug : polymer ratio, HPMC viscosity grade, compression pressure, and so on [1–7]. However, these prediction models must be established for each drug. We have reported the relationships between the release of water-soluble drugs from HPMC matrices and their physicochemical properties [8]. In this paper, the influence of drug solubility on the release of slightly water-soluble drugs from HPMC matrices was investigated when theophyline, tinidazole, propylthiouracil, and sulfamethoxazole were selected as model drugs.

The volumes of drug molecules (V, nm^3) were calculated from the molecular geometries optimized using the semiempirical self-consistent field molecular orbital calculation AM1 method [9]. The atomic radii used to calculate molecular volumes were those used by Clark [10]. The molecular volumes of theophyline, tinidazole, propylthiouracil, and sulfamethoxazole are 0.1981 nm^3, 0.2759 nm^3, 0.2023 nm^3, and 0.2668 nm^3, respectively.

The following regression equations were obtained from stepwise multiple regression analysis for the fractions of these drugs released from HPMC matrices shown in Tables 1–3 when regression variables were release time, HPMC concentration, and molecular volume.

When HPMC concentration was 16.5% (w/w),

$$\log (M_t/M_\infty) = -1.087 + 1.058 \log t - 0.2237 (\log t)\, C_s + 0.2488 C_s \quad (1)$$

$$n = 31 \quad r = 0.9983 \quad s = 0.02288 \quad F = 2759$$

When HPMC concentration was 33%,

$$\log (M_t/M_\infty) = -1.346 + 1.057 \log t - 0.2574 (\log t)\, C_s + 0.3647 C_s \quad (2)$$

$$n = 34 \quad r = 0.9954 \quad s = 0.03325 \quad F = 1082$$

When HPMC concentration was 55%,

$$\log (M_t/M_\infty) = -1.574 + 1.051 \log t - 0.2337 (\log t)\, C_s + 0.4245 C_s \quad (3)$$

$$n = 33 \quad r = 0.9985 \quad s = 0.01830 \quad F = 3130$$

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), Cs is drug solubility in distilled water at 37 °C (g/100 ml), n is the number of samples, r is the correlation coefficient, s is the standard deviation, F is the F-statistic.

Above equations showed strong statistical significance. The $\log (M_t/M_\infty)$ values of these slightly water-soluble drugs were well correlated with their solubilities in water. Eqs. (1)–(3) were different from the regression equations obtained for water-soluble drugs, in which the $\log (M_t/M_\infty)$ value was independent of drug solubility when HPMC concentration was not more than 33% [8]. As there was no molecular volume term in above equations, the size of the drug molecule seemed to have little effect on the release rate of slightly water-soluble drugs.

Eqs. (4)–(6) can be derived from eqs. (1)–(3).

When HPMC concentration was 16.5% (w/w),

$$M_t/M_\infty = \exp (-2.503 + 0.5729\, C_s)\, t^{1.058 - 0.2237 Cs} \quad (4)$$

When HPMC concentration was 33%,

$$M_t/M_\infty = \exp (-3.099 + 0.8398\, C_s)\, t^{1.057 - 0.2574 Cs} \quad (5)$$

When HPMC concentration was 55%,

$$M_t/M_\infty = \exp (-3.624 + 0.9774\, C_s)\, t^{1.051 - 0.2337 Cs} \quad (6)$$

Compared with the well-known power equation [11]:

$$M_t/M_\infty = kt^n \quad (7)$$

In eq. (7), k is a kinetic constant, and n is the diffusional exponent indicative of the release mechanism.

Table 1: Fractions (%) of drugs released from HPMC matrices when HPMC concentration is 16.5%

t(h)	Theophyline		Tinidazole		Propylthiouracil		Sulfamethoxazole	
	Exp.	Calc.*	Exp.	Calc.*	Exp.	Calc.*	Exp.	Calc.*
0.5	12.12	13.04	9.47	8.93	5.19	4.79	4.64	4.53
1	21.39	21.04	16.52	15.62	9.51	9.56	7.90	9.16
2	33.11	33.94	28.47	27.31	18.33	19.10	17.84	18.50
3	42.86	44.89	40.47	37.87	29.35	28.62	27.10	27.91
4	51.74	54.74	50.21	47.75	38.91	38.13	35.16	37.38
5	61.93	63.85	59.32	57.16	ND	–	ND	–
6	69.70	72.41	68.23	66.21	56.15	57.14	60.21	56.40
7	83.28	80.53	75.47	74.97	ND	–	ND	–
8	ND	–	82.73	83.49	75.74	76.14	76.49	75.52
10	ND	–	ND	–	ND	–	ND	–
12	ND	–	ND	–	ND	–	ND	–

ND: not determined; * from eq. (1)

Table 2: Fractions (%) of drugs released from HPMC matrices when HPMC concentration is 33%

t(h)	Theophyline		Tinidazole		Propylthiouracil		Sulfamethoxazole	
	Exp.	Calc.*	Exp.	Calc.*	Exp.	Calc.*	Exp.	Calc.*
0.5	11.23	11.58	7.15	6.82	ND	–	ND	–
1	18.00	17.96	11.45	11.61	6.71	5.66	4.18	5.30
2	27.16	27.86	19.69	19.75	12.18	11.21	9.78	10.66
3	33.96	36.01	29.83	26.96	17.15	16.73	16.71	16.04
4	40.68	43.21	36.53	33.62	21.41	22.23	23.18	21.43
5	ND	–	43.03	39.89	ND	–	ND	–
6	51.67	55.86	49.58	45.88	30.54	33.18	30.44	32.24
7	ND	–	53.32	51.64	ND	–	ND	–
8	63.92	67.03	59.71	57.21	43.33	44.08	42.12	43.07
10	77.35	77.20	67.59	67.89	54.38	54.95	51.51	53.93
12	ND	–	ND	–	67.77	65.79	65.93	64.80

ND: not determined; * from eq. (2)

Table 3: Fractions (%) of drugs released from HPMC matrices when HPMC concentration is 55%

t(h)	Theophyline		Tinidazole		Propylthiouracil		Sulfamethoxazole	
	Exp.	Calc.*	Exp.	Calc.*	Exp.	Calc.*	Exp.	Calc.*
0.5	8.53	8.40	4.96	4.64	ND	–	ND	–
1	13.20	13.33	7.74	8.02	ND	–	ND	–
2	20.16	21.15	14.10	13.84	7.32	6.89	5.88	6.47
3	27.82	27.71	19.95	19.05	9.62	10.28	10.12	9.73
4	33.13	33.57	23.67	23.90	13.70	13.66	13.67	12.99
5	ND	–	27.58	28.49	ND	–	ND	–
6	41.77	43.98	31.24	32.89	20.29	20.39	19.76	19.54
8	53.13	53.27	40.95	41.26	26.42	27.09	25.61	26.09
10	62.06	61.81	51.89	49.19	32.72	33.77	33.54	32.66
12	72.19	69.80	60.52	56.78	39.46	40.43	40.59	39.23

ND: not determined; * from eq. (3)

As shown in eqs. (4)–(6), the solubility of slightly water-soluble drug not only affected the diffusional exponent but also the kinetic constant in eq. (7). When drug solubility decreased, the kinetic constant decreased but the diffusional exponent increased.

Experimental

1. Materials

Theophyline, tinidazole, propylthiouracil, and sulfamethoxazole were selected as model drugs, due to their range of desirable solubilities in water. Theophyline, tinidazole, propylthiouracil, and sulfamethoxazole have the solubilities of 1.646 g/100 mL, 1.126 g/100 mL, 0.2699 g/100 mL, and 0.1938 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 272 nm for theophyline, 317 nm for tinidazole, and 274 nm for propylthiouracil, and 266 nm for sulfamethoxazole.

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