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Mathematical modeling of drug release profiles for modified hydrophobic HPMC based gels

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Hydroxypropyl methylcellulose (HPMC) is now available in modified hydrophobic forms (Sangelose). In this paper, the effect of viscosity grade and HPMC concentration on *in vitro* release kinetics of a topically applied drug were studied using gel formulations of a nonsteroidal anti-inflammatory drug (NSAID), diclofenac potassium (DP), with different viscosity grades of the polymer (60L, 60 M, 90 M for hydrophobic HPMC and 50 cPs for conventional hydrophilic HPMC) in different proportions. It was found that hydrophobic HPMC-based gels having a higher viscosity and lower polymer concentration release a notably higher amount of drug compared with hydrophilic HPMC-based gels containing a higher concentration of polymer but with lower viscosity. For gels, the suitability of different common empirical (zero-order, first-order, and Higuchi), and semi-empirical (Ritger-Peppas and Peppas-Sahlin) models, and some new statistical (logistic, log-logistic, Weibull, Gumbel, and generalized extreme value distribution) models to describe the drug release profile were tested through non-linear least-square curve fitting. A general purpose mathematical analysis tool MATLAB was used. Further, instead of the widely used transformed linear fit method, direct fitting was used in the paper to avoid any form of truncation and transformation errors. The results revealed that the log-logistic distribution, amongst all the models investigated, was the best fit for hydrophobic formulations. For hydrophilic ones, the semi-empirical models and Weibull distribution worked best, although log-logistic also showed a close fit. The shape parameter for the log-logistic and Weibull distribution conveys vital information about the rate of release and helps improve understanding of drug release profiles.

1. Introduction

Gels have the advantages of being loaded with solutes with specific therapeutic properties and releasing these solutes in a controlled manner. They have been found suitable for various biological applications such as tissue engineering (Burdick et al. 2002; Nguyen et al. 2002; Aimetti et al. 2009) as well as for drug delivery systems (Peppas et al. 2000). Among the different gels, topical gels are becoming a very popular dosage form for drugs that have been reported to cause various side effects after oral administration (Abaci et al. 2009; Song and Shin 2009). Not surprisingly, a variety of polymers, mostly cellulose derivatives (Wang et al. 2001; Ji et al. 2010), are available commercially for topical gel formulations. In a gel based system, drug release kinetics and the mechanism of drug release are greatly influenced by the extent of polymer swelling, erosion, and diffusion of the drug through the polymer network (Bamba et al. 1979; Sinha and Rosesa 2002; Gohel et al. 2000). By using a higher proportion of polymer or a high viscosity grade of polymer, the tortuosity or gel strength of the polymer can be increased. This in turn obstructs polymer erosion and delays drug diffusion, both of which help to maintain the rate of drug release within the desired range. Hydroxypropyl methylcellulose (HPMC) is one of the cellulose derivatives favoured for use in topical formulations. It is cheap, non-toxic in nature, and rapidly swellable, and it can accommodate high levels of drug (Vueba et al. 2004). In addition, by altering the molar mass and/or by inserting different chemical groups on the main polymer backbone (Viriden et al. 2010), different substituents and viscosity grades of HPMC may be derived, further enhancing control over the rate of drug release (Chun et al. 2009). One such example is hydrophobic HPMC which is obtained by combining basic HPMC with a long chain alkyl group. The drug release kinetics, mechanism of drug release, and rate of release for hydrophobic HPMC differ significantly from those of conventional hydrophilic HPMC due to the difference in chemical composition and viscosity. Thus, mathematical modeling of drug release profiles for hydrophobic HPMC-based gels is of utmost importance as it is well known that the effectiveness of a gel always depends on the extent and rate of drug release from the base.

A thorough literature survey reveals that existing works relating to HPMC are essentially restricted to the hydrophilic polymer form. A close inspection also reveals that most of the authors preferred model-based release kinetics. Further, inferences were drawn after fitting the experimental data to only a few common empirical models, e.g. the zero-order, first-order, and Higuchi and power law models (Ritger-Peppas model and Peppas-Sahlin

model). As an indicative example, the work of Gohel and Panchal (1999) may be cited where all these models were applied to describe the drug release kinetics of different test formulations containing hydrophilic HPMC as the polymer. The criterion for selecting the most appropriate model was based on the goodness-of-fit test. On the other hand, Tas et al. (2003) and Escudero et al. (2008) showed the effect of different viscosity grades and different concentrations of hydrophilic HPMC on the *in vitro* release profile of chlorpheniramine maleate and theophylline respectively. The model-based kinetic equations for interpreting drug release from hydrophilic HPMC were derived in the work of Reza et al. (2003) while in a separate study Vueba et al. (2004) worked on release kinetics of a different drug, ketoprofen. However the models used in their papers are quite familiar in nature and belong to the class of common models, as stated earlier. In this regard, one important contribution is that of Koester et al. (2004) who performed a mathematical evaluation of *in vitro* release profiles of hydrophilic HPMC matrix tablets containing carbamazepine. They established the supremacy of the Weibull model for release modeling as applicable to *in vitro* dissolution profiles. Another recent paper on carbamazepine is by Barakat et al. (2009), who elucidated the effect of hydrophilic HPMC on the release mechanism through empirical and power law models. Some other articles worth mentioning include work by Kiortsis et al. (2005), in which the mechanism of drug release from tableted wet granulations comprising hydrophilic HPMC was studied, and the work of Lin et al. (2005) where the authors studied the *in vitro* release kinetics of methylephedrine HCl from membrane moderated transdermal delivery systems (HPMC being one of the components), again using common mathematical models. In the later paper, linear regression analyses were used to determine the suitability of these models.

In our present research, some topical gels were formulated using conventional hydrophilic HPMC (50 cPs) while others were formed with the recently developed hydrophobic HPMC of different viscosity grades (60 M, 60L and 90 M) in different proportions, using diclofenac potassium (DP) as a model drug. This is a nonsteroidal anti-inflammatory drug (NSAID), widely used for its strong analgesic, antipyretic and anti-inflammatory effects (Avachat et al. 2007). DP is marketed as injections, oral sustained release tablets and topical formulations. Although it is one of the best tolerated NSAIDs, gastropathy occurs following oral administration and because of its short biological half-life, the drug has to be administered frequently. Therefore, to make the drug safer, it has been widely suggested to use topically applied NSAIDs instead. Diclofenac potassium, having a molecular weight of 341.88 Da and a melting point of 222 °C, may be considered an ideal model drug for topical gel formulation. In the present paper, the effects of different variants of HPMC (hydrophilic and hydrophobic form), viscosity grades, and polymer concentration on the kinetics of DP release were studied by *in vitro* release of different topical formulations. *In vitro* release was carried out in a Franz-diffusion cell, and both the drug content and the viscosity of the gels was determined. In vitro release studies and mathematical modeling (Hardy et al. 2007; Reis et al. 2007; Muschert et al. 2009; Barba et al. 2009; Rothstein et al. 2009; Siepmann et al. 2010) always help to give a better understanding of the release process and can serve as a basis for the design of controlled release type formulations. The contribution of this paper is mainly threefold. Firstly, a detailed comparison of different common empirical and semi-empirical models (zero-order, first-order, Higuchi, Ritger-Peppas, and Peppas-Sahlin), along with some new and traditional statistical models (logistic, log-logistic, Gumbel, Weibull, generalized extreme value), for release data fitting was performed. The suitability of all these models with respect to the experimental data was compared on the basis of the regression coefficient (r^2) and sum-of-square residuals (SSR). The reasons for choosing such statistical models are described in detail in the materials and methods section. The second novelty lies in considering both the hydrophilic and hydrophobic variants of HPMC, as opposed to earlier studies which were confined to the hydrophilic form. In addition, the effect of viscosity grade and polymer concentration on drug release were considered. In comparison with the hydrophilic form, a relatively lower concentration of hydrophobic HPMC is enough to produce a gel of high viscosity. Therefore it is necessary to investigate whether concentration or viscosity has more control over drug release. In one of our recent papers (Ghosal et al. 2010), the predominance of concentration over viscosity was shown when using 90L grade hydrophobic HPMC. In the current paper, we investigate whether similar conclusions also hold for other viscosity grades (60 M, 60L, and 90 M) of hydrophobic HPMC. The third contribution is that all the model fitting analyses were performed by non-linear direct fitting through minimization of SSR. A general purpose mathematical analysis tool MATLAB^{TM} was used for the purpose. Linear transformation methods were deliberately avoided as these methods generally take the input in transformed logarithmic form instead of the original data and thereby open up the possibility of carrying on approximation errors of any sort.

2. Investigations, results and discussion

2.1. Drug content

The drug content of all formulations was in the range of 94% to 98%, showing content uniformity. An average of six readings with standard deviation (SD) is given in Table 1.

2.2. pH Determination

If the pH of a topical formulation is outside the range of skin pH, it may cause skin irritation, rendering it unsuitable for transdermal use. The pH of the gel prepared with hydrophobic HPMC was slightly higher than normal skin pH and was adjusted by adding phosphate buffer. However, the pH of the hydrophilic HPMC-based gel was even closer to skin pH. An average of six readings with standard deviation (SD) is given in Table 1.

2.3. Effect of viscosity and concentration

As the concentration of polymer is increased, the chain density becomes higher, causing retardation of release. This shows that the drug release rate is inversely proportional to polymer concentration. In the present study it was seen that the previous statement holds true for both hydrophilic and hydrophobic formulations.

Considering hydrophobic formulations first, for formulation F1 (60 M polymer), as seen from Table 1 and Table 2, the concentration of polymer used was 1% w/w and the cumulative drug release at 6 h was about 69% w/w. Keeping the same grade of polymer, when the polymer concentration was increased, drug release generally decreased significantly. In case of formulation F2 (using the same grade of polymer), cumulative drug release at 6 h was about 58% at a concentration of 3% w/w. Similar results may be seen for the other four hydrophobic formulations. In the case of formulations F3 and F4 (having 1.5 % and 3% w/w concentrations of 60L polymer, respectively), the cumulative drug release at 6 h was about 69% and 61% respectively. For formulations F5 and F6 (90 M polymer), cumulative drug release at 6 h was about 65% at a polymer concentration of 1.5% w/w and about 59% at a concentration of 2% w/w, respectively. Formulations F7 and F8 were prepared using

Table 1: Compositions of gels

Formulation code	Hydrophilic HPMC (%w/w)	Hydrophobic HPMC (%w/w)			DP (%w/w)	Glycerol (mL)	Phosphate buffer	Propyl paraben (mg)	Distilled water and IPA
		60 M	60 L	90 M					
F1	–	1.0	–	–	1	0.5	proper amt	10	q. s.
F2	–	3.0	–	–	1	0.5	proper amt	10	q. s.
F3	–	–	1.5	–	1	0.5	proper amt	10	q. s.
F4	–	–	3.0	–	1	0.5	proper amt	10	q. s.
F5	–	–	–	1.5	1	0.5	proper amt	10	q. s.
F6	–	–	–	2.0	1	0.5	proper amt	10	q. s.
F7	12	–	–	–	1	0.5	–	10	q. s.
F8	15	–	–	–	1	0.5	–	10	q. s.

q. s. = quantity sufficient

hydrophilic HPMC (50 cPs). For F7 (12% concentration), the cumulative drug release at 6 h was about 37% w/w and for F8 the cumulative drug release at 8 h was 33% at 15% w/w concentration. Thus, it was observed that the drug release rate decreases with increased polymer concentration. For hydrophilic HPMC formulations, a much larger amount of polymer is required than for hydrophobic formulations. From Table 2, it may be observed that the range of viscosity of hydrophobic formulations (F1 to F6) was from 136 poise to 176 poise, while for hydrophilic formulations the viscosity range was from 25 poise to 30 poise. In short, for hydrophobic formulations having a higher viscosity with lower a polymer concentration, a notably higher amount of the drug is released compared with hydrophilic formulations with a higher polymer concentration but lower viscosity. Thus, from the findings it may be concluded that polymer concentration is more important and effective than viscosity in determining drug release when a polymer with derivatives with different viscosities is used.

2.4. Empirical modeling

The *in vitro* release data were analyzed with different empirical release kinetics (zero-order, first-order and Higuchi) to understand the mechanism of release from the formulations, r^2 and SSR values being used to decide the best-fit model. Table 3 shows that the highest r^2 values (0.9528–0.9970) and lowest SSR values (1.33–250.62) were obtained for the Higuchi model. This clearly indicates that release from all the formulations is diffusion controlled.

2.5. Semi-empirical modeling

While empirical modeling confirms that release is diffusion-controlled in all cases, semi-empirical models reveal the type of diffusion. From Table 4, it can be observed that the Ritger-Peppas model shows good linearity with time (the r^2 value varies from 0.9417 to 0.9978 and the SSR value varies from 0.9916 to 353.44). Table 4 also gives the value of the parameter n. For hydrophobic formulations, n varies from 0.46 to 0.50 which implies Fickian type diffusion. On the other hand, for hydrophilic formulations, the value of n is between 0.56 and 0.86, indicating anomalous diffusion, i.e., the drug is released due to both diffusion and erosion.

The fraction of drug (F) released due to Fickian diffusion may be calculated from Eq. (6). The calculated values of F at 3 h are 1.02, 0.68, 1.07, 0.88, 0.98 and 0.74 for formulations F1, F2, F3, F4, F5 and F6, respectively (Table 5). The calculated values for F7 and F8 are 0.74 and 0.35 respectively. These values denote that for hydrophobic formulations drug release is mainly dominated by Fickian diffusion, while for hydrophilic polymer-based formulations, drug release is governed by both diffusion and erosion. The amount of drug released due to diffusion will diminish with increased polymer concentration.

2.6. Best fitting model

Fig. 1 a-h shows the suitability of different models considered in the paper during the curve fitting exercise. In all the figures, the independent horizontal axis denotes time (in h) while the percentage of cumulative drug released as a function of time is plotted along the dependent vertical axis. The first six figures, Fig. 1 a-f, portray the time-absorbance curve for hydrophobic HPMC where statistical models clearly outperform the empirical (E) or semi-empirical (SE) models. In all these cases, the log-logistic distribution was found to give the best fit, while the Weibull distribution emerged as the second best. For comparison, best fit among the empirical and semi-empirical models (best E/SE) is also depicted. The Peppas-Sahlin (F1 and F3), Ritger-Peppas (F4), and Higuchi (F2, F5, and F6) models were found to be more suitable than the widely-used zero-order or first-order models.

The last two figures portray model fitting results for hydrophilic HPMC based gels (F7 and F8) where the empirical and semi-empirical models, like the Higuchi, Peppas-Sahlin, and Ritger-

Table 2: Release parameters of diclofenac potassium from different topical formulations

Formulation code	% drug content (mean ± SD)	pH (mean ± SD)	Viscosity in poise (mean ± SD)	Cumulative amount of release at 6 hour ($\mu g/cm^2$)	Cumulative amount of release at 6 hour (%)
F1	98.00 ± 2.01	7.56 ± 0.05	144 ± 2.23	1734 ± 121	69
F2	97.50 ± 3.03	7.89 ± 0.03	160 ± 2.69	1455 ± 101	58
F3	98.20 ± 2.19	7.73 ± 0.09	136 ± 3.01	1739 ± 70	69
F4	98.45 ± 1.22	7.74 ± 0.05	150 ± 1.98	1539 ± 40	61
F5	98.00 ± 2.54	7.69 ± 0.06	154 ± 2.47	1640 ± 89	65
F6	99.64 ± 1.98	7.97 ± 0.07	176 ± 2.33	289 ± 54	12
F7	97.98 ± 3.20	6.92 ± 0.04	25 ± 3.13	693 ± 44	37
F8	96.44 ± 2.23	6.94 ± 0.05	30 ± 1.96	625 ± 75	33

SD = standard deviation

Table 3: Parameters, correlation coefficient, and SSR for zero-order, first-order and Higuchi model

Model	Parameters	Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
Zero-order $Q_t = K_0 t + C_0$	K_0	9.50	8.65	8.83	8.21	10.63	9.33	4.64	5.00
	C_0	22.88	11.81	23.48	18.64	13.73	13.05	10.27	4.78
	r^2	0.8607	0.9343	0.8897	0.8980	0.8779	0.8676	0.9941	0.9910
	SSR	740.34	266.20	489.37	387.88	794.97	671.99	2.23	4.00
First-order $Q_t = Q_0 \exp\left(-K_f^t\right)$	K_f	0.282	0.1705	0.2639	0.2062	0.2340	0.1959	0.0867	0.0727
	r^2	0.8711	0.9386	0.8127	0.8243	0.9545	0.9196	0.8283	0.9779
	SSR	684.78	248.94	830.59	668.00	296.47	407.98	65.10	9.81
Higuchi $Q_t = K_H\sqrt{t} + C_H$	K_H	30.61	27.20	28.23	26.21	34.00	29.93	16.16	17.48
	C_H	1.69	–6.46	4.11	0.70	–9.61	–7.58	–2.67	–9.25
	r^2	0.9528	0.9868	0.9713	0.9762	0.9593	0.9542	0.9957	0.9970
	SSR	250.62	53.39	127.16	90.48	264.87	232.94	1.65	1.33

Table 4: Parameters, correlation coefficient, and SSR for Ritger-Peppas and Peppas-Sahlin model

Model	Parameters	Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
Ritger-Peppas $Q_t = K_{RP} t^n$	K_{RP}	33.26	21.14	33.08	27.58	25.61	23.50	13.56	9.05
	n	0.46	0.49	0.44	0.47	0.49	0.57	0.57	0.74
	r^2	0.9570	0.9807	0.9777	0.9784	0.9457	0.9417	0.9972	0.9978
	SSR	228.31	78.01	98.98	82.30	353.44	295.90	1.07	0.9916
Peppas-Sahlin $Q_t = K_1 t^{0.45} + K_2 t^{0.90}$	K_1	34.59	16.76	35.03	27.73	20.66	19.84	11.41	4.34
	K_2	–0.56	4.62	–1.40	0.32	5.43	4.15	2.34	4.90
	r^2	0.9572	0.9755	0.9796	0.9772	0.9363	0.9326	0.9982	0.9969
	SSR	227.54	99.45	90.32	86.80	414.79	342.19	0.68	1.39

Peppas, are on a par with the statistical models. Referring to Fig. 1 g, one may observe that these models perform slightly better than the Weibull model. The Peppas Sahlin model gives the best fit as it can combine Fickian diffusional behavior with non-Fickian diffusion in a linear manner. For F8, as seen from Fig. 1 h, although the Weibull model gives the best fit, other semi-empirical models also fit well. Interestingly, among the statistical models, the Weibull model gives better fits than the log-logistic model for both the hydrophilic HPMC formulations.

2.7. Statistical modeling

The logistic family of distribution considered in the paper has two members. The basic logistic distribution has a scale (a_L) and a location (c_L) parameter that may be varied to fit the experimental data. The results, as seen from Table 6, are not very encouraging, except for formulations F7 and F8. The scale parameter (a_L) is higher for even numbered formulations, which have a higher polymer concentration than odd numbered formulations. A higher a_L denotes a lesser slope of the CDF curve, i.e., cumulative drug release is less. The log-logistic distribution is undoubtedly the best fit model for the hydrophobic polymers under study. The r^2 values with log-logistic fit for formulations F1 to F6 are the highest of all the models, while the SSR values obtained are the lowest. The logistic-family may be used to characterize *S*-shaped drug release profiles (Costa et al. 2003). For log-logistic models, the slope of this *S* is determined by the shape parameter (b_{LL}), which is here found to be close to unity. Fig. 2a depicts that (for even numbered formulations), b_{LL} decreases with increasing concentration, suggesting that the *S*-shaped release profile is more delayed, i.e. more inclined towards the horizontal axis.

Having regard to the r^2 and SSR values from Table 7, the Weibull can be considered a good model and it can characterize the *in vitro* curve in term of shape parameter (b_W). As is evident from Fig. 2b, when the value of b_W is less than 1, the curve is steeper compared with an exponential distribution (a special case of Weibull when $b_W = 1$). The log-Weibull or Gumbel model does not exhibit such a close fit. However the shape parameter (b_G) also helps to understand the characteristics of the *in vitro* release profile curve. While comparing two formulations made with the same grade of polymer but at different concentrations, it was found that the value of b_G increases with the polymer concentration. A higher b_G value renders the CDF more sluggish in nature, portraying the basic fact that a higher concentration of polymer causes sustained drug release. Finally, the GEV model was not suitable for any *in vitro* release profile under study.

In summary, among the different statistical models used, the log-logistic distribution was found to be the best fit for hydrophobic formulations (F1 to F6) whereas the Weibull dis-

Table 5: Fraction of drug released due to Fickian diffusion at 3 h

Formulation code	Fraction of drug released at 3 h
F1	1.02
F2	0.68
F3	1.07
F4	0.88
F5	0.98
F6	0.74
F7	0.74
F8	0.35

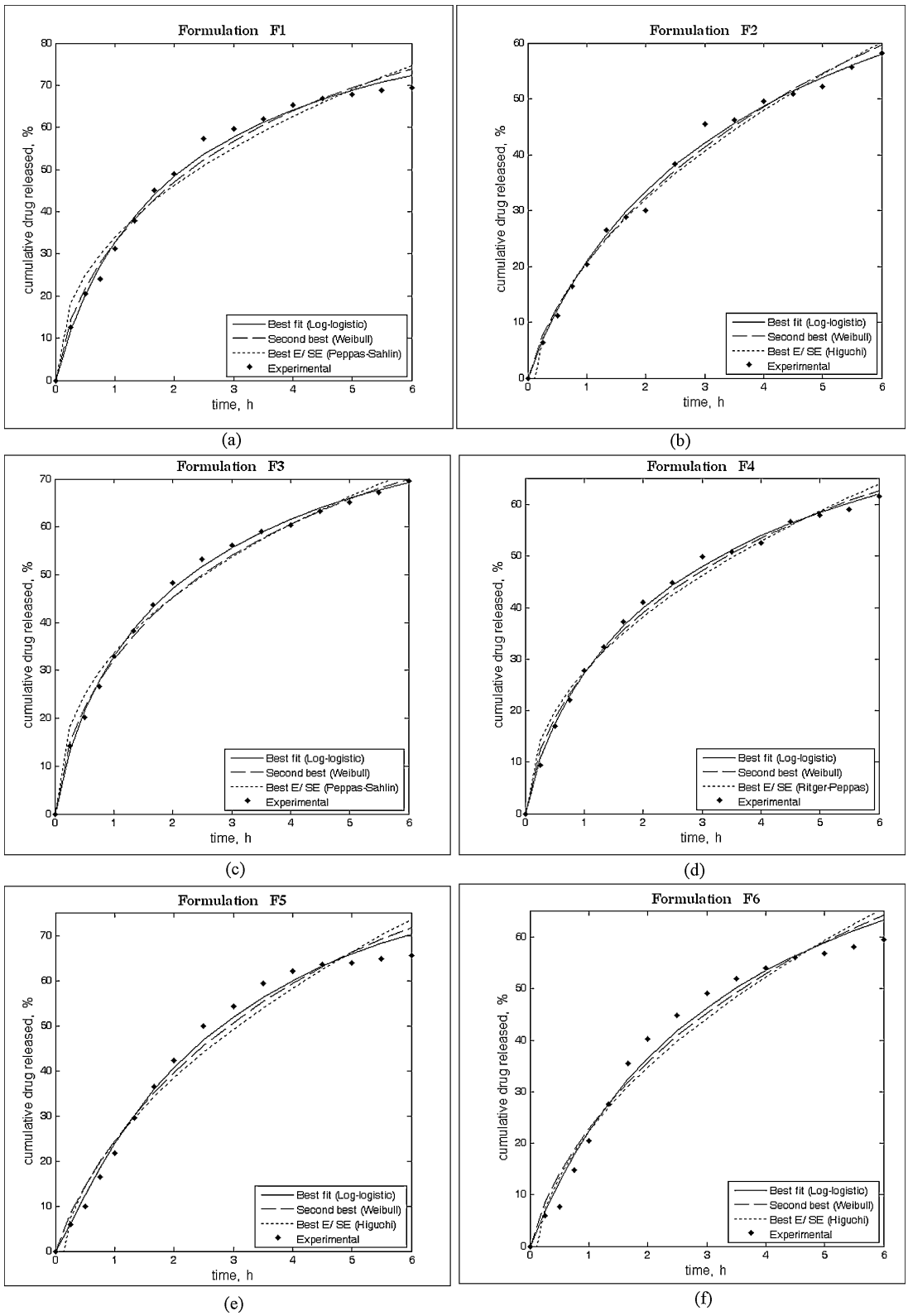
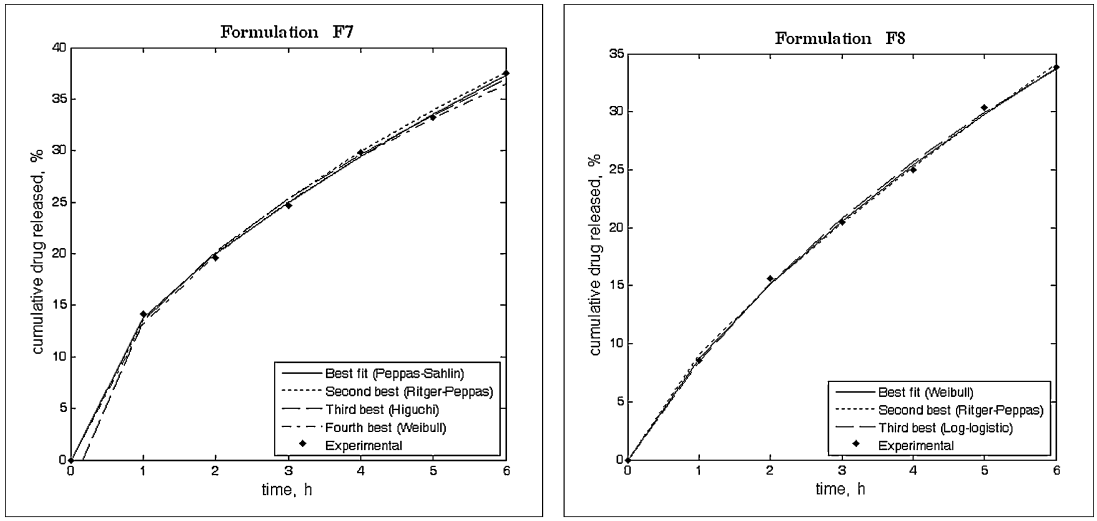


Fig. 1: Time-absorbance curves for hydrophobic HPMC formulations F1–F8

tribution works best for hydrophilic (F7 to F8), although the log-logistic distribution also shows a close fit.

2.8. Conclusions

In this paper a wide variety of empirical, semi-empirical, and statistical models were tested for describing the drug release profile of HPMC-based gels. Both the conventional hydrophilic and the newly derived hydrophobic variants were investigated and formulations with different polymer concentrations and viscosity grades were prepared to study the effect of concentration and viscosity grade on the drug release rate. In the case of different variants of similar polymer formulations, it was found that having a higher viscosity with a lower polymer concentration released a higher amount of drug compared with the formulations containing a higher concentration of polymer but with a lower viscosity. Further, it was shown that although



(g) (h)

Fig. 1: (*Continued*).

the traditional semi-empirical models can describe hydrophilic HPMC-based drug delivery systems precisely, their performance is much inferior to statistical models like log-logistic and Weibull in the case of hydrophobic HPMC-based systems.

3. Experimental

Hydrophobic hydroxypropyl methylcellulose (HPMC; 60L, 60 M and 90 M): Hydroxypropyl methylcellulose combined with a long chain alkyl group to give hydroxypropyl methylcellulose steroxy ether, was donated by Daido Chemical Corporation (Tokyo, Japan). Hydrophilic hydroxypropyl methylcellulose (HPMC, 50 cPs) was supplied by SRL Pvt. Ltd. (Mumbai, India). Diclofenac potassium (DP) IP grade was kindly donated by Kontest Chemicals (Kolkata, India) as a faintly yellowish white powder. Dialysis membrane (Batch 0706119; average diameter 17.5 mm, average width 29.31 mm) was supplied by Hi Media Chemical Laboratories (Mumbai, India). Dialysis membrane was used as a diffusion barrier. All other chemicals used were of analytical grade.

3.1. Preparation of gel

For preparation of the gels, polymers at different concentrations were taken in a 100 ml beaker and wetted in a mixture of water, isopropyl alcohol (IPA) and glycerol for 24 h. Diclofenac potassium and propyl paraben were dissolved in a small amount of water. The solution was added to the wetted gel base and mixed well under constant stirring in a homogenizer. All the formulations prepared contained 1.0% (w/w) DP.

3.2. Drug content studies

The drug content of the gels was determined by dissolving an accurately weighed quantity of gel (about 100 mg) in 50 ml of 0.1 (M) NaOH. Then 1 ml of the initial solution was diluted with 50 ml of pH 6.8 phosphate buffer in a volumetric flask. The resulting solution was then filtered through membrane filters before being subjected to spectrophotometric analysis for DP at 276 nm.

3.3. Determination of viscosity

A TV-10 Viscometer viscosity meter (Toki Sangyo Co. Ltd., Tokyo, Japan, M4 spindle, No.23 cord) was used. The viscosities of gels of different formulations were measured at 20 rpm at a controlled temperature ($37 \pm 1\,^{\circ}C$).

3.4. Determination of pH

Gel pH was measured using a digital type pH meter (Systronics digital-DI-707, India), by dropping the glass electrode and reference electrode completely into the gel system, so as to cover the electrode. Before pH measurement, calibration of the pH meter was performed with buffered solutions at pH 4, 7, and 10.

3.5. In vitro release study

In vitro diffusion studies were performed in a Franz diffusion cell using phosphate buffer (pH 6.8) as the receptor fluid and the dialysis membrane as a diffusion barrier. The volume of receptor liquid was 20 ml and it was slowly stirred by a magnetic stirrer at 40–50 rpm. Outside the receptor compartment, water from a constant temperature ($37 \pm 0.5\,^{\circ}C$) bath was allowed to flow continuously through the jacket. A 0.5 g quantity of gel of different formulations was applied to one side of the membrane attached to the donor compartment. The other side of the membrane was exposed to the receptor compartment. Samples of 1 ml were withdrawn from the receptor compartment at non-uniform time intervals up to 6 h. During the first hour of the study (when the concentration gradient is high) the interval between sampling was set at 15 min, and increased to 20 min in the second hour, and for last 4 h (when concentration gradient is relatively low) the interval between samples was further increased to 30 min. This was done because the relationship between concentration and time can be best determined by

Table 6: Parameters, correlation coefficient, and SSR for logistic and log-logistic distributions

Distribution	Parameters	Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
Logistic $Q_t = \frac{1}{1+\exp\left(-t+\frac{c_L}{a_L}\right)}$	a_L (scale)	2.40	2.67	2.66	2.91	2.16	2.95	4.20	3.50
	c_L (location)	2.75	4.44	2.94	3.81	3.34	3.96	7.93	8.08
	r^2	0.8682	0.8982	0.8863	0.8755	0.8605	0.8306	0.9761	0.9590
	SSR	711.13	412.47	504.07	473.48	908.22	859.62	9.07	18.15
Log-logistic $Q_t = \frac{1}{1+(t/a_{LL})^{-b_{LL}}}$	a_{LL} (scale)	2.15	4.23	2.30	3.30	2.79	3.48	12.44	12.22
	b_{LL} (shape)	0.94	0.92	0.85	0.82	1.13	1.00	0.75	0.95
	r^2	0.9906	0.9929	0.9975	0.9968	0.9867	0.9786	0.9916	0.9977
	SSR	49.84	28.61	11.29	12.17	86.33	108.51	3.19	1.02

Table 7: Parameters, correlation coefficient, and SSR for different extreme value distributions – Weibull, Gumbel, and GEV

Distribution	Parameters	Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
Weibull $Q_t = 1 - \exp\left(-\frac{t^{bW}}{aW}\right)$	a_W (scale)	2.52	4.31	2.57	3.13	3.55	3.86	7.07	10.94
	b_W (shape)	0.68	0.76	0.63	0.63	0.84	0.77	0.65	0.84
	r^2	0.9811	0.9895	0.9925	0.9909	0.9727	0.9642	0.9948	0.9982
	SSR	100.53	42.39	33.18	34.79	177.45	181.56	1.98	0.79
Gumbel $Q_t = \exp\left[-\exp\left(\frac{c_G - t}{b_G}\right)\right]$	b_G (shape)	3.19	4.04	3.60	4.16	2.99	3.65	7.48	6.60
	c_G (location)	1.46	2.85	1.50	2.16	2.08	2.47	5.68	6.28
	r^2	0.9045	0.9328	0.9184	0.9091	0.9062	0.8765	0.9882	0.9775
	SSR	507.64	272.44	361.66	345.69	610.36	626.29	4.47	9.94
GEV $Q_t = \exp\left[-\left(1 + \frac{b_{GEV}t}{a_{GEV}}\right)^{-1/b_{GEV}}\right]$	a_{GEV} (scale)	7.06	–10.21	8.52	16.11	10.96	17.73	–	–
	b_{GEV} (shape)	–0.62	9.79	–0.90	–2.26	–1.42	–2.53	–	–
	r^2	0.7001	0.2156	0.7170	0.5355	0.5260	0.3908	–	–
	SSR	1593.7	3178.8	1255.0	1766.3	3085.4	3091.2	–	–

taking samples more frequently in the initial stage when the release rate is very high. After each sampling, 1 ml of pH 6.8 phosphate buffer was added to maintain a fixed volume of receptor fluid. The samples were analyzed by UV spectrophotometry at 276 nm against fresh receptor fluid as blank.

3.6. Kinetic analysis of in vitro release profile

Diclofenac potassium release from the gels was studied using various mathematical models. These models were applied taking into account the amount of drug released from 15 min to 6 h at the various intervals specified in the *in vitro* release study. Model-independent methods (difference factor f_1 and similarity factor f_2) were not used as they do not consider the correlation or variability of the data and the method is sensitive to the number of data points. ANOVA based methods also have shortcomings, especially ignoring correlation between the time points (Koester et al. 2004).

The models used for mathematical analysis in this paper can be broadly classified into two major categories, *empirical/semi-empirical models* and *statistical models*. The first category includes zero-order linear equation, first-order exponential form, Higuchi's square root of time equation, Ritger-Peppas' power law equation, and Peppas-Sahlin's weighted sum of non-linear time function, whereas the statistical models considered in the present paper are logistics, log-logistics, Weibull, Gumbel, and generalized extreme value (GEV) distribution. The mathematical expressions for the empirical/semi-empirical models are as follows:

$$\text{zero-order model}: \; Q_t = K_0 t + C_0 \tag{1}$$

$$\text{first-order model}: \; Q_t = Q_0 \exp\left(-K_f t\right) \tag{2}$$

$$\text{Higuchi model}: \; Q_t = K_H \sqrt{t} + C_H \tag{3}$$

$$\text{Ritger-Peppas model}: \; Q_t = K_{RP} t^n \tag{4}$$

$$\text{Peppas-Sahlin model}: \; Q_t = K_1 t^{0.45} + K_2 t^{0.90} \tag{5}$$

where Q_t is the cumulative percentage of drug released at time t, Q_0 is the initial amount of drug in the gel, K_0, K_f, K_H, K_{RP}, K_1, K_2 are release rate constants, and C_0, C_H are the respective intercepts with the vertical axis of the absorbance vs. time curve. While the first three models are empirical models, semi-empirical models like Ritger–Peppas and Peppas-Sahlin model were specifically used to explore the release mechanism and the fraction of drug released (due to diffusion) respectively. In the process of fitting the Ritger-Peppas model, we obtained a value for the release exponent n, which conveys information about the release mechanism (whether it is Fickian, non-Fickian, or case II transport). On the other hand, using the Peppas-Sahlin model, the fraction of drug release

$$F = \left[1 + (K_2/K_1)\, t^{0.45}\right]^{-1} \tag{6}$$

due to diffusion at a given instant of time t can be calculated from Eq. (6) if values of the parameters K_1 and K_2 are available.

After discussing the empirical/semi-empirical models and the knowledge about the release process that can be gained from them, we direct our attention to the statistical models. The basic idea of using statistical distribution in drug release modeling is to match the cumulative distribution function (CDF) of a particular distribution (Balakrishnan and Nelbzorov 2003) with the cumulative drug release; the underlying random variable (RV) being time t. The expressions for CDF in terms of the RV are summarized here:

$$\text{log istic distribution}: \; Q_t = \frac{1}{1 + \exp\left[-(t - c_L/a_L)\right]} \tag{7}$$

$$\text{log -logistic distribution}: \; Q_t = \frac{1}{1 + (t/a_{LL})^{-b_{LL}}} \tag{8}$$

$$\text{Weibull distribution}: \; Q_t = 1 - \exp\left(-t^{bW}/a_W\right) \tag{9}$$

$$\text{Gumbel distribution}: \; Q_t = \exp\left[-\exp\left((c_G - t)/b_G\right)\right] \tag{10}$$

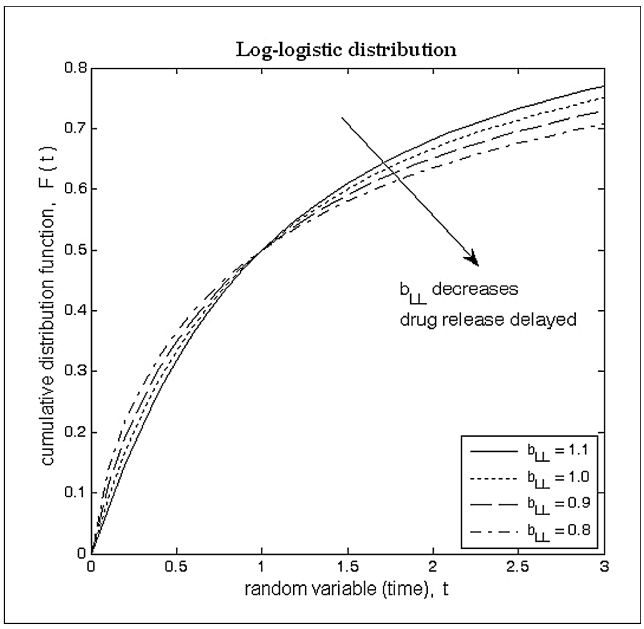
$$\text{GEV distribution}: \; Q_t = \exp\left[-(1 + t b_{GEV}/a_{GEV})^{-1/b_{GEV}}\right] \tag{11}$$

where, as usual, Q_t is the total amount of drug released up to time t. The parameters a, b, c denote scale, shape and location respectively while the subscripts L, LL, W, G, and GEV account for the particular distribution type. The logistic distribution is named after its CDF which is a logistic function. The S-shaped CDF pattern resembles the diffusion and subsequent substitution pattern of new technologies, products etc. and is widely accepted for modeling in many domains of market research. The log-logistic distribution (also known as the Fisk distribution) gives the probability distribution of a RV whose logarithm has a logistic distribution and is suitable for characterizing events whose rate initially increases and later decreases (Johnson et al. 1995). As the drug release profile is also S-shaped and the release rate is initially high but saturates later on, both of these distributions might prove useful for release modeling. It may be noted that logistic and log-logistic distributions are similar in shape to normal and log-normal distributions respectively, but have heavier tails, i.e. with higher kurtosis.

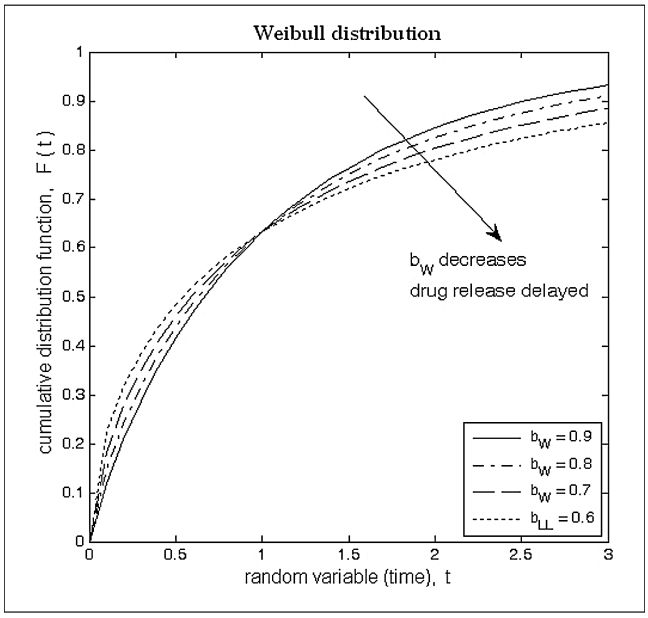
The other class of statistical distributions under study is that of extreme value distributions (Kotz and Nadarajah 2000; Evans et al. 2000) from which the Weibull, Gumbel, and GEV distributions are considered in this paper. Actually, data fitting with extreme value distributions was inspired by the success of one member of this class; the Weibull distribution, in modeling drug release. The claim may be substantiated by citing some previous work on HPMC where the researchers have shown that the Weibull model often emerges as one of the models giving the best fit. In addition, the shape parameter in Weibull models is important in describing the kinetic properties of the drug. The Gumbel distribution (also known as a log-Weibull distribution) gives the probability distribution of a RV whose logarithm has a Weibull distribution. It is also sometimes called the double-exponential distribution as the CDF contains an exponential of exponential function of the RV and it is useful when the sample data are of exponential type (Costa et al. 2003). Finally, the GEV or Fisher-Tippett distribution is a general purpose (it can be shown that both Weibull and Gumbel distributions are special cases of the GEV) extreme value distribution defined over the range $[-\infty, \infty]$. However, as time is a non-negative quantity, only positive values of the RV have been considered.

3.7. Computer programs

As stated in the introduction, comparison of goodness-of-fit for all empirical/semi-empirical and statistical models was carried out by fitting the models directly to the experimental data. From the accuracy point of



(a)



(b)

Fig. 2: Effect of shape parameter on the drug release rate with log-logistic (a) and Weibull (b) distribution

view, direct fitting is preferred to transformed linear fit methods. Although transformed linear fit methods are easier to handle, this advantage comes at the expense of truncation and transformation errors. Optimal parameters for every model were found through computer programs run on a Dell Latitude D820 laptop (1.83 GHz, 667 MHz FSB Core2Duo processor, 2MB L2 cache, 1GB DDR2RAM, and 7200RPM 60GB HDD) with the Windows XP operating system. The programs were executed in a MATLAB^{TM} v7.1 (a general purpose mathematical tool for simulation and modeling used in almost every branch of engineering) environment, and minimization of SSR was achieved by using a built-in MATLAB^{TM} function *lsqnonlin*(.). The function uses a trust-region-reflective algorithm (the Levenberg-Marquardt algorithm may also be used), solves nonlinear least-squares curve fitting problems of the form $\min_x \| f(x) \|_2^2$, and returns the minimum value $\bar{x}$ as well as the value of the squared 2-norm of the residual at $\bar{x}$. During the statistical model fitting procedure, experimental data, given as percentages, was normalized to a scale of [0, 1] by dividing the percentage of drug absorbed by 100. For empirical and semi-empirical models, no such scaling was necessary except for the first order model where Q_t actually denotes the amount of drug yet to be dissolved as given in (2), and thus 100- Q_t was used instead of Q_t.

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