International Journal of Pharmaceutics 414 (2011) 125–130

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Hildebrand solubility parameter to predict drug release from hydroxypropyl methylcellulose gels

P. Bustamante*, J. Navarro-Lupión, M.A. Peña, B. Escalera

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Alcalá, Alcalá de Henares, E-28871 Madrid, Spain

ARTICLE INFO

Article history:
Received 17 February 2011
Received in revised form 26 April 2011
Accepted 2 May 2011
Available online 19 May 2011

Keywords:
Solubility parameters
Drug release
Hydroxypropyl methylcellulose
Caffeine
Theophylline
Paracetamol
Salicylic acid
Naproxen
Diclofenac

ABSTRACT

An equation including the Hildebrand solubility parameter δ of the drugs is used for the first time to model drug release from hydroxypropyl methylcellulose (HPMC) gels: $\ln M = -21.578 + 2.102\delta - 0.037\delta^2 + 0.48 \ln t + 1.028 \ln C_i$ ($r^2 = 0.94$ for a total of 286 cases). The experimentally determined release data of six drugs having different polarity (caffeine, theophylline, paracetamol, salicylic acid, naproxen and diclofenac) at several initial concentrations C_i were included in the equation. In general, the amount of drug delivered is linear at the first 5–6 h of the release profiles and the zero order constants K_0 increase as the solubility parameter of the drugs become larger. The Peppas exponential law $M/M_\infty = Kt^n$ is applicable to larger fractional release, until 67–87% (48–51 h) for the less polar drugs (diclofenac and naproxen, lower δ values) and more than 80% (26–28 h) for the more polar drugs (higher δ values, theophylline, salicylic acid, caffeine and paracetamol). The Peppas release rate ($\ln K$) shows a parabolic relationship with the drug solubility parameter. The diffusional exponent n varies between 0.40 and 0.58 indicating that drug release is mainly controlled by diffusion. An extended form of the Peppas equation is also tested for each drug including all the initial concentrations: $\ln M = a + b \ln t + c \ln C_i$ ($r^2 = 0.88$–0.94). The logarithm of the octanol–water partition coefficients can also be used in combination with the drug concentrations.

1. Introduction

Hydroxypropylmethylcellulose (HPMC) is widely employed for controlled delivery due to its low toxicity and compatibility with many drugs. The influence of a number of physicochemical and technological factors on drug release from HPMC matrix tablets has been studied (Roberts et al., 2007). The release is faster as the HPMC molecular weight decreases for the lower viscosity grades (Kim and Fassihi, 1997a,b) whereas little differences are observed among the largest viscosity grades (Kurahashi et al., 1996). Drug delivery also depends on the loading dose and drug solubility (Kurahashi et al., 1996; Xu and Sunada, 1995). Large concentrations of highly soluble drugs show increased release rates from HPMC matrices (Kim and Fassihi, 1997a). However, the diffusion coefficient of oxprenolol hydrochloride (water soluble) is lower than that of theophylline (less water-soluble), a fact that was attributed to drug–polymer interactions (Bettini et al., 1995). Drug delivery from hydrophilic matrices is accomplished via swelling, dissolution and/or erosion and the release kinetics may be Fickian or non-Fickian (Kim and Fassihi, 1997a). Swelling of HPMC is not influenced by variations of ionic strength and pH, due to the non-ionic nature of the polymer (Kim and Fassihi, 1997c). The relative importance of diffusion and macromolecular relaxation on the mechanism of drug release can be analyzed from the exponent value of the Peppas power law (Peppas et al., 2000):

$$\frac{M}{M_\infty} = Kt^n \quad (1)$$

M_∞ is the amount of drug delivered at infinite time, being equal to the initial loading M_0 if the total dose is released, and M is the amount of drug released at time t. The Peppas model is generally applied to the first 60% of the total amount of drug released ($M/M_\infty \leq 60\%$). K is a kinetic constant (t^{-n}) and the exponent n is related to the transport mechanism (Kim and Fassihi, 1997a; Pérez-Marcos et al., 1996). Water-soluble drugs as sodium naproxen are mainly released by diffusion whereas poorly water-soluble drugs as naproxen are delivered by polymer erosion (Katzhendler et al., 2000). The diffusional exponent n is lower for less soluble drugs (Kim and Fassihi, 1997b) but this is not a general rule (Fu et al., 2004). Loading dose and matrix composition may influence the release mechanism. Prednisolone follows Case II transport ($n > 0.95$) from pectin–HPMC matrices (Kim and Fassihi, 1997a). The n values range from 0.29 to 0.80 for indomethacin depending on HPMC–lactose ratio in the tablets. The kinetics changes from first order to nearly zero order at high HPMC contents (Xu and Sunada,

* Corresponding author. Tel.: +91 8854659; fax: +91 8854658.
E-mail address: pilar.bustamante@uah.es (P. Bustamante).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.05.011

1995). Fu et al. (2004) developed regression equations for HPMC matrix tablets using polymer concentration, aqueous solubility and molar volume of the drugs.

The studies on drug delivery from HPMC gels are less frequent than those related to matrix tablets (Mitchell et al., 1990; Shin et al., 2004; Sawant et al., 2010). Hydrogels have excellent potential for controlled delivery of low molecular weight drugs and proteins (Peppas et al., 2000) and the release mechanisms and design criteria have been reviewed (Lin and Metters, 2010). The aim of this work is to develop a model combining drug concentration and solubility parameters for drug release from HPMC hydrogels. Empirical models can help to predict drug release and to elucidate the mechanisms involved in the release process. The solubility parameter δ is the square root of the cohesive energy density and it is a measure of polarity (Barton, 1991) ant it forms a polarity scale ranging from about 14 to 48 $MPa^{1/2}$ from the least to the most polar compound. This parameter is widely used for solvent selection in polymer science and it has potential application to drug release. However the studies using δ in pharmaceutical and biological sciences are scarce (Bustamante and Sellés, 1986; Sloan et al., 1986; Jiang et al., 1998; Ghafourian et al., 2010). In pharmaceutical technology, the solubility parameter has been used for lipid selection in solid lipid nanoparticles (Jensen et al., 2010) and in formulation of microspheres (Matsumoto et al., 1997; Lee et al., 2002) and solid dispersions (Fini et al., 2011). Six drugs with different polarity have been chosen. The gels were loaded with concentrations below and above the aqueous solubility of the drugs. The solubility parameter of the drugs is tested for its correlation with the release constants obtained from a zero-order model (K_o) and the Peppas exponential model (K).

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC, Sigma, batch 105H0611), 28–30% methoxy and 7–12% hydropropoxy groups, 4000 cP average viscosity (2% aqueous solution), average molecular weight 86 kDa. The following drugs were purchased from Sigma–Aldrich®, St. Louis (USA): anhydrous caffeine (74H0886), theophylline (68H0610), paracetamol (123H0169), salicylic acid (26H3429), naproxen (12K3727). Diclofenac (967005) was purchased from Unique Pharmaceuticals Laboratories (India). The purity degree of the drugs was ≥99% (w/w). Deionized water (Milli-Q) was used for all experiments.

2.2. HPLC analysis

A Beckman Gold System, 116 or 126 pump, Genesis C-18 column (4 μm, 4.6 mm × 15 mm), 116 UV-V detector at variable wavelength and Gold System Software for data collection and storage was used. The mobile phases were mixtures of methanol (MeOH) and glacial acetic acid (Ac) or phosphate buffer aqueous solutions. The following concentrations, flow rates and UV wavelengths were used. Caffeine: 39:61 MeOH + Ac (1%), 1.5 ml/min, 272 nm. Theophylline: 50:50 MeOH + Ac (1%), 1.5 ml/min, 272 nm. Paracetamol: 35:65 MeOH + Ac (1.25%), 1 ml/min, 254 nm. Salicylic acid: 65:35 MeOH + Ac (1.7%), 1.2 ml/min, 303 nm. Naproxen: 80:20 MeOH + Ac (2%), 1.2 ml/min, 254 nm. Diclofenac: 75:25 MeOH + phosphate buffer (pH 2.5), 1.1 ml/min, 276 nm. Reference solutions were prepared for each drug to calibrate the system and to determine the volume to be injected to obtain a satisfactory response. 20 μl of the solutions were injected intercalating reference solutions. Drug concentrations were determined from peak areas and the coefficients of variation CV were less than 2%. The method was validated for each drug according to ICH/CPMP to determine the following parameters: specificity, linearity, accuracy, precision, robustness and stability after 24 h storage.

2.3. Solubility experiments

Since the solubility parameter of HPMC is near that of water (Bustamante et al., 2005), the aqueous solubility of the drugs was measured to estimate the concentrations needed to obtain saturated and non-saturated gels. A slight excess of drug was added to 50 ml of solvent in 100 ml flasks that were placed in a thermostat shaking bath (Heto SH 02/100) at 32 ± 0.2 °C until equilibrium solubility was reached. The time needed to reach equilibrium was tested for each drug by plotting the concentration dissolved against time. The samples were taken at the asymptotic region of the plots. The solid non-dissolved phases were separated by filtration through Durapore® membranes (0.2 μm pore size) and the clear solutions were assayed by HPLC. All the experiments were performed in triplicate and the coefficient of variation (CV = SD × 100/mean) was within 3% in all cases.

2.4. Preparation of the hydrogels

6% (w/w) HPMC was dispersed in hot water (70 °C) and then cooled under continuous agitation until formation of a homogeneous gel. Drug concentrations below and above their water solubility were dispersed or dissolved in a water volume as small as possible and incorporated during the preparation of the gel. The formulations were centrifuged (3000 rpm, 15 min) to eliminate air bubbles and they were allowed to stay for at least 24 h before the experiments. All the formulations were prepared by triplicate.

2.5. Release experiments

Three Franz type diffusion cells with a receptor volume of 10 ml of distilled water and a diffusional area of 1.98 cm^2 were used for each formulation. In the case of diclofenac and naproxen the volume employed was 70 ml to ensure sink conditions. Franz cells were placed on a multiple magnetic stirrer allowing continuous agitation to obtain the same conditions for each of the triplicate experiments. The temperature was kept at 32 °C using a thermostatic water pump which circulated water through each chamber jacket. Two grams of each formulation were placed into the donor compartment. The donor and receptor compartments were separated by a hydrophilic membrane Durapore® (0.45 μm pore size). The membrane only serves as a mechanical support allowing free diffusion of the drug from the gel to the receptor medium. The membranes did not interfere the HPLC assay. Drug recovery was ensured in previous experiments filtering and analyzing several drug concentration solutions. Samples (50-μl) were taken at time intervals previously determined (0.5–196 h) and the volume was replaced with fresh medium equilibrated at the experimental temperature. The CV among replicated experiments was less than 3% in most cases.

3. Results and discussion

3.1. Release behavior at several initial drug concentrations

Table 1 includes the experimental water solubility (S_w) and the initial drug concentration ranges C_i used. By visual inspection, the saturated gels appear turbid while the non-saturated gels are transparent. The cumulative amount M released as a function of time is shown in Fig. 1. Drug delivery initially shows steeper concentration gradients which are declining with time until an asymptotic region is reached. For most drugs the maximum

Table 1
Water solubility (S_w) and initial drug concentration ranges (C_i) for saturated (turbid) and non-saturated (transparent) gels.

Drug	S_w (mg/ml)	% C_i ranges	
		Transparent	Turbid
Naproxen	0.24	0.01–0.02	0.04
Diclofenac	0.28	0.01–0.03	0.035–0.05
Theophylline	8.4	0.5–1	2–5
Salicylic acid	3.5	0.10–0.20	0.25–0.35
Caffeine	25	0.5–1.5	2–2.5
Paracetamol	20.7	1–1.5	2–5

amount released M_∞ increases as the drug initial concentration C_i becomes larger. In swollen matrices this has been attributed to greater channel formation at higher drug loadings (Kim and Fassihi, 1997a). The exception is diclofenac where no appreciable differences are observed for the saturated gels containing the higher concentrations (C_i = 0.04–0.05% Fig. 1b). The gels do not deliver the total dose, a fact that can be related to hindered diffusion. The polymer chains are entangled with polar groups closely located and water molecules may simultaneously hydrogen bond with two or more polar groups becoming highly immobilized (Katzhendler et al., 2000). An average of 2.3 water molecules is bound on the HPMC K4M monomer unit (Baumgartner et al., 2002).

Fig. 2 compares the fraction of the initial dose (M/M_0) released from gels containing the lowest drug concentration required to achieve saturation. The initial drug concentrations C_i used are different (Table 1) due to the solubility differences of the drugs in water and in the polymer. The gels saturated with an excess of non-dissolved drug (a suspension) show the highest thermodynamic activity and facilitates comparison of the release behavior among drugs. The maximum per cent of release fraction varies between 30 and 90% and it increases with the water solubility of the drug (Table 1 and Fig. 2). The release behavior can be also related to drug polarity using two indexes, the solubility parameter δ and the octanol–water partition coefficient log P (Table 2). The more lipophilic drugs (corresponding to smaller δ values or larger log P values) release lower amounts of drug at the asymptotic region of the curve (30–42% of the initial dose for diclofenac and naproxen, Fig. 2). Conversely, the most hydrophilic drugs with larger solubility parameter values display the highest per cent released (77–88% of the initial dose for caffeine and salicylic acid, Fig. 2).

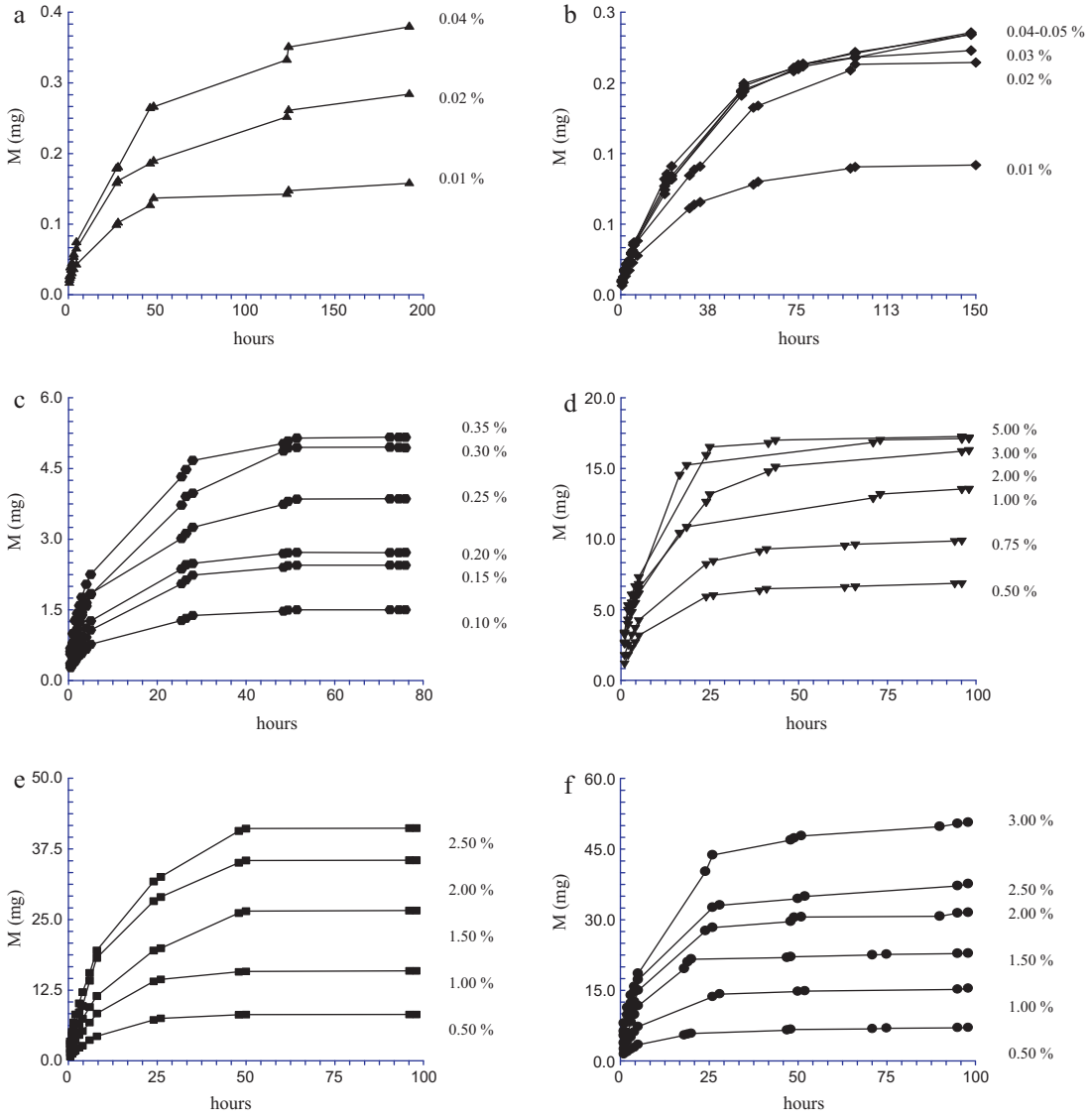

Fig. 1. Cumulative amount (mg) released at several per cent drug initial concentrations. Key: (a) naproxen; (b) diclofenac; (c) salicylic acid; (d) theophylline; (e) caffeine; (f) paracetamol.

Table 2
Polarity parameters (δ and log P), molar volume of the drugs (V), rate constant (K_o) and fractional release (% M/M_∞) according to zero-order kinetics for saturated gels.

Drug	δ (MPa$^{1/2}$)	Log P	V (cm^3/mol)	K_o (μg h^{-1})	M/M_∞ (%) (5–6 h)
Naproxen	23.4	3.34	178.3	13.2	9
Diclofenac	24.7	4.32	182.9	87	6
Theophylline	25.3	−0.02	114.6	725	17
Salicylic acid	25.6	2.19	90.9	266	37
Caffeine	26.8	−0.06	134.6	1952	46
Paracetamol	27.8	0.49	105.4	2217	37

Table 3
Total amount (M) and fraction (% M/M_∞) of drug released according to Eq. (1) from several initial drug concentrations C_i and diffusional exponent (n).

C_i (%)	Naproxen (t = 48 h)			Diclofenac (t = 51 h)		
	M (mg)	M/M_∞ (%)	n	M (mg)	M/M_∞ (%)	n
0.01	0.14	87	0.45	0.08	72	0.55
0.02	0.19	67	0.45	0.11	55	0.57
0.03	–	–	–	0.18	47	0.59
0.035[a]	–	–	–	0.18	44	0.58
0.04[a]	0.27	70	0.56	0.18	45	0.58
0.05[a]	–	–	–	0.18	49	0.58

[a] Saturated gels.

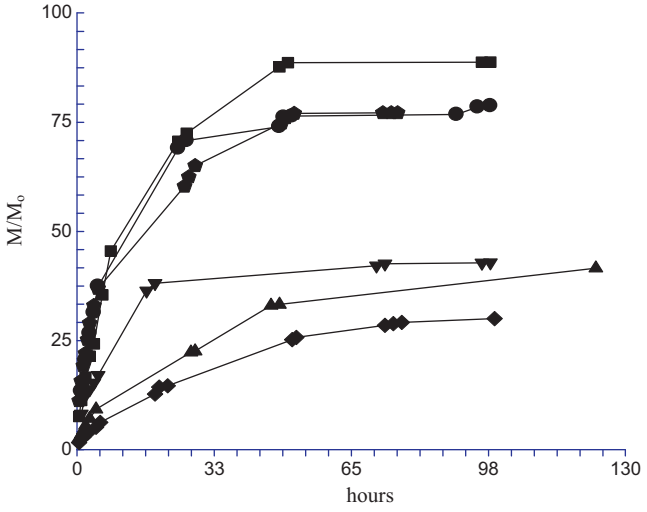

Fig. 2. Release fraction (M/M_o) from saturated gels. Key: (▲) naproxen; (♦) diclofenac; (⬟) salicylic acid; (▼) theophylline; (■) caffeine; (●) paracetamol.

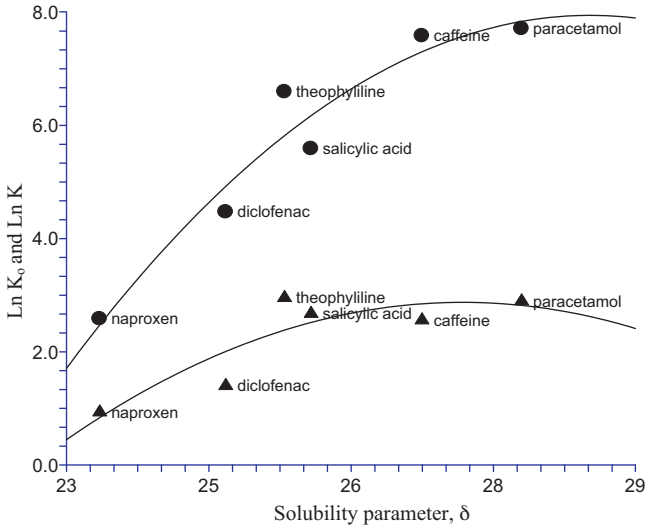

Fig. 3. Relationship between the zero order and Peppas release rate constants and the drug solubility parameters. Key: (●) ln K_o; (▲) ln K.

3.2. Zero order release

The amount of drug delivered over time is linear only at the initial part of the release profiles (until 5–6 h). The maximum release fraction M/M_∞ according to a zero order process varies between 6 and 46% (Table 2). The values of the apparent zero order constants K_o (μg/h) increase with the drug initial concentration and tend to level off for the saturated gels. In the saturated gels K_o also increases as the solubility parameter δ becomes larger (Table 2). The release rate of salicylic acid is smaller than expected from its solubility parameter value. This drug may self-associate through hydrogen bonding, decreasing its actual solubility parameter to a value of about 20 MPa$^{1/2}$ (Sloan et al., 1986). The trend is similar when the partition coefficient is used as a measure of polarity; K_o tends to increase for the most hydrophilic molecules (lower log P values). There is not a clear relationship between the zero-order release rates and the molar volume of the drug, in particular if salicylic acid is considered (Table 2). The molar volumes of the drugs were obtained from the Fedors group contribution method (Barton, 1991). Fig. 3 shows that the relationship between δ and ln K_o tends to be parabolic, as suggested from regular solution theory. Parabolic relationships with the solubility parameter have also been found for the permeability coefficients of drugs through the skin (Sloan et al., 1986) and protein binding (Bustamante and Sellés, 1986).

3.3. Peppas exponential model

Eq. (1) is tested for each drug initial concentration C_i. Since not all the loaded dose is released, the maximum amount delivered

Table 4
Total amount (M) and fraction (% M/M_∞) of drug released according to Eq. (1) from several initial drug concentrations C_i and diffusional exponent (n).

C_i (%)	Salicylic acid (t = 28 h)		
	M (mg)	M/M_∞ (%)	n
0.10	1.38	92	0.40
0.15	2.24	91	0.46
0.20	2.49	92	0.45
0.25[a]	3.25	84	0.52
0.30[a]	3.98	80	0.47
0.35[a]	4.67	90	0.46

[a] Saturated gels.

Table 5
Total amount (M) and fraction (% M/M_∞) of drug released according to Eq. (1) from several initial drug concentrations C_i and diffusional exponent (n).

C_i (%)	Theophylline (t = 26 h)			Caffeine (t = 26 h)			Paracetamol (t = 28 h)		
	M (mg)	M/M_∞ (%)	N	M (mg)	M/M_∞ (%)	n	M (mg)	M/M_∞ (%)	n
0.5	6.0	86	0.48	7.5	93	0.58	–	–	–
0.75	8.5	86	0.47	–	–	–	–	–	–
1	10.8	80	0.48	14.4	96	0.58	5.8	83	0.47
1.5	–	–	–	19.9	77	0.57	14.2	92	0.49
2[a]	15.2	89	0.53	29.0	83	0.59	21.6	95	0.55
2.5[a]	–	–	–	32.5	81	0.58	28.3	90	0.50
3[a]	16.5	82	0.48	–	–	–	33.1	88	0.48
5[a]	13.2	81	0.47	–	–	–	43.1	86	0.52

[a] Saturated gels.

Table 6
Coefficients of Eq. (2), number of cases N and initial drug concentration ranges C_i included in the analysis.

Drug	a	b	c	r^2	N	C_i ranges[a]
Naproxen	4.6525	0.49	0.333	0.97	30	0.01–0.05
Diclofenac	3.8086	0.58	0.295	0.99	54	
Theophylline	7.6818	0.48	0.356	0.88	42	0.50–5.00
Salicylic acid	7.8413	0.44	0.875	0.99	66	0.10–0.35
Caffeine	7.7486	0.58	0.933	0.99	50	0.50–5.00
Paracetamol	7.4568	0.50	1.139	0.94	44	

[a] The detailed initial concentrations are given in Tables 3–5.

M_∞ corresponds to the asymptotic region of the curves (Fig. 1). For the compounds studied here, Eq. (1) is applicable to release fractions larger than 60%. For the least polar drugs a fraction until M/M_∞ = 67–87% (naproxen) and 44–72% (diclofenac) is released in 48–51 h according with the power law (Table 3). For the most polar drugs (theophylline, salicylic acid, caffeine and paracetamol) more than 80% is released according to the Eq. (1) in a shorter time, 26–28 h (Tables 4 and 5). Fu et al. (2004) found that the Peppas equation was valid for delivered fractions above 60% for several drugs in HPMC tablets.

The diffusional exponents of the drugs n vary between 0.40 and 0.58 (Tables 3–5). The values for diclofenac (n = 0.55–0.59) and caffeine (n = 0.57–0.59) are very similar although the former is much less water soluble than caffeine (Table 1). In general, the diffusional exponents tend to be somewhat larger in the saturated gels. The highest value (n = 0.6, Tables 3–5) is closer to n = 0.5 than to n = 1. This indicates that drug release is mainly controlled by diffusion and in some extent by relaxation/dissolution.

The Higuchi equation relates the drug released with the square root of time and was also tested. The Peppas model was selected to test correlations with the solubility parameter because this model is applicable to a wider release range for all drugs.

3.4. Extended Peppas model

Eq. (2) is tested for each drug to predict the cumulative amount M delivered at time t including all the initial drug concentrations C_i used in the saturated and non-saturated gels:

$$\ln M = a + b \ln t + c \ln C_i \quad (2)$$

The coefficients a, b and c are obtained from multiple regression analysis. Eq. (2) is an extension of the Peppas power law. Taking logarithms into Eq. (1):

$$\ln M = \ln M_\infty + \ln K + n \ln t \quad (3)$$

Comparing Eqs. (2) and (3):

$$\ln M_\infty + \ln K = a + c \ln C_i \quad (4)$$

The coefficient b of Eq. (2) represents the diffusional exponent n of the Peppas model.

Table 6 summarizes the regression coefficients, r^2 values, number of cases N and concentration ranges included for each drug.

The n exponent is ≤0.50 for naproxen, theophylline, paracetamol and salicylic acid (Table 6) and Fickian diffusion can be assumed for these drugs. For caffeine and diclofenac n = 0.58, a value closer to n = 0.5 than to n = 1. This suggests that Fickian diffusion is also the main release mechanism.

Eq. (2) can be also written using the release fractions of drug M/M_∞ delivered where M_∞ is the amount delivered at the asymptotic region of the release curves in Fig. 1(a–f):

$$\ln\left(\frac{M}{M_\infty}\right) = a + b \ln t + c \ln C_i \quad (5)$$

Comparing Eq. (3) and the Peppas model (Eq. (1)):

$$\ln K = a + c \ln C_i \quad (6)$$

Eq. (5) is tested with all the initial concentrations C_i of each drug. Table 7 summarizes the regression coefficients, r^2 values, number of cases N and concentration ranges included for each drug. The apparent kinetic constants K (h^{-n}) calculated from Eq. (6) are also

Table 7
Coefficients of Eq. (5), number of cases N, release constant K (Eq. (6)) and initial drug concentrations ranges C_i included in the analysis.

Drug	a	b	c	r^2	N	K (h^{-n})	C_i ranges[a]
Naproxen	1.233	0.49	−0.299	0.98	30	2.54	0.01–0.05
Diclofenac	1.542	0.58	−0.143	0.99	54	4.05	
Theophylline	2.968	0.48	−0.011	0.98	42	19.15	0.50–5.00
Salicylic acid	2.804	0.44	−0.132	0.98	66	14.46	0.10–0.35
Caffeine	2.659	0.58	−0.101	0.99	50	12.9	0.50–5.00
Paracetamol	2.999	0.50	−0.106	0.98	44	18.04	

[a] The detailed initial concentrations are given in Tables 3–5.

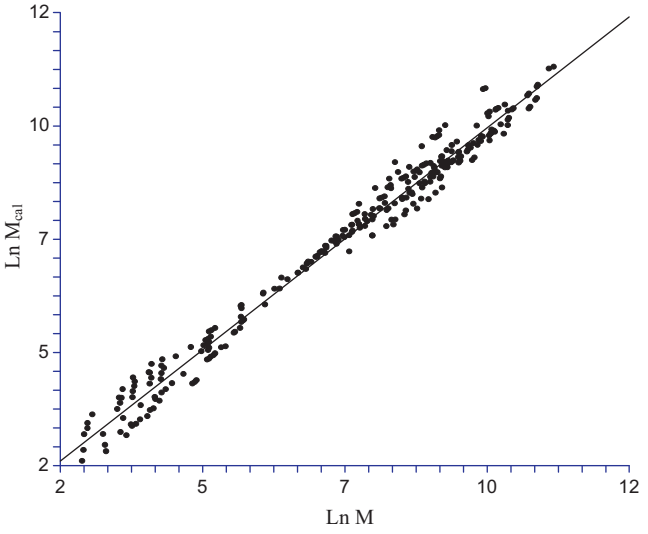

Fig. 4. Relationship between the logarithm of the experimental and calculated amounts of drug delivered (mg) using Eq. (9).

included. Fig. 3 shows that the ln K values increase as the solubility parameter of the drug becomes larger, according to a parabolic relationship.

3.5. Modelling drug release with solubility parameters

A common equation including all the drugs and the overall initial drug concentrations is written:

$$ln\,M = C_0 + C_1\delta - C_2\delta^2 + C_3\ \ln\ t + C_4\ \ln\ C_i \quad (7)$$

Eq. (7) assumes a parabolic relationship between the apparent kinetics constant K and the solubility parameter (the quadratic term δ_1, δ_1^2) as suggested in Fig. 3. Comparing Eq. (7) with the extended Peppas model (Eq. (2)):

$$ln\,K = C_0 + C_1\delta - C_2\delta^2 + C_4\ \ln\ C_i \quad (8)$$

Eq. (7) is tested including all the drugs and drug concentrations:

$$ln\,M = -21.578 + 2.102\delta - 0.037\delta^2 + 0.48\ \ln\ t + 1.028\ \ln\ C_i \quad (9)$$

$$r^2 = 0.94,\ N = 286,\ \mathrm{SD} = 0.54,\ F = 1118$$

The relationship between the experimental and calculated values is good (r^2 = 0.94, Fig. 4) considering the large number of cases included (N = 286) and the different structure of the drugs. The coefficient C_3 = 0.48 of Eq. (9) (corresponding to the exponent n of the Peppas model) is very close to 0.5 indicating that a Fickian diffusion process can be assumed for all drugs. According to Eq. (9) the amount delivered increases as the initial concentration and the solubility parameter of the drug becomes larger.

The drug release can also be modeled using the logarithm of the octanol–water partition coefficient log P of the drugs as a polarity index:

$$ln\,M = 7.9563 - 0.4713\ \log\ P + 0.4860\ \ln\ t + 0.7673\ \ln\ C_i \quad (10)$$

r^2 = 0.95, N = 286, SD = 0.22, F = 2074

According to Eq. (10), the amount released decreases as the partition coefficient increases.

The results show that the release of drugs from HPMC gels can be modeled with a common equation including the drug concentration and the solubility parameter or the partition coefficient of the drug. The results provide useful criteria to facilitate hydrogel drug formulation. The larger the solubility parameter of the drugs the greater the amount delivered and the release rate.

References

Barton, A.F.M., 1991. Handbook of Solubility Parameters and Other Cohesion Parameters. CRC Press, Boca Raton, Florida.

Baumgartner, S., Lahajnar, G., Sepe, A., Kristl, J., 2002. Investigation of the state and dynamics of water in hydrogels of cellulose ethers by 1H NMR spectroscopy. AAPS Pharm. Sci. Technol. 3, 1–8.

Bettini, R., Colombo, P., Peppas, N.A., 1995. Solubility effects on drug transport through pH-sensitive, swelling-controlled systems: transport of theophylline and metoclopramide monohydrochloride. J. Control. Release 37, 105–111.

Bustamante, P., Navarro-Lupión, J., Escalera, B., 2005. A new method to determine the partial solubility parameters of polymers from intrinsic viscosity. Eur. J. Pharm. Sci. 24, 229–237.

Bustamante, P., Sellés, E., 1986. Relationship between the solubility parameter and the binding of drugs to plasma proteins. J. Pharm. Sci. 75, 639–643.

Fini, A., Cavallari, C., Ospitali, F., González-Rodríguez, M.L., 2011. Theophylline-loaded compritol microspheres prepared by ultrasound-assisted atomization. J. Pharm. Sci. 100, 743–757.

Fu, X.C., Wang, G.P., Liang, W.Q., Chow, M.S.S., 2004. Prediction of drug release from HPMC matrices: effect of physicochemical properties of drug and polymer concentration. J. Control. Release 95, 209–216.

Ghafourian, T., Samaras, E.G., Brooks, J.D., Riviere, J.E., 2010. Validated models for predicting skin penetration from different vehicles. Eur. J. Pharm. Sci. 41, 612–616.

Jensen, L.B., Magnusson, E., Gunnarsson, L., Vermehren, C., Nielsen, H.M., Petersson, K., 2010. Corticosteroid solubility and lipid polarity control release from solid lipid nanoparticles. Int. J. Pharm. 390, 53–60.

Jiang, R., Benson, H.A.E., Cross, S.E., Roberts, M.S., 1998. In vitro human epidermal and polyethylene membrane penetration and retention of the sunscreen benzophenone-3 from a range of solvents. Pharm. Res. 15, 1863–1868.

Katzhendler, I., Mäder, K., Friedman, M., 2000. Structure and hydration properties of hydroxypropylmethylcellulose matrices containing naproxen and naproxen sodium. Int. J. Pharm. 200, 161–179.

Kim, H., Fassihi, R., 1997a. Application of a binary polymer system in drug release modulation. 1. Characterization of release mechanism. J. Pharm. Sci. 86, 316–322.

Kim, H., Fassihi, R., 1997b. Application of a binary polymer system in drug release modulation. 2. Influence of formulation variables and hydrodynamic conditions on release kinetics. J. Pharm. Sci. 86, 323–328.

Kim, H., Fassihi, R., 1997c. A new ternary polymeric matrix system for controlled drug delivery of highly soluble drugs. I. Diltiazem hydrochloride. Pharm. Res. 14, 1415–1421.

Kurahashi, H., Kami, H., Sunada, H., 1996. Influence of physicochemical properties on drug release rate from hydroxypropylmethylcellulose matrix tablets. Chem. Pharm. Bull. 44, 829–832.

Lee, T.H., Wang, J.G., Wang, C.H., 2002. Double-walled microspheres for the sustained release of a highly water soluble drug: characterization and irradiation studies. J. Control. Release 83, 437–452.

Lin, C., Metters, A.T., 2010. Hydrogels in controlled release formulations: network design and mathematical modeling. Adv. Drug Deliv. Rev. 58, 1379–1408.

Matsumoto, A., Matsukawa, Y., Suzuki, T., Yoshino, H., Kobayashi, M., 1997. The polymer-alloys method as a new preparation method of biodegradable microspheres: principle and application to cisplatin-loaded microspheres. J. Control. Release 48, 19–27.

Mitchell, K., Ford, J.L., Amstrong, D.J., Elliott, P.C.N., Rostron, C., Hogan, J.E., 1990. The influence of additives on the cloud point, disintegration and dissolution of hydroxypropylmethylcellulose gels and matrix tablets. Int. J. Pharm. 66, 233–242.

Peppas, N.A., Bures, P., Leobandund, W., Ichikawa, H., 2000. Hydrogels in pharmaceutical formulations. Eur. J. Pharm. Biopharm. 50, 27–46.

Pérez-Marcos, B., Ford, J.L., Amstrong, D.J., Elliot, P.N.C., Rostron, C., Hogan, J.E., 1996. Influence of pH on the release of propranolol hydrochloride from matrices containing hydroxypropylmethylcellulose K4M and carbopol 974. J. Pharm. Sci. 85, 330–334.

Roberts, M., Cespi, M., Ford, J.L., Dyas, A.M., Downing, J., Martini, L.G., Crowley, P.L., 2007. Influence of ethanol on aspirin release from hypromellose matrices. Int. J. Pharm. 332, 31–37.

Sawant, P.D., Luu, D., Ye, R., Buchta, R., 2010. Drug release from hydroethanolic gels. Effect of drug's lipophilicity (log P), polymer–drug interactions and solvent lipophilicity. Int. J. Pharm. 396, 45–52.

Shin, S.C., Cho, C.W., Yang, K.H., 2004. Development of lidocaine gels for enhanced local anaesthetic action. Int. J. Pharm. 287, 73–78.

Sloan, K.B., Koch, A.M., Siver, K.G., Flowers, F.P., 1986. Use of solubility parameters of drug and vehicle to predict flux through skin. J. Invest. Dermatol. 87, 244–252.

Xu, G., Sunada, H., 1995. Influence of formulation change on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Chem. Pharm. Bull. 43, 483–487.