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EVALUATION OF HYDROXYPROPYLMETHYLCELLULOSE (HPMC) HYDROGEL MATRIX FOR DELIVERY OF TRIAMCINOLONE

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ABSTRACT: The main purpose of this study was to evaluate hydrogel matrix systems of hydroxypropylmethylcellulose (HPMC) for oral release of poorly water-soluble drugs, by using triamcinolone (TR) as drug model. The influence of HPMC ratio (%) and compaction force (Kgf) on system performance were studied. Thus, several batches of tablets containing 10 mg of TR were prepared using distinct proportions of HPMC (30, 50 and 60 %; w/w), and characterized by: dimensions, weight, hardness, friability, disintegration time, swelling and dissolution. Regarding the dissolution profiles, several mathematical models were tested and the experimental data were fitted to a zero-order release. Additionally, the correlation between the swelling kinetics and the drug dissolution rate was established, suggesting the importance of the dependency of drug release from the swelling profile for all tested systems. However, there were not improvements for the system containing HPMC ratio higher than 30 % (w/w). To conclude, for the comparative evaluation of the system's properties, the best technological conditions achieved were for the matrix produced under 7.5 kgf and using 30% HPMC.

INTRODUCTION: Hydrogel matrix systems consist of a molecular or particle dispersion of drugs into a hydrophilic swelling polymer, which is resistant to disintegration [1-3].

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This system is an interesting alternative to develop oral modified-release drug delivery systems, since it has specific advantages such as versatility, efficiency, low cost and production involving conventional solid pharmaceutical dosage forms [1].

Hydroxypropylmethylcellulose (HPMC) is a cellulose ether and one of the most common hydrophilic carriers for the preparation of oral controlled drug delivery systems, due to its swelling ability when in contact with water or biological fluid and its consequent polymer chain

relaxation and volume expansion allowing the drug diffusion through polymeric barrier [4-8]. Three main steps can be related to drug release from hydrogel matrices, these are i) swelling with drug diffusion in gel region, ii) polymer erosion with drug dissolution and diffusion from solid region and, finally, iii) drug dissolution in solid region with diffusion through swelled polymeric barrier. In all the steps the polymer swelling is involved with drug release, which may be controlled using different formulation parameters, such as hydrogel polymer concentration [9-11].

Thus, the swelling kinetics is directly correlated with the drug dissolution and diffusion of hydrogel polymeric systems [4, 5, 12], which may support relevant information to establish predicting models that could consider the involvement of formulation parameters in the drug release rate [13]. A large number of factors, including the physicochemical properties of the drug and polymeric barrier, as well as the drug/hydrogel polymer/excipients ratios and manufacturing parameters can drastically influence the drug release behavior [14]. Therefore, the establishments of accurate models to predict the physic-chemical phenomena that manage the drug delivery from such matrices remain a significant challenge [4, 5].

Thus, the purpose of this study was to formulate and evaluate HPMC matrices containing triamcinolone, in order to investigate the matrix behavior and drug release profile.

MATERIALS AND METHODS:

Materials

Hydroxypropylmethylcellulose Methocel K100 LV PR USP, lot IF10803 was donated by COLORCON®, Brazil. Triamcinolone was purchased from GALENA®, Brazil. Microcrystalline cellulose (M101, lot NR71271) and magnesium stearate (lot NR808022) were purchased from MINGTAI® and INBRA®, Brazil respectively.

Production procedure and evaluation of HPMC matrices

Different components for distinct formulations described in **Table 1** were mixed for 10 minutes. Subsequently the lubricant was added and mixed for another five minutes. After this, formulations were compressed in a single stage, using a 9-mm-diameter die rotary machine with 10 sets of punches (Lawes®, Model 2000-10 PSO). The average weight of the tablets was adjusted for 250 mg and different hardnesses (5.0, 7.5 and 10.0 kgf) were tested for each formulation. All experiments were conducted in triplicate. After preparing procedure, all formulations were stored overnight in dark hermetically closed flasks in desiccators before quality control assays. The tablets containing triamcinolone were prepared only for 7.5 kgf hardness.

TABLE 1. COMPOSITION OF DIFFERENT HPMC MATRICES.

Components	Formulation		
	F1	F3	F4
Hydroxypropylmethylcellulose (%)	30	50	60
Microcrystalline Cellulose (%)	69.5	49.5	39.5
Magnesium Stearate (%)	0.5	0.5	0.5
Triamcinolone (mg)*	10	10	10

*Prepared only for hardness at 7.5kgf

Physical characteristics: Tablet dimensions, average weight, hardness, friability and disintegration time

The height and diameter of the tablets were determined using a digital caliper (Digimess®, Model 100.174BL) to measure 20 tablets. The average weight was determined according to parameters established by the United States Pharmacopoeia [17].

The hardness was determined using a hardness tester (Nova Ética, Model 298-AT) to analyze 20 tablets. Friability was determined according to USP by submitting 20 previously weighed tablets to falling shocks for five minutes in a friabilator (Nova Etica, Model 300), set at 25 rpm [17]Afterwards, tablets were reweighed and the friability percentage was calculated.

The disintegration test was performed according to parameters established by the United States Pharmacopoeia [15] for immediate release tablets, using a disintegrator (Nova Etica, Model 301 – AC).

Drug content

Analytical drug content in different HPMC hydrogel matrices was assessed by a previously validated spectrophometry methodology [16]. Thus,

twenty tablets were pulverized in a mortar and a sufficient amount of powder was dissolved in aqueous solution of ethanol 10 % (v/v) and diluted in purified water to obtain a triamcinolone concentration of 10 µg ml^{-1}, which was analyzed at 240 nm.

The drug concentration was calculated using the straight line equation from the standard curve of the fitted plot. The analyses were performed in triplicate and the drug percentage was calculated from the ratio between the analytical and theoretical drug contents.

Swelling Studies

Tablet swelling tests were performed in purified water (osmosis purification system, mod. OS50 LX, Gehaka, Brazil) at 37.0 °C ± 0.2 °C in thermostatized bath, in which each tablet was placed in a steel basket.

The HPMC hydrogel systems were weighed at intervals (0.5, 1.0, 2.0, and 4.0, 6.0 and 8.0 hours) and the swelling index (%SI) was calculated using the equations 1 and 2 [17]:

$$SI = \frac{W_2 - W_1}{W_2} \cdot 100 \qquad \text{(Eq. 1)}$$

Where W_1 is the dried tablet weight and W_2 is the tablet weight after immersion in water. This experiment was conducted in triplicate and expressed as means ± SD.

Dissolution studies

The drug dissolution study of different HPMC hydrogel matrix systems was performed in a dissolution instrument (Mod. ATTS 299, Nova Ética) using HCl 0,01N as dissolution medium at 37 °C ± 0.2 °C [15] with apparatus II at 100 rpm. Sample volumes of 2.0mL were collected at 30, 60, 90, 120, 150, 180, 240, 300, 360, 420, 480 minutes and the triamcinolone released content was determined by spectrophotometry at 242 nm using a previously validated methodology [18].

Regarding the dissolution profiles for the systems, the drug release data were fitted to common release kinetic models and described in **Table 2.**

TABLE 2. MATHEMATIC MODELS USED TO EVALUATE THE DRUG DISSOLUTION [19, 20].

Model	Equation
Zero-order	$f_i = k_0 \cdot t$
First-order	$\ln Q = \ln Q_0 - k_1 \cdot t$
Higushi	$f_1 = k_H \cdot t^{0,5}$
Weibull	$\log[-\log(1-m)] = b \cdot \log(t - T_i) - \log a$
Kosmeyer -Peppas	$\frac{Mt}{M\infty} = kt^n$

Experimental data were evaluated for dissolution efficiency (DE %) (equation 4), similarity (*f1*) and difference factors (*f2*) (equations 2 and 3, respectively).

$$f1 = \left\{ \left[\sum_{i=1}^{P} |R - T| \right] / \left[\sum_{i=1}^{P} R \right] \right\} \cdot 100 \qquad \text{(Eq. 2)}$$

$$f2 = 50 \log \left\{ \left[1 + \left(\frac{1}{P} \right) \sum_{i=1}^{P} (R - T)^2 \right]^{-1/2} \cdot 100 \right\} \qquad \text{(Eq. 3)}$$

$$DE = \frac{ASC_{(o-t)}}{ASC_{TR}} \cdot 100\% \qquad \text{(Eq. 4)}$$

RESULTS AND DISCUSSION:

Preparing and characterizing HPMC hydrogel matrices

The use of hydrogel polymers in modified drug delivery system development occurs due to its ability to permit drug release simultaneously with elastic transition of polymeric chains after hydration. This phenomenon depends on manufacturing parameters, nucleus structure (reservoir or matrix system) and formulation parameters such as hydrogel type and its ratio in the tablets. In this study, the manufacturing parameters were established and the influence of HPMC/microcrystalline cellulose ratio on matrix swelling and triamcinolone release were studied.

The matrices were obtained by direct compression at three compression force levels to produce tablets which had hardnesses of 5, 7.5 and 15 kgf, respectively. All formulations and manufacturing conditions provide suitable tablets with low

friability (< 1%) and they do not disintegrate **(Table 3).**

Swelling curves for different HPMC matrices obtained at each hardness level are presented in **Figure 1**. Only slight differences could be observed in the swelling profiles for the different HPMC ratios. In fact, the increment of the HPMC ratio did not lead to a noticeable enhancement of tablet volume expansion. On the other hand, a clear change in the swelling profile among the hardness levels was observed. The matrices subjected to lower compression force (hardness = 5 kgf) showed a faster swelling rate, achieving the maximum volume (about 150 %) after one hour and was followed by a slower phase until six hours after the experiment began. Regarding the other systems (hardness of 7.5 and 15 kgf), the maximum expansion volume occurred after two hours followed by slow hydration, until six hours.

Overall, the data suggest that the relationship between swelling behavior and densification degree of each system plays an important role. In this sense, tablets with lower hardness present higher porosity and thus lower resistance against water penetration. If this fact is taken into account, it can be expected that the relaxed structure of such tablets is followed by polymer disentanglement. This phenomenon provides the water exchange in the diffusion layer around the surface of the system, decreasing the hydrostatic pressure in the tablet core and reducing the ability of system expansion. Subsequently, the swelling is more intense in the initial phase, in which a rapid core hydration occurs with a stabilization of matrix volume.

Regarding the higher density tablets, the decrease in the porosity improves the core resistance to water permeation, and consequently slows down the swelling velocity. However, the densification degree of tablets provides a greater ability for volume expansion and better swelling response, which could be observed for harder tablets (7.5 and 10 kgf). On the other hand, the swelling data suggest that the higher densification degree of harder tablets (10 kgf) reduces their swelling ability. In fact, this behavior can be attributed to the resistance to water uptake due to the degree provided by the compaction force. Thus, when comparing tablets manufactured under compaction force to produce a hardness of 7.5 and 10 kgf, the second showed a deleterious effect on expansion abilities from such matrices.

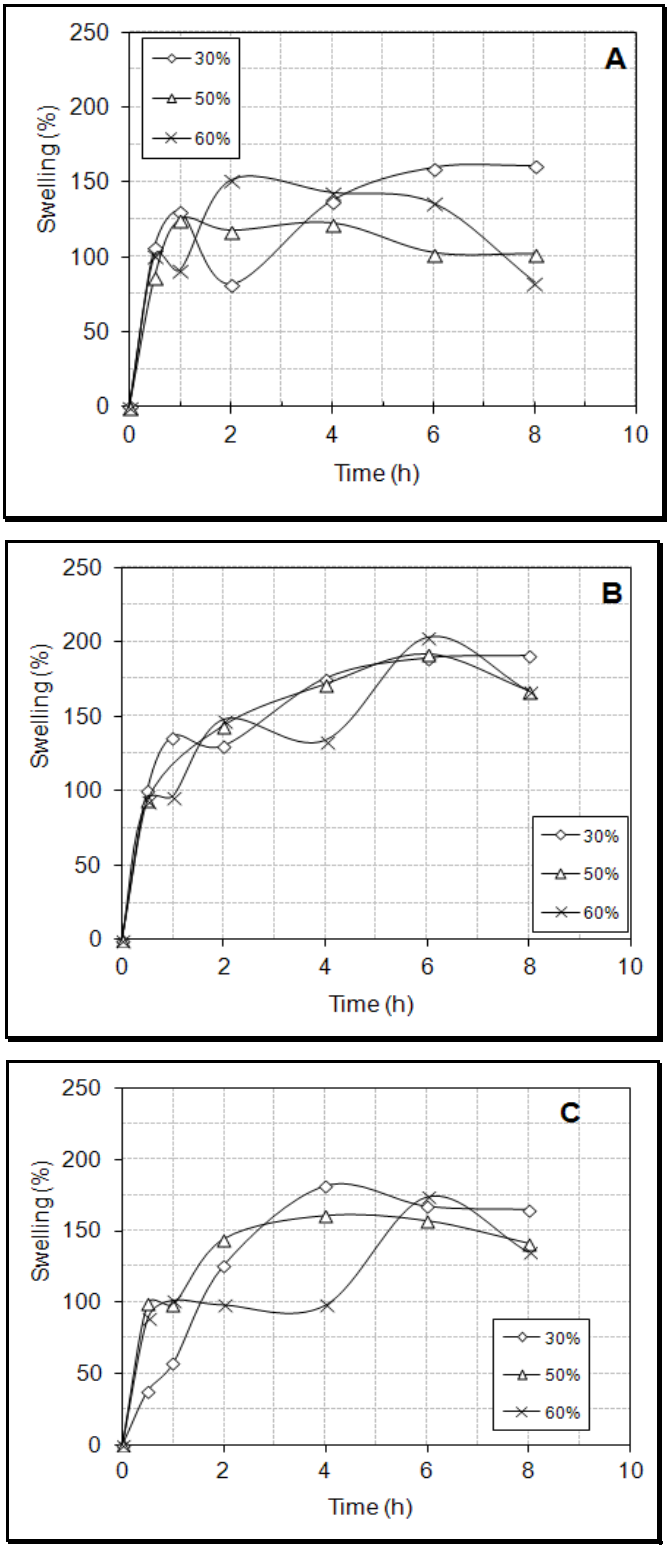


FIGURE 1. SWELLING CURVES OF HPMC MATRICES IN ACCORDANCE TO THEIR HARDNESS: 5 (A), 7.5 (B) AND 10 kgf (C).

TABLE 3. PHYSICOCHEMICAL PROPERTIES OF MATRICES.

Formulation	H (kgf)	AW (mg)	Friability (%)	height (mm)	diameter (mm)	DT
HPMC 30%						
5.0 kgf	4.69 ± 0.21	231.9 ± 4.7	0.129	4.72 ± 0.01	8.93 ± 0.01	not disintegrated
7.5 kgf	7.16 ± 0.81	231.8 ± 3.1	0.042	4.37 ± 0.01	8.99 ± 0.01	not disintegrated
10 kgf	10.61 ± 0.59	232.3 ± 3.5	0.021	4.12 ± 0.02	8.89 ± 0.01	not disintegrated
HPMC 50%						
5.0 kgf	5.33 ± 0.59	233.5 ± 3.0	0.022	4.67 ± 0.06	8.96 ± 0.04	not disintegrated
7.5 kgf	7.07 ± 0.60	232.6 ± 2.5	0.110	4.45 ± 0.03	8.97 ± 0.01	not disintegrated
10 kgf	9.35 ± 0.94	232.2 ± 2.2	0.065	4.25 ± 0.02	8.97 ± 0.01	not disintegrated
HPMC 60%						
5.0 kgf	5.43 ± 0.49	232.4 ± 1.4	0.087	4.67 ± 0.01	8.97 ± 0.02	not disintegrated
7.5 kgf	7.01 ± 0.25	231.9 ± 1.6	0.021	4.52 ± 0.01	8.97 ± 0.02	not disintegrated
10 kgf	10.79 ± 0.79	231.7 ± 3.0	0.514	4.15 ± 0.02	8.98 ± 0.01	not disintegrated

H = hardness; AW = average weight; DT = disintegration test.

Nevertheless, tablets with a hardness of 7.5 kgf **(Figure 1 B)** showed a homogeneous swelling profile and an important expansion of volume. On basis of this result, a new batch of such matrices was produced and characterized **(Table 2).**

TABLE 2. PHYSICOCHEMICAL PARAMETERS OF MATRICES OBTAINED AT HARDNESS OF 7.5 kgf.

Formulations	H (kgf)	AW (mg)	F(%)	h (mm)	d (mm)	D (%)
HPMC30T	6.71±0.39	244.07±6.36	0.030	4.55±0.02	8.98±0.01	97.09
HPMC50T	7.06±0.61	253.10±4.44	0.067	4.89±0.01	8.98±0.01	100.55
HPMC60T	6.98±0.54	251.69±4.57	0.102	4.90±0.02	8.98±0.01	90.68

H = hardness; AW = average weight; F = friability; h = height; d = diameter; D= drug content

Regarding the physicochemical evaluation of the systems, the tablets were in accordance of the pharmacopoeial specifications for modified release dosage forms. Additionally, the Triamcinolone-loaded matrices maintained their integrity during the disintegration test, ensuring essential properties for an extended drug release system.

Dissolution studies

The *in -vitro* dissolution study was performed using apparatus type II USP XXXII for all triamcinolone-load HPMC matrices prepared at hardness of 7.5 kgf. The release curves are presented in **Figure 2.**

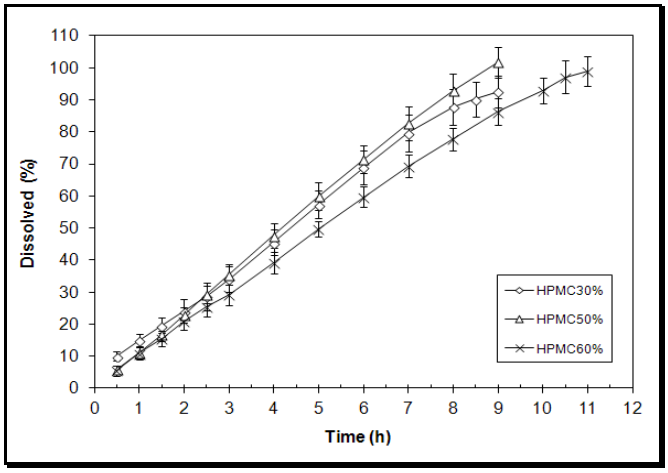


FIGURE 2. *IN-VITRO* RELEASE CURVES FOR TRIAMCINOLONE-LOADED HPMC MATRICES.

The evaluation of release profiles showing a slight burst effect was observed in the matrix containing 30 % of HPMC. After that, with regard to other systems, the drug release takes place after polymer hydration and swelling. Overall, the data suggest that drug release was not affected by the content of HPMC. Thus, the increase in the polymer concentration provides the drug release reduction by slower polymer swelling and/or diffusion barrier.

Since the data obtained from dissolution curves showed similar profiles, the drug releases were also evaluated by the fit factors (f1 and f2) and dissolution efficiency (DE%). The DE% is useful when comparing drug dissolution profiles of different formulations or pharmaceutical dosage forms obtained from different manufacturers [20, 21, 23].

The statistical analysis of these DE % values guarantees a careful interpretation of experimental data in different drug dissolution profile comparisons [23]. The experimental data of DE% of all formulations are presented in **Table 3**. The results showed that the dissolution efficiency of matrix containing 30% of HPMC was significantly higher than the other formulations. In fact, the

lower polymeric concentration can explain such behavior, including the burst effect [21].

Thus, a comparison of averages was executed despite having an acceptable variability for the DE% mean, which showed no significant difference for matrix prepared with 50 or 60 % HPMC. The following DE% was observed for different systems: HPMC30T > HPMC50T = HPMC60T

TABLE 3. DISSOLUTION EFFICIENCY (DE) AND RESPECTIVE CONFIDENCE INTERVALS (95%) FOR THE TRIAMCINOLONE-LOADED MATRICES.

	DE %	
Formulations	**x ± SD (RSD%)**	**Confidence intervals**
HPMC30T	55.02 ± 0.74 (1.35)	54.25 – 55.80
HPMC50T	49.80 ± 1.27 (2.55)	48.47 – 51.14
HPMC60T	51.45 ± 1.95 (3.40)	49.40 – 53.50

$t_{critical\ (\alpha/2 = 0.025;\ df = 5)} = 2.57$

The comparison between drug dissolution profiles of different formulations is routinely performed using similarity (f1) and difference factors (f2) [22]. The experimental data used to evaluate these parameters are shown in **Table 4**. In this step of the study, the first system (HPMC30T) was considered as reference and, as recommended, the comparison of experimental data was performed for every point until 85 % of drug amount released. For other cases, systems were considered equivalent.

TABLE 4. SIMILARITY (f1) AND (f2) DIFFERENCE FACTORS IDENTIFIED AMONG DRUG DISSOLUTION PROFILES FOR DIFFERENT HPMC HYDROGEL MATRIX SYSTEMS.

Comparisons	$t_{experimental}$	***f1***	***f2***
HPMC30TxHPMC50T	12.93 (*p = 0.00003*)	5.80	76.28
HPMC30TxHPMC60T	4.53 (*p = 0.00309*)	13.50	59.45
HPMC50TxHPMC60T	-1.60 (*p = 0.08500*)	11.56	58.20

$t_{\ critical\ (0.05;\ 5.5)} = 2.015$

Besides using DE% and similarity or difference factors in comparative drug dissolution studies, these parameters did not provide any information about involved kinetic of drug release, which makes these parameters suitable for evaluating drug dissolution for immediate solid dosage forms. In preformulation studies of any modified drug delivery system it is fundamental to establish relevant information about the manufacturing parameters, the formulation differences and the influence of resulting physicochemical properties in controlling the drug transport and the involved mechanism [13, 23].

Despite the involved difficulties in identifying fitting models, some important variables may be used to predict or simulate the oral drug release rate in specific conditions, such as different pH, specific enzymatic presence, gastric emptying time or different gastrointestinal compartments. The establishment of a specific model that explains the kinetic involved in drug release supported the screening of excipient, manufacturing parameters and optimized formulations.

This allows the selection of the best conditions involved with modified drug release system conception and characteristics required for drug release in specific sites [15 23, 24]. However, in this study the release profile of all formulations were quite linear and their correlation coefficients were higher than 0.99 (0.9956 to 0.9985). In order to study the mechanism of drug release from all HPMC matrices, all dissolution data were fitted to widely known release kinetic models. The parameters calculated for each model, including the involved constant and determination coefficients are summarized in **Table 5.**

TABLE 5. PARAMETERS AND COEFFICIENTS OF DETERMINATION FOR TRIAMCINOLONE RELEASE CURVES FROM HPMC MATRICES.

Specific Model	**Correlation Parameters**	**HMPC30T**	**HMPC50T**	**HMPC60T**
Zero-order	k_0	11.88	11.63	11.23
	R^2	0.9982	0.9994	0.9995
First-order	k_1	-0.82	-1.01	-0.95
	R^2	0.9881	0.9994	0.9996
Higuchi	k_H	42.83	43.19	42.03
	R^2	0.9721	0.9787	0.9750
Kosmeyer-Peppas	k_{KP}	0.82	1.02	0.96
	R^2	0.9862	0.9995	0.9995
Weibull	β	1.19	1.32	1.24
	R^2	0.9224	0.9817	0.9783
	Td	4.41	5.15	5.26
	α	-0.77	-0.94	-0.89

Involved drug release: k_0, k_1, k_H, k_{KP}; Specific factor: β; required time to release 63.2% of the drug: Td; scale factor: α; and coefficients of correlation: R^2

Linear models are suitably applied when high coefficients (R^2) are observed; these represent the correlation between the independent factors and dependent experimental variable established for the

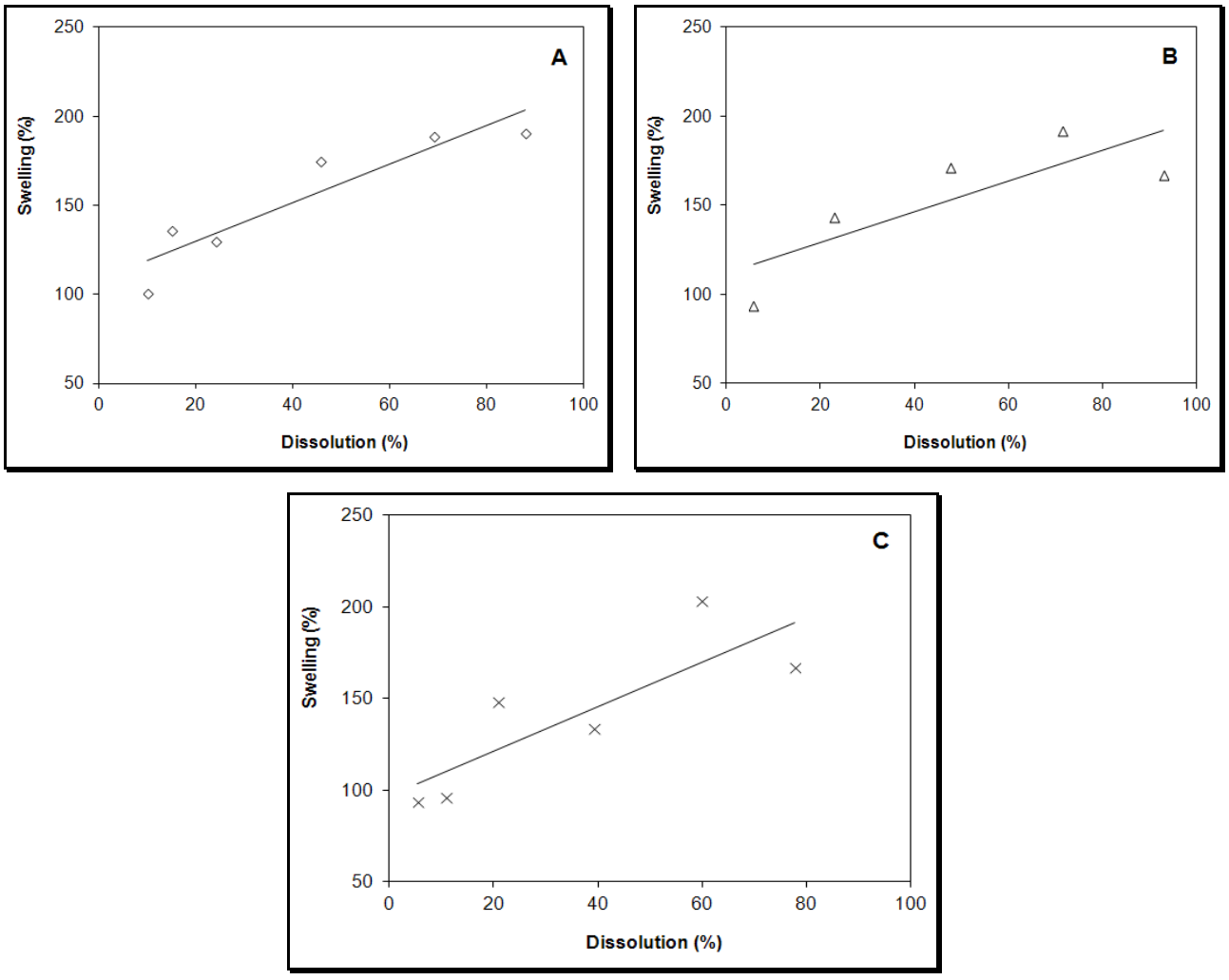
study. The different models applied to fit the experimental data **(Table 5)** demonstrated an involvement of adjusted zero-order kinetics in drug release. This is typical behavior of non-disintegrable matrix systems with a slow drug release through polymeric barriers in a non-equilibrium condition, due to the high concentration gradient for a specific time interval [20].

The HPMC50T and HPMC60T systems presented a satisfactory first order model with correlation coefficient of R^2 = 0.9994 and 0.9996, respectively. The Korsmeyer-Peppas model presented a correlation coefficient of R^2 = 0.9995 for both systems, which is more suitable for describing the drug release behavior of hydrogel polymeric carrier.

Swelling / dissolution correlation study

The drug dissolution and consequent diffusion through swelled polymeric barriers occur simultaneously with the core hydration. Thus, a perfect correlation between swelling and drug release rate may be performed in order to clarify the contribution of the involved formulation variables [25]. However, this seems to be a theoretical affirmation that is not always observed experimentally.

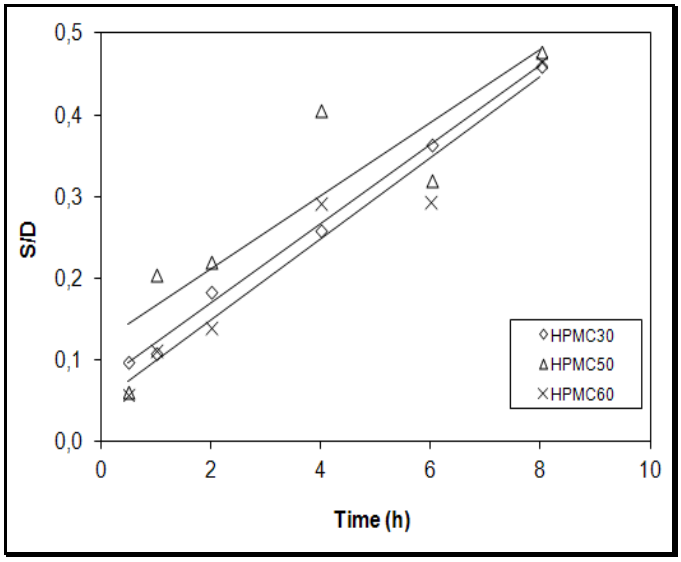
In this study, a positive relation between the swelling and drug release from HPMC matrices was observed **(Figure 3).** According to the regression data, it is possible to establish a reasonable correlation between both release parameters, which reinforces the theory that the hydration degree and drug dissolution from HPMC matrix play important roles in the prediction of drug release rate for such systems.



*Coefficient of determination and rate constant for **A:** R^2 = 0.8504 and k = 1.076; **B:** R^2 = 0.6229 and k = 1.409; and, **C:** R^2 = 0.6502 and k = 0.858.

FIGURE 3. CORRELATION* BETWEEN DRUG DISSOLUTION AND SWELLING PERCENTAGE OF DISTINCT HYDROGEL MATRICES PREPARED WITH (A) 30, (B) 50 AND (C) 60 % OF HPMC.

Since the matrices swelling are involved in drug release, the relationship between mass improvement of matrix and drug release % should be high. In order to evaluate this correlation, the ratio of matrices swell (S) and drug released (D) were plotted against the experimental time **(Figure 4).**



*Coefficient of correlation for **HPMC30:** R^2 = 0.9960 and k = 0.0485;

HPMC50: R^2 = 0.7860 and k = 0.0449; and, **HPMC60:** R^2 = 0.9505 and k= 0.0496.

FIGURE 4. CORRELATION* BETWEEN SWELLING: DISSOLUTION RATIO (S/D) VERSUS TIME (h) FOR HYDROGEL MATRICES PREPARED WITH 30, 50 AND 60% HPMC.

The data were evaluated by linear regression and the results showed important coefficients of determination for all formulations tested, the matrices containing 30 % of HPMC showed the best performance with R^2 = 0.996. Notwithstanding the regression data that could explain most of the experimental variability (from 78 to 99%), the angular coefficients (k) were very similar for all cases (0.0449 to 0.0496), suggesting that if the swelling behavior is taking into account, the drug release shows a tendency for a predictable profile.

CONCLUSIONS: The HPMC matrices could successful control the triamcinolone release. The matrices obtained by direct compression presented suitable quality parameters for modified-release drug delivery systems. The study showed an important correlation between swelling degree and dissolution profile, suggesting the dependence of drug release from systems expansion. The matrix based on the blend containing 30 % of HPMC (HPMC30) was found to be appropriate in terms of uniformity of drug content and the drug-release parameters (dissolution efficiency, f1, f2 and release profiles).

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