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Investigation of the Effects of Cellulose Derivatives on the Kinetics of Drug Release from Cellulose-Based Hydrogel Using a Response Surface Method

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Abstract

The aim of this work was to investigate the effects of the nature and concentration of cellulose derivatives on the release kinetics of ibuprofen from hydrogel matrices using a response surface method (RSM). A series of cellulose derivatives, as methyl, hydroxyethyl, hydroxypropyl and hydroxypropyl methyl celluloses (MC, HEC, HPC and HPMC) were used as polymer platforms and their impacts on drug release were studied and compared to those obtained with a reference formulation prepared with HEC. It was shown that the use of HPMC in the gel formulation contributes to the improvement of drug release and consequently its biodisponibility. Indeed, the increase in HPMC concentration forms a controlled system release because polymer chains relaxation. The drug is released under the effects of two phenomena: diffusion and relaxation of polymeric chains. Thus, the kinetic release passes from the kinetics of case II towards Fickian diffusion.

Keywords: Cellulose derivatives, Hydrogel, Formulation, Release kinetics, RSM.

1 INTRODUCTION

Gels are semisolid networks containing two interpenetrating phases, a gelling agent and liquid. When the liquid is water, these systems are called hydrogels. Hydrogels have the particularity to absorb and release water solutions in a reversible manner (Robinson *et al*., 1993).

Among the polymers used to form hydrogels, polysaccharides of natural origin have interesting and original properties in comparison with synthetic polymers (Manjanna *et al*., 2010). In the last decade, cellulose ethers were used in many pharmaceutical formulations (Bajpai *et al*., 2008). Their use as matrices in the formulation of hydrogels has received an increasing attention because of their smart swelling behavior and biocompatibility (Hirsch and Spontak, 2002; Faroongsarng and Sukonrat, 2008; Sannino *et al*., 2009). Depending on the structure of the particular cellulose ether used, the drug release results from the complex combination of swelling, diffusion and erosion mechanisms.

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The most common cellulose ether derivatives include hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), methylcellulose (MC) and hydroxypropyl methylcellulose (HPMC). The chemical and physical characteristics of cellulose derivatives used in pharmaceutical applications have been described in relation to their use in sustained-release formulations (Chang *et al*., 2010). So, the use of HPMC in control drug release has been widely investigated (Salsa *et al*., 2003; Kiil and Dam-Johansen, 2003; Nakayama *et al*., 2009). However, little information discusses the drug-release processes from both MC and HPC (Sultana *et al*., 2006; Alvarez-Lorenzo *et al*., 2000; Marsano *et al*., 2003). It was suggested from the controlled release studies that HPMC encourages a strong, tight gel formation compared to other derivatives. As a result, drug-release rates have been sustained longer with HPMC than with equivalent levels of MC, HEC, or CMC. For these reasons, HPMC is considered as a polymer of choice over other cellulose ethers.

Feroro *et al*. (2008) have investigated the self-diffusion of water and other solvent, in hydrogels made of HPMC, HEC and HPC of varying polymer weight fraction and molecular weight. They found that the solute diffusivity is not significantly affected by the substitution type of the cellulose ether. The polymer matrix displayed the same retarding effect at equal weight fraction. Their results suggest that solute molecules can only diffuse in the void space occupied by the solvent.

Many models and mechanisms were proposed in the literature (Peppas *et al*., 1980; Siepmann and Peppas, 2001) in order to describe the drug release from delivery systems based on swellable cellulose derivatives.

The objective of this work was the evaluation of the effects of the nature and concentration of cellulose derivatives on the drug release kinetics. A hydrogel formulated with HEC and containing ibuprofen as drug was taken as reference. In this formulation, HEC was replaced by MC, HPC and HPMC respectively. For this purpose, response surface method (RSM) was employed in order to investigate the influences of individual factors and their interactions on the release kinetics of the formulated hydrogels.

2 MATERIAL AND METHODS

2.1 Materials

Four different water-soluble cellulose ethers polymers: hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), methylcellulose (MC), and hydroxypropyl methylcellulose (HPMC) were used as received from Hercules (USA). All other chemicals are of analytical or pharmaceutical grade and, were used without further purification.

2.2 Preparation of ibuprofen hydrogels

The gel components were put in a volume of water which supports the drug dissolution with the addition of sodium hydroxide solution, under vigorous agitation. After the addition of two alcohols quantities, the polymer powder was added gradually in the aqueous solution. The mixing of aqueous gel was maintained for 30 min. Thus, the prepared gel was left at rest during 24 hours at ambient temperature so that the macromolecules can adopt a stable arrangement in solution. Hydrogel formulations containing ibuprofen (5 % in wt.) were prepared according to the factor compositions listed in the design matrix.

2.3 Drug release from hydrogel matrix

In vitro drug release studies were realized by placing loaded sample in definite volume of releasing medium at 37°C, during 2 h. The amount of drug release was measured using a spectrophotometer at 235 nm (Thermospectronic scientific Helios UV–VIS spectrophotometer). The release kinetics mechanism was analyzed according to the equations of zero order (Eq. (1)), Higuchi (Eq. (2)), Korsmeyer *et al*. (Eq. (3)) and Peppas and Sahlin (Eq.(4)) (Higuchi, 1963; Korsmeyer *et al*., 1983; Peppas and Sahlin, 1989):

$$M_t/M_\infty = k_0 . t \quad (1)$$

$$M_t/M_\infty = k_h . t1^{/2} \quad (2)$$

$$M_t/M_\infty = k_p . t\, n \quad (3)$$

$$M_t/M_\infty = k_1 . t\, m + k_2 . t\, 2m \quad (4)$$

where M_t/M_∞ is the fraction of drug released; k_0, k_h and k_p are kinetic constants; *n* is a exponent which depends on the release mechanism and on the shape of swelling device. k_1 is the diffusional constant; k_2 is the relaxational constant and *m* is the diffusional exponent which depends on the geometrical shape of the releasing device through its aspect ratio.

2.4 Experimental design

Response surface method (RSM) and in particular a D-optimal design was applied to evaluate the influence of the nature and concentration of polymers on the gel properties. RSM is a statistical technique for designing experiments, building models, evaluating the effects of several factors, and searching optimum conditions for desirable responses (Myers and Montgomery, 2002).

The D-optimal method is relatively a new technique, related to response surface methodology, used for carrying out the design of experiments, the analysis of variance, and the empirical modelling. Plans with high D-value are constructed from the data by a computer algorithm.

The main effects of three independent factors (X1, X_2 and X_3) were investigated using a D-optimal design (Table 1). X1 and X_2 are quantitative factors and represent the polymer and water concentrations respectively. X_3 represents the polymer nature where the value (-1) is allowed to the low level and (+1) to the high level in the studied field. For HEC and HPC, X_1 varies between 5.0 and 6.0% (in wt.) and, X_2 varies between 73.5 and 74.5% (in wt.) However for MC and HPMC, X_1= varies between 3.0 and 4.0% (in wt.) and, X_2 varies between 75.5 and 76.5% (in wt.). These values were deduced from a preliminary study. For the responses, the constants of the Korsmeyer model (Kp and n) were selected for this study.

Table 1: Factors and their levels

Factor	Specification	Experimental Field	Unity
X_1	Polymer concentration	-1 to 1	% in wt.
X_2	Water concentration	-1 to 1	% in wt.
X_3	Polymer nature	HEC, HPC, MC, HPMC	

Experimental data were fitted to a second-order polynomial model and regression coefficients were obtained. The generalized second-order polynomial model used in the response (Y_i) surface analysis was as follows:

$$Y = a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_{11}X_1^2 + a_{22}X_2^2 + a_{33}X_3^2 + a_{12}X_1X_2 + a_{13}X_1X_3 + a_{23}X_2X_3 \quad (5)$$

Where a_0, a_i and a_{ij} are the regression coefficients, Y is the response and X_1, X_2 and X_3, the independent factors. The model of surface response corresponding to the D-optimal design takes into account all the principal retained factors and their interactions.

3 RESULTS AND DISCUSSION

3.1 Preliminary experiments

A reference gel based on HEC was characterized in terms of sustained release of drug. The release study on the HEC-based gel was realized by using the

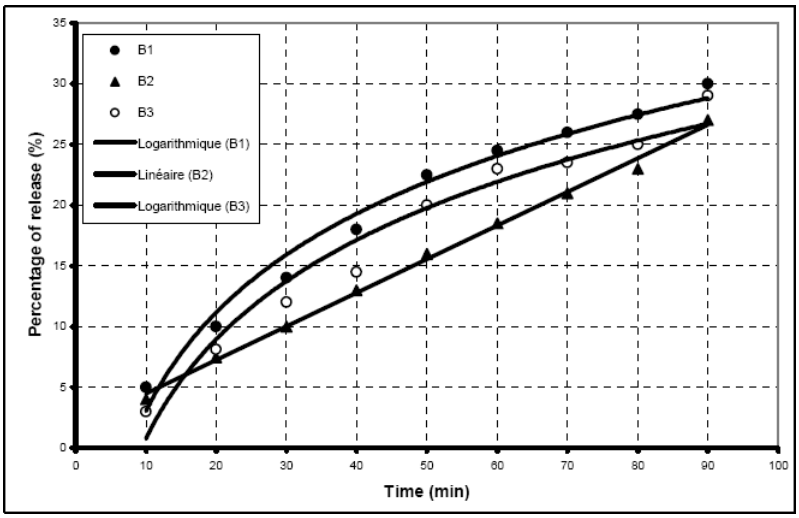

Figure 1: Percentage of drug release as a fuction of time of the reference formulation

dissolution test. This test makes it possible to obtain the profiles of dissolution which result in the quantity of drug released according to time (Figure 1).

From this figure, we can note that the percentage of drug release increases with the time to reach around 90 min a maximum value (around 27%). The same behavior is observed for two batches, however, for the third batch, there is an almost linear evolution. Nevertheless, it should be noted that the amount released after 90 min is the same for all three samples.

The rate of the release of drug (ibuprofen) according to time is presented in Figure 2**.**

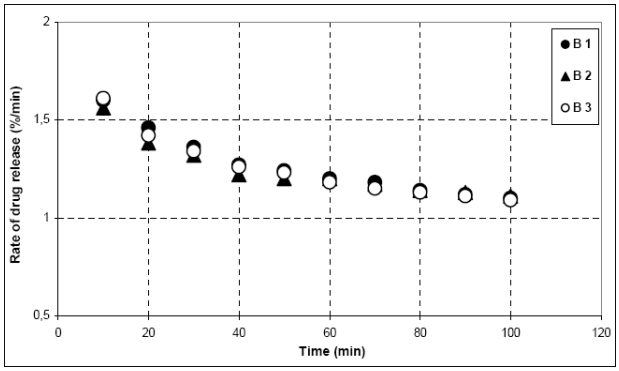

Figure 2: Rate of drug release versus time of the reference formulation

This rate was calculated by differentiating the function of the cumulative fraction versus time.

It appears from the presented curves, the existence of two quite distinct zones for the three studied batches (B1, B2 and B3). In the first, a release of 50% of drug is obtained in the first 30 min. The second zone corresponds to a decrease in the rate of release. Indeed, at the end of 90 min, the drug release reaches a constant value corresponding to a maximum release. This observed behavior can be explained as follows: during the drug absorption by diffusion, through the skin, its capacity of penetration is very fast at the beginning, then the diffuse layers saturate in relation to the diffusion coefficient of ibuprofen through the transdermic walls, that slowed down the diffusion of the drug and thus the release from the gel. This is characterized by the first zone of dissolution where a rapid drug release is observed, then a second zone where a deceleration of drug release is observed corresponding to its saturation at the surface and thus the rate tends to a constant value. The same results were observed by Langer and Peppas (Langer and Peppas, 1981). They postulate that for the second zone, the gel reached its rate of maximum swelling, a deceleration of drug release is observed at the time of its saturation.

These observed behaviours were fitted in mathematical models describing the release kinetics. The models retained for this study are of Korsmeyer and of Peppas and Sahlin respectively. The first model which is a general model, where the constant of dissolution (kp) as well as the diffusion exponent (n) give information about the phenomenon which prevails at the time of dissolution. The second model (Peppas and Sahlin) expresses the competitive relation which exists between the diffusion and the relaxation of the polymer chains forming the gel matrix.

Each model is applied to the whole of the experimental results translating the cumulated percentage of drug contained in the reference product, dissolved according to time. The calculation of the characteristic parameters of the various models was obtained by mathematical adjustment. The mathematical models were applied with the assumption that the cumulated percentage of drug is 100%. The results of this statistical analysis are represented in Table 2.

A first selection of the suitable model was carried out by taking into account the coefficient of adjustment (the highest). Basing on this criterion, the exploitation of the Korsmeyer model was retained in order to determine the phenomena well appearing during the drug dissolution.

The characterization of the reference product made it possible to have a data of the release kinetics parameters. These basic characteristic data will be exploited for the realization of the generic gels formulated with cellulose derivatives.

Table 2: Coefficients adjusting the parameters of different models of dissolution

A.	Model	Parameter	Average value
B.	Peppas and Sahlin	K_1	2.80
C.		K_2	3.72
D.		R^2	0.95
E.	Korsmeyer *et al*.	K_p	4.44
F.		N	0.76
G.		R^2	0.97

Several formulations were prepared by replacing HEC in the reference formulation by other cellulose derivatives (HPC, MC, HPMC) as shown in Table 1.

The polymer concentrations were selected in order to obtain similar formulations to the prepared one with HEC.

3.2 D-OPTIMAL EXPERIMENTS

3.2.1 Statistical analysis

The arrangements of D-optimal experiments are listed in Table 3, which include 23 sets of experiments. The tests will be performed in a random order (randomized) and within a goal of reducing systematic errors that could suffer the response measurements.

By using multiple regression analysis, the responses Y_1 (K_p) and Y_2 (n) were correlated with the three design factors using the second-order polynomial (Eq. 5). The quadratic regression models are given by Eq. 6 and Eq. 7 respectively:

$$\begin{aligned} Y_1 = {} & 4.240 + 0.308\,X_1 - 0.049\,X_2 - 1.256\,X_3(\text{HEC}) \\ & + 2.266\,X_3(\text{HPC}) - 0.820\,X_3(\text{MC}) - 0.188\,X_3(\text{HPMC}) \\ & - 0.234\,X_1^2 - 0.149\,X_2^2 + 0.029\,X_1X_2 + 0.137\,X_1X_3(\text{HEC}) \\ & + 0.039\,X_1X_3(\text{HPC}) - 0.623\,X_1X_3(\text{MC}) + 0.447\,X_1X_3(\text{HPMC}) \\ & + 0.044\,X_2X_3(\text{HEC}) - 0.178\,X_2X_3(\text{HPC}) + 0.065\,X_2X_3(\text{MC}) \\ & + 0.069\,X_2X_3(\text{HPMC}) \end{aligned} \quad (6)$$

Table 3: Experimental matrix

Run	X1	X2	X3	Y1 (Kp)	Y2 (n)
1	-1	-1	HEC	2.01	0.89
2	1	-1	HEC	3.02	0.72
3	-1	1	HEC	2.12	0.88
4	1	1	HEC	2.89	0.78
5	-1	-1	HPC	6.07	0.71
6	1	-1	HPC	6.45	0.78
7	-1	1	HPC	5.30	0.80
8	1	1	HPC	6.31	0.75
9	-1	-1	MC	3.30	0.60
10	1	-1	MC	2.60	0.81
11	-1	1	MC	3.35	0.57
12	-1	0	MC	3.32	0.59
13	1	0	MC	2.80	0.79
14	0	-1	MC	3.25	0.61
15	0	1	MC	3.22	0.64
16	-1	-1	HPMC	2.80	0.62
17	1	-1	HPMC	4.28	0.92
18	-1	1	HPMC	2.81	0.63
19	1	1	HPMC	4.35	0.89
20	0	0	HPMC	4.13	0.82
21	0	0	HPMC	4.02	0.79
22	0	0	HPMC	4.12	0.81
23	0	0	HPMC	4.01	0.79

$$Y_2 = 0.774 + 0.0435\ X_1 + 0.027\ X_2 + 0.638\ X_3(\text{HEC}) + 0.0064\ X_3(\text{HPC}) - 0.0899\ X_3(\text{MC}) + 0.0196\ X_3(\text{HPMC}) + 0.0220\ X_1^2 - 0.0429\ X_2^2 - 0.0080\ X_1X_2 - 0.1110\ X_1X_3(\text{HEC}) - 0.0385\ X_1X_3(\text{HPC}) + 0.0532\ X_1X_3(\text{MC}) + 0.0964\ X_1X_3(\text{HPMC}) + 0.0097\ X_2X_3(\text{HEC}) + 0.0122\ X_2X_3(\text{HPC}) - 0.0142\ X_2X_3(\text{MC}) - 0.0077\ X_2X_3(\text{HPMC}) \quad (7)$$

The quality of these models and their power of prediction, are related to the variance coefficient. The good correlations between the measured values and those predicted by the model (Figure 3 and Figure 4) confirm the qualities of these models.

In addition, the two models give high values of R^2 ($R^2 = 0.996$ for Y_1 and $R^2 = 0.960$ for Y_2). These values confirm that the equations of the models are highly reliable. This indicates also that the model terms are significant. The models are also reproducible.

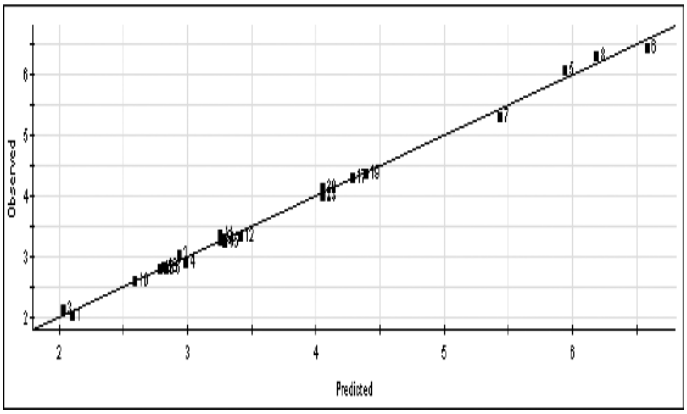

Figure 3: Relation between experimental and predicted values of the coefficient, Kp

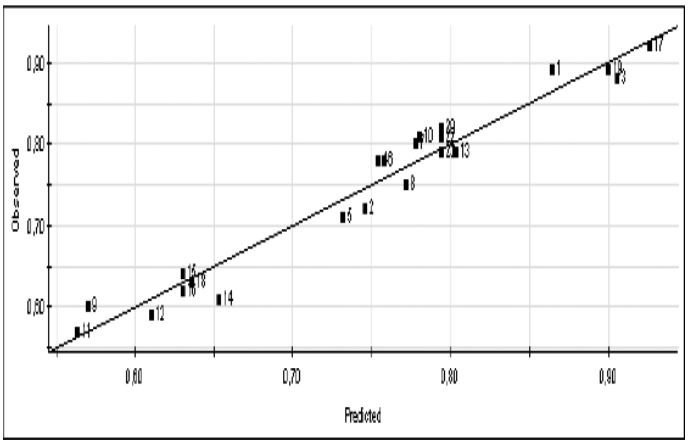

Figure 4: Relation between experimental and predicted values of the release exponent, n

The statistical significance of the ratio of mean square variation due to regression and mean square residual error was tested using the analysis of variance (ANOVA). The ANOVA of these responses demonstrated that the model is highly significant as is evident from the value of $F_{statistic}$ (the ratio of mean square due to regression to mean square to real error), (F_{model} = 143.689 for Y_1 and F_{model} = 13.642 for Y_2) and very low probability values (P = 0.001). The low values of probability indicate that the models are considered statistically significant.

3.2.2 Effects of factors on the drug release kinetics

The mechanism of drug release from matrices containing swellable polymers is complex. Some systems may be classified as either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms (Siepmann and Peppas, 2001). In addition, the absence of interactions between polymers and drugs in the mechanism of release from such systems has been confirmed. Madgulkar *et al*. (2009) have studied the presence of interactions between drug (miconazole) and excipients with help of IR. Their results confirm the absence of interactions between drug and the used polymers.

The kinetics of ibuprofen release from the various hydrophilic matrices was analyzed using the Korsmeyer equation (Eq. 3), where k is the apparent release rate constant that incorporates the structural and geometric characteristics of the drug delivery system and n is the diffusional exponent which characterizes the transport mechanism of the drug. The transport mechanisms were classified based on the value that n assumes. For thin slabs, values of $n = 0.5$ indicate Fickian release, values of $0.5<n<0.9$ indicate an anomalous (non-Fickian or coupled diffusion/relaxation) drug release, whereas values of $n = 1.0$ indicate a case II (relaxation-erosion controlled) drug release (Peppas and Sahlin, 1989).

Fig.5 shows the effects of water and polymer concentration on the apparent release constant Kp of gels formulated with HEC (Fig.5-a), HPC (Fig.5-b), MC (Fig.5-c) and HPMC (Fig.5-d) respectively. In the case of HEC and HPC, it was noticed that the constant Kp increases with the increase in the polymer concentration. Water seems to have a negligible effect compared to that of polymer. The effect of polymer becomes significant when the concentration is higher than 5.5 (% in wt). In the case of HEC, an optimal field is obtained for a concentration varying between 5.5 and 6.0 % (in wt.). K_p reaches a maximum value of about 3.13 (%/min) for HEC and an optimal value of 6.63 (%/min) for HPC. It seems that HPC which has a higher molecular weight improves the structure of gel. The rate of drug release from HPC matrix is almost the double of that obtained with HEC matrix.

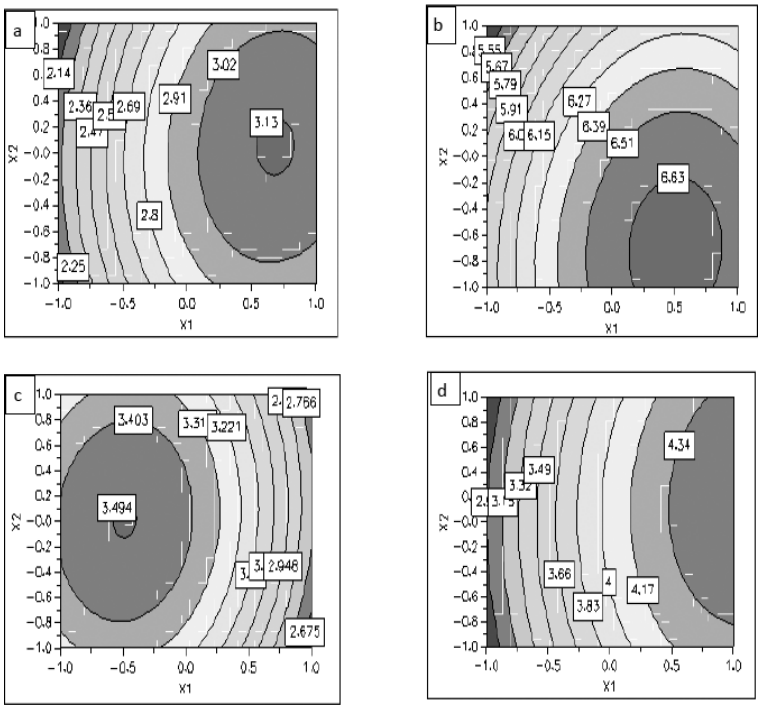

Figure 5: Factors effects on Kp : a) HEC; b) HPC, c) MC, d) HPMC

In the case of MC, an optimal field of release is obtained for the concentration values varying between 3.0 and 3.5 (% in wt.), whereas for HPMC, the optimal field is obtained for polymer concentration values higher than 3.75 (% in wt.). With regard to the matrices based on HPMC, the constant Kp increases with the increase in polymer concentration. This observation was in accordance with previous studies that have underscored the importance of such swellable polymers and their concentrations on the release of drug from the matrix tablets (Wan *et al*., 1993). Matrices that contained MC and HPMC released the drug by Fikian diffusion.

Figure 6 shows the effect of the studied factors on the release exponent (n) of the Korsmeyer model. The value of n indicates the nature of the diffusion which governs the drug release from the polymer matrices. In the case of HEC, the increase in polymer leads to the reduction in the value of n which passes from 0.92 to 0.78, but while keeping the same type of anomalous diffusion where there are two phenomena which contribute to the drug release: diffusion and relieving of the polymeric chains. On the other hand in the case of HPC polymer, an increase in the concentration of this polymer leads to an increase in n.

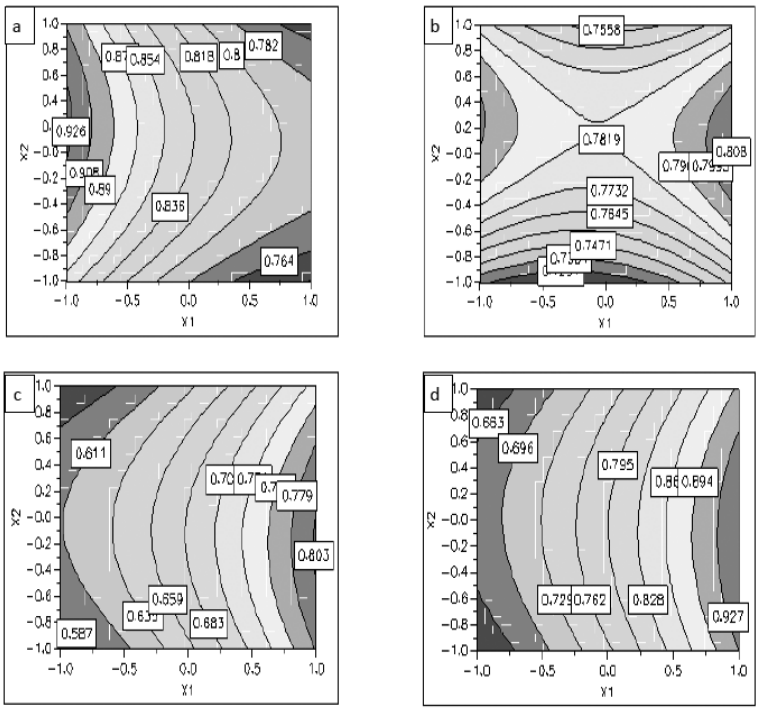

Figure 6: Effects of factors on release exponent: a) HEC; b) HPC; c) MC; d) HPMC

This increase shows the passage of Fickian diffusion towards the appearance of a second phenomenon which is the relieving of the polymeric chains. Roy and Rohera (2002) also observed that the drug release rate from HEC matrices was higher compared to the release rate from HPC matrices due to relatively higher hydrophilicity of HEC. However, the use of MC and HPMC implies an opposite phenomenon. The increase in the concentration of these polymers leads to an increase in n; it passes from 0.61 to 0.80 for MC and from 0.66 to 0.92 for HPMC respectively. In the two cases, the drug release through the polymeric matrix passes from kinetics of case II, towards a Fickian diffusion.

4 CONCLUSION

The values of the kinetic constant k were in accordance with those of n, the diffusional exponent, with k having lower values when the transport mechanism was Case II and higher values for formulations that released the drug by Fickian diffusion. The Korsmeyer model gave a good fit to most of the dissolution data of the swellable matrices.

The polar character of investigated polymers depends on the nature of the substituent present and the degree of substitution. The hydrophilicity of cellulose ethers increases with a decrease in an alkyl chain length. Thus, it is not surprising that HEC exhibited a considerable higher polarity as compared to HPMC, MC and HPC. The presence of small substituent groups in the structure of HEC is responsible for interaction with water and faster disentanglement threshold of polymer chains and form network for water uptake.

From the deduced results, it is clear that HPMC is proving to be the best polymer. It offers the best factors of gel formulation with a minimum concentration for better bioavailability of the drug in the diffusion and transport case II, present simultaneously in the gel. This fact clearly demonstrates the interest of copolymerization.

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