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Research paper

Drug release from tableted wet granulations comprising cellulosic (HPMC or HPC) and hydrophobic component

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Abstract

The effects of component nature, proportion and processing on the release rate and mechanism were investigated for tablets comprising drug, cellulosic polymer and hydrophobic components. Four drugs differing in solubility (diclofenac sodium, ibuprofen, naproxen and indomethacin), two cellulosic polymers (HPC and HPMC) and hydrophobic Emvelop® were used in two levels of mass fraction and weight ratio of drug:carrier and of cellulosic–hydrophobic component. Compression was applied after granulation or physical mixing. Drug release was evaluated in pH 6.5 phosphate buffer BP and elucidation of the release mechanism was attempted by fitting kinetic models. Statistical significance of the effects of formulation variables on the release rate and mechanism expressed by the coefficient, k, and exponent, n, of the power law kinetic model, respectively, was evaluated by ANOVA. It was found that for the release mechanism most significant is the effect of drug solubility followed by cellulosic polymer type, mixing procedure and drug mass fraction. Significant interaction between drug solubility and type of cellulosic polymer indicated that alteration in the swelling of HPMC and HPC is caused by the drug solubility. Weight ratio of cellulosic–hydrophobic component does not affect the release mechanism, but only the release rate. Similarly, for the release rate most significant was found the effect of drug solubility, followed by cellulosic polymer type, weight ratio of cellulosic–hydrophobic component, mixing method and drug mass fraction. Also significant were the interactions of drug solubility with the type and proportion of the cellulosic polymer and the processing applied. Depending on the drug solubility and type of polymer present, wet granulation can increase or decrease the release rate.

Keywords: Controlled release; Cellulosic–hydrophobic (gel forming) matrix; Wet granulation; Solubility; Diffusion–erosion kinetics

1. Introduction

Drug release from tablets containing cellulosic gel-forming polymers is of particular interest justifying the various approaches that appear in the literature for its description and the number of polymer brands offered for release programming and control.

For the release description, theoretical approaches have focused on mechanistic modeling of the release kinetics and distinguished pure Fickian diffusion either under the assumption of sink conditions inside the diffusion layer [1] or under the assumption of saturation [2] and matrix erosion [3]. For porous matrices, the hindering effect on drug diffusion from the pore structure was modeled by a time-dependent 'effective' diffusion coefficient, while matrix erosion has been modeled by Heller and Baker using an increasing with time 'effective' diffusion coefficient for biodegradable matrices, assuming that polymer bond cleavage follows first-order kinetics [3].

With matrix erosion the modeling complexity increases, because drug release by diffusion is accelerated, since not only eroded fragments of the matrix carry amounts of drug to the solution, but also the pore structure undergoes significant dilation. Therefore, researchers have followed two different approaches, using either semi- and purely-empirical kinetic equations or structural modeling of drug release by the concomitant operation of two additive mechanisms such as drug diffusion and polymer relaxation or diffusion and matrix erosion. Semi-empirical model is that developed by Peppas and Sahlin [4], which is an extension to the power law model [5] and applied for analysis of the swelling (relaxation) and drug release mechanism [6]. Other models allow for a quantitative evaluation of the relative contributions of drug

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diffusion and matrix erosion, on the basis of the values of equation coefficients [7,8]. Furthermore, experimental quantitative evaluation of matrix swelling and erosion has been based on the weight change (increase or decrease, respectively), measured by withdrawal of tablets from the dissolution media at specific time intervals and weighting either immediately (wet) or after drying [9–11]. Recently Lemaire et al. suggested structural modeling of drug release from biodegradable porous matrices based on a combined diffusion/erosion process [7]. Alternatively, Charlier et al. developed an exponential law function of time, which applied to the late stages of dissolution, while in the early stages the Higuchi model was applied [8]. This latter two-step fitting procedure provides the release rate constants due to both drug diffusion and polymer degradation (or matrix erosion).

Theoretical approach of controlling and programming the drug release is difficult because it combines transfer from porous, swelling and eroding matrices involving hydration and development of two separate fronts: a swelling and an erosion front. Swelling facilitates drug release through Fickian diffusion, while erosion results in anomalous diffusion and have been reported as case I (square root of time release) and case II transport (zero order release) [12]. The kinetics of those two fronts is complex and influenced by a large number of factors, such as the nature and the proportion of the components besides the processing conditions. In practice for the controlling and programming of drug release from matrix tablets, different types of modified cellulose polymers are usually employed, either alone or in mixtures with other swellable polymers [13–16] and with hydrophobic polymers, which may alter the release mechanism and rate [17]. Hydroxypropyl cellulose (HPC) and Hydroxypropyl methylcellulose (HPMC) differing in molecular weight and degree of substitution (proportion of methoxy and hydroxypropoxy groups) are available and it was thought possible to manipulate matrix swelling-erosion kinetics and control the mechanism and rate of drug release through the selection of their nature and the incorporation of hydrophobic constituent. Therefore, in the present study the effect of some formulation variables on drug release is investigated. They are drug solubility, type or brand of cellulosic polymer, mass fraction of drug in the tablet matrix and weight ratio of cellulosic–hydrophobic component, besides wet granulation. Finally, elucidation of the relative contribution of drug diffusion and matrix erosion is attempted.

2. Materials and methods

2.1. Materials

Diclofenac sodium (Heumann Pharma Gmbh, Nurnberg, Germany), Ibuprofen (Boots Co., Nottingham, UK), Naproxen (Syntex, Ireland) and Indomethacin (Geopharma, Milan, Italy), were used as active ingredients of different solubility. Hydroxypropyl methyl-cellulose (HPMC, Methocel K4M, Dow Chemicals and Colorcon, Orpington, UK), with methoxy/hydroxypropoxy group ratio: 22:8 and Hydroxypropyl-cellulose (HPC-H, Nisso, Nippon Soda Co. Ltd, Tokyo, Japan) with high hydroxypropoxy-substitution (60–74%), were employed as hydrophilic cellulosic-polymer components. Hydrogenated vegetable oil NF XVI (Emvelop, m.p. 61–66 °C, E. Mendel Co., Carmel, NY, USA) was used as insoluble hydrophobic (non-wetting) component. Isopropyl alcohol (Merck, Darmstadt, Germany) was used as granulating liquid.

2.2. Characterization of drugs

Solubility of the active ingredients was determined for the liquid medium employed in the release testing (pH 6.5 phosphate buffer BP). Excess powdered active ingredient (1.5 g) was dispersed in 50 ml buffer and shaken for 72 h in water bath, at 25 °C. Aliquots of the supernatant solution were withdrawn, filtered and assayed spectrophotometricaly for drug content. Means of three replicate determinations were calculated. They were: 10.23 mg/ml for diclofenac sodium, 1.04 mg/ml for ibuprofen, 0.77 mg/ml for naproxen and 0.23 mg/ml for indomethacin.

2.3. Preparation of granules

One hundred-fifty gram batches of the powdered materials (drug, cellulosic and hydrophobic component) were mixed in a specially constructed shear mixing and massing apparatus (wet-kneading rheometer) already described [18]. Four different ratios of mass fraction for drug/cellulosic/hydrophobic component were employed: 0.333/0.222/0.444, 0.333/0.444/0.222, 0.666/0.111/0.222 and 0.666/0.222/0.111. They correspond to weight ratio for drug/carrier and for cellulosic/hydrophobic component-ratios of 1:2 and 2:1. The granules contained either HPMC or HPC as the cellulosic (hydrophilic) constituent but not combinations of them. After 3-min dry mixing, isopropyl alcohol was gradually added, in quantity sufficient to achieve the funicular state of agglomeration (end of phase S4). The quantity of isopropyl alcohol had been previously determined on the basis of over-wetting tests. Mixing ceased right after the addition of isopropyl alcohol and the wet mass was allowed to pass through a sieve of 2-mm diameter without pressing, so that the resultant granules were solely affected by the wet mixing and massing. The passing granules were dried in an oven, at 40 °C for 24 h, then left to cool down at room temperature. The 425–1000 μm sieve fraction was obtained and stored in glass jars after spectophotometrical determination of its drug content.

2.4. Compression and release testing

Tablets were prepared by compression of granules and of corresponding physical mixtures. Physical mixing, for

40 min, was performed in a planetary mixer (WAB Turbula system, T2C-Willy A. Bachofen, AG, Basel, Switzerland). Amounts of the 425–1000 μm sieve fraction of granules and of the physical mixtures were weighed (± 1 mg) and compressed on a manually operated hydraulic press. Thirteen millimeter diameter flat face punch and die set was used and pressures in the range of 190–280 MPa were applied for 10 s, resulting in minimal attainable (close to zero) compact porosity (saturated compacts). The amounts of granules or physical mixtures were selected on the basis of their true density, which was determined by an air-comparison pycnometer (Beckmann, model 930), in order to prepare tablets (cylindrical compacts) of the same thickness (2 mm): amounts required to achieve zero porosity at 2 mm thickness were calculated by setting the relative density of the compact equal to the true density of the granules/physical mixtures and solving the equation to find the corresponding granules/physical mixtures mass. This was allowing drug release from certain initial surface area of compacted granules and mixes and maintenance of sink conditions throughout the dissolution testing, since the maximum amount of drug in the formulations in no case exceeded 20% of its solubility in the dissolution medium.

Drug release was determined in an automated dissolution testing system. It consisted of a water circulator and a water bath containing six round bottom dissolution testing vessels (Vandercamp, VK 650A, Vankel Industries, Edison, NJ), a peristaltic pump (Ismatec, Zürich, Switzerland), a spectrophotometer (Camspec, M330) and a computer equipped with appropriate software (Camspec Tablet Dissolution Package, Camspec Ltd, Cambridge, UK). The paddle method of dissolution was applied (USP method II) with 1000 ml of dissolution medium (pH 6.5 phosphate-buffer) containing 0.2%, w/w Polysorbate 80 and stirring at 100 rpm. Aliquots from the dissolution medium were transferred to the spectrophotometer in preset time intervals for the assay of drug after filtration through paper filters (Whatman No 41). The wavelength of 275 nm was selected for diclofenac sodium, 265 nm for ibuprofen, 272 nm for naproxen, and 318 nm for indomethacin. After measurement, the aliquots were returned in the dissolution vessels by the peristaltic pump. The test was repeated three times for each formulation due to limitations in the amount of granules available, and mean values were calculated. Relative standard deviation was in all cases lower than 3%.

2.5. Release data modeling

The following kinetic models were fitted to the raw release data:

(a) the zero order model, describing release from porous (erodible) matrices [19]:

$$M = k_0 t \tag{1}$$

(b) the square root of time or Higuchi model, describing release by Fickian diffusion through a porous matrix:

$$100 - M = k_2\sqrt{t} \tag{2}$$

(c) the cube root law, or Hixson-Crowell model, describing release from monolithic drug particles:

$$100^{1/3} - M^{1/3} = k_3 t \tag{3}$$

(d) the power law model of Peppas [4], which for certain values of the exponent (1 and 0.5) converts to the zero order or square root of time model:

$$M/M_\infty = k_p t^n \tag{4}$$

where M is the percentage of undissolved drug, M_∞ is the drug dissolved after infinite time, k_p is the release rate constant and n is a characteristic exponent (n acquires values between 0.43 and 1.0 depending on matrix geometry and release mechanism, in cases of coupling diffusion and polymer relaxation phenomena or anomalous transport), and finally

(e) the theoretical model describing drug release by diffusion and matrix degradation [8]:

$$M = A\sqrt{\frac{e^{k_C t} - 1}{k_C}} \tag{5}$$

where M is the percentage of dissolved drug, A is the Higuchi constant, calculated by fitting the square root model to the initial part of the curve, and k_C is the matrix erosion constant, calculated by fitting Eq. (5) to the final part of the dissolution curve. The model assumes first order degradation kinetics and it was chosen due to the apparent analogies between degradation of the polymer matrix and erosion by the action of mechanical forces in a disintegration-like manner.

The goodness of fit was compared on the basis of the correlation coefficients (R) and lag times (intercept or theoretical times at which the fraction of drug remaining is 100%, practically representing the time needed for hydration of the matrix in order to initiate drug transport to the solution). Models with best fit are considered those of highest (closest to 1) correlation coefficients and lag times least deviating from zero. Eq. (5) cannot be directly compared with the rest of the models since it is fitted by a two-stage procedure involving non-linear regression. It is used to evaluate the contributions of diffusion and erosion processes on total drug release by comparing the ratio of the erosion over diffusion kinetic constants.

2.6. Statistical analysis of dissolution data

The parameters of the power law model (release rate constant, k_p, and exponent, n) were selected for further statistical analysis (ANOVA), since in this model the exponent n may characterize the mechanism of drug transport besides to the release rate (expressed by the constant, k_p, under fixed n). The R Statistical Language

and Environment [20] was used for the kinetic model fitting and the analysis of variance. Only the main effects and two-factor interactions were evaluated and all higher-order interaction was assigned to the error term.

3. Results and discussion

In Figs. 1 and 2 are presented plots of % release from tableted wet granulations and corresponding physical mixtures of the different drugs in high and low mass fraction (0.666 and 0.333) and containing different weight ratio (1/2 and 2/1) of cellulosic–hydrophobic component. In Fig. 3 are presented plots of % cumulative release at 8 h versus drug solubility for the different formulations of tableted wet granulations and corresponding physical mixtures. In Tables 1–6 are given the results of kinetic model fitting. They are the release rate constants, $k_0, k_2, k_3, k_p, A, k_C$, the ratio k_C/A, the exponent n, the correlation coefficients, R, and the lag times. Granulations containing HPC at high proportion and diclofenac sodium were not obtained due to extensive adhesivity during wet mixing and therefore corresponding tablets are not considered (Figs. 1b and 3b, Tables 1 and 3). Finally, in Table 7 are summarized the results of statistical analysis (ANOVA) for the effects of the experimental variables (drug solubility, type of cellulosic polymer, mixing method, drug mass fraction, cellulosic–hydrophobic component ratio) and all 2-factor interactions.

3.1. Release rate

From the plots in Figs. 1 and 2 it can be seen that cumulative release and release rate is affected by the drug solubility. Diclofenac sodium has highest solubility and shows highest and fastest release. Ibuprofen and naproxen of median solubility show median release and the practically insoluble indomethacin gives the slowest release. Fig. 3 shows that cumulative release at 8 h is logarithmically related to the drug solubility and this indicates that the release mechanism changes with the drug solubility.

For the controlled release device under investigation, which is a matrix-tablet comprising drug, cellulosic and hydrophobic components, the release should follow three steps. First step is the penetration of the dissolution medium in the tablet matrix (hydration). Second step is the swelling with concomitant or subsequent dissolution or erosion of the matrix and third step is the transport of the dissolved drug, either through the hydrated matrix or from the parts of the eroded tablet, to the surrounding dissolution medium. The co-existence of the hydrophobic Emvelop should affect all the aforementioned steps or processes. Particularly it may affect initially the liquid uptake and therefore the hydration

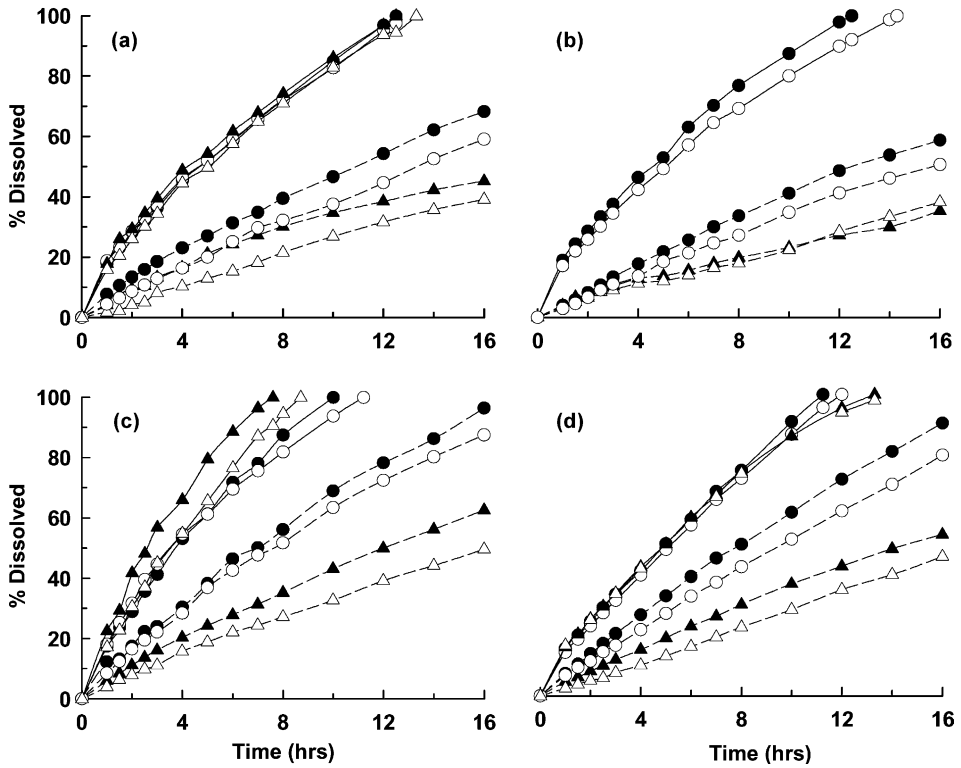

Fig. 1. Plots of % drug released for sodium diclofenac (solid lines) and ibuprofen (dashed lines) from tableted granulations (full symbols) or physical mixtures (empty symbols) containing HPMC (●, ○) or HPC (▲, △) at different mass fraction of drug: polymeric–hydrophobic constituent: (a) 0.333:0.222:0.444, (b) 0.333:0.444:0.222 (c) 0.666:0.111:0.222 and (d) 0.666:0.222:0.111.

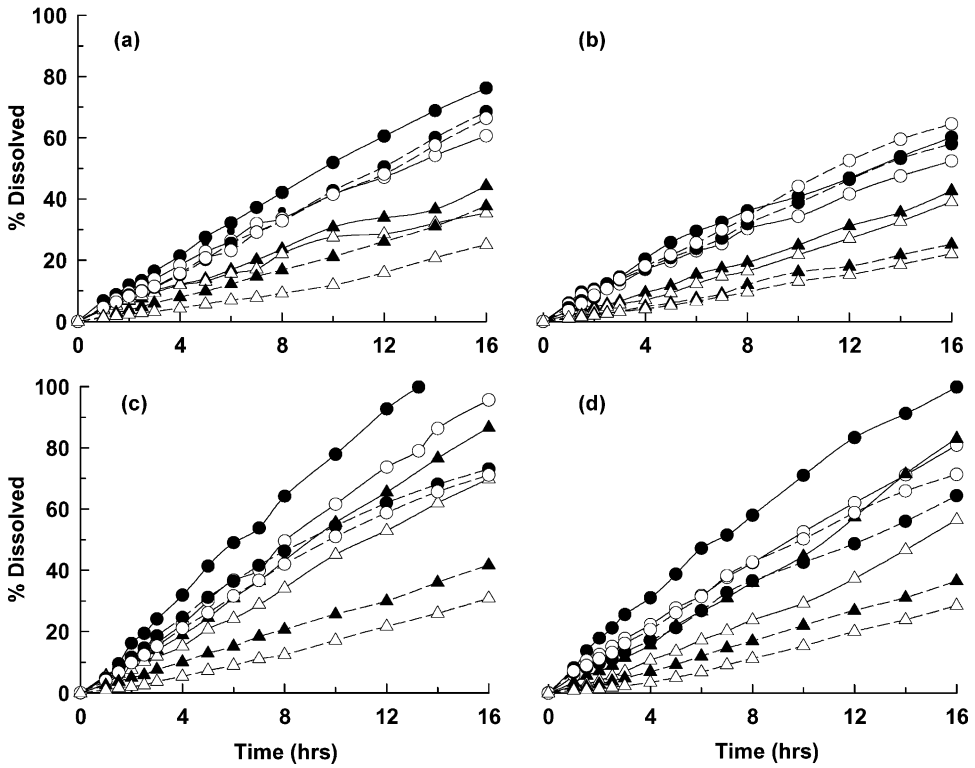

Fig. 2. (a–d). Plots of % drug released for naproxen (solid lines) and indomethacin (dashed lines). Key as in Fig. 1.

rate, the swelling of the cellulosic component and the dissolution of the active ingredient as well. Also, it may reduce the relief of stress developed in the hydrated tablet matrix due to swelling and therefore promote the occurrence of erosion. Finally, it may affect the transport of the dissolved drug through the matrix pores, through the developed cellulosic gel or directly from drug surface of the eroded matrix to the surrounding liquid.

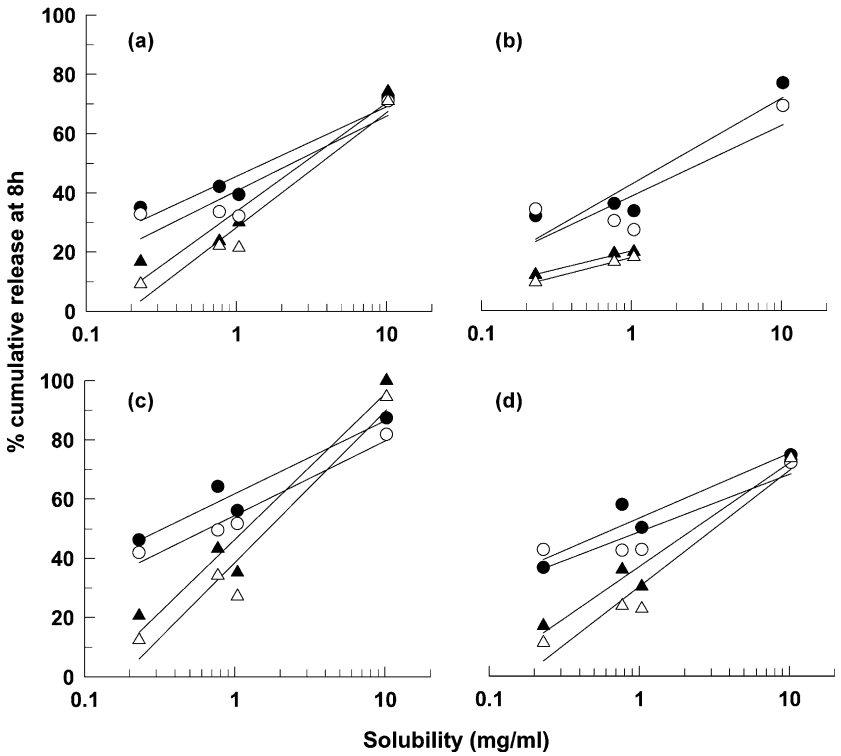

Fig. 3. (a–d). Plots of cumulative release at 8 h versus logarithm of drug solubility with linear fit trends (solid lines). Key as in Fig. 1.

Table 1
Results of kinetic model fitting (release rate constants k_i and exponent n, together with the correlation coefficients, R, and the lag times) for tableted wet granulations containing HPC as cellulosic polymer

Drug	Mass fraction of Drug, HPC and Emvelop	Zero order			Square root			Cube root			Power law			
		R	k_0 (h^{-1})	Lag time (h)	R	k_2 ($h^{-0.5}$)	Lag time (h)	R	k_3 (h^{-1})	Lag time (h)	R	k_p (h^{-n})	Lag time (h)	n
Diclofenac	0.333:0.222:0.444	0.994	6.86	−2.5	0.999	32.09	0.2	0.959	0.28	0.7	0.999	0.19	0.5	0.66
	0.333:0.444:0.222[a]	–	–	–	–	–	–	–	–	–	–	–	–	–
	0.666:0.111:0.222	0.984	10.2	−1.1	0.993	41.34	0.4	0.977	0.32	0.4	0.996	0.17	0.5	0.81
	0.666:0.222:0.111	0.976	6.22	−2.7	0.994	31.74	0.3	0.979	0.28	0.9	0.997	0.16	0.4	0.71
Ibuprofen	0.333:0.222:0.444	0.985	2.76	−1.8	0.998	14.12	0.6	0.992	0.05	−1.1	0.993	0.05	0.3	0.84
	0.333:0.444:0.222	0.997	1.95	−2.0	0.991	9.77	0.5	0.997	0.03	−1.4	0.996	0.04	0.2	0.72
	0.666:0.111:0.222	0.998	3.76	−1.2	0.994	18.90	0.7	0.999	0.08	−0.2	0.999	0.06	0.3	0.84
	0.666:0.222:0.111	0.998	3.36	−0.6	0.993	16.85	0.9	0.999	0.07	0.1	0.999	0.04	0.3	0.91
Naproxen	0.333:0.222:0.444	0.998	2.71	−0.5	0.986	13.52	0.9	0.998	0.05	0.1	0.997	0.04	0.3	0.88
	0.333:0.444:0.222	0.998	2.61	0.2	0.975	12.88	1.2	0.994	0.05	0.6	0.991	0.03	0.3	0.95
	0.666:0.111:0.222	0.999	5.56	0.3	0.982	27.56	1.8	0.986	0.14	1.4	0.997	0.05	0.3	1.02
	0.666:0.222:0.111	0.997	5.25	0.8	0.973	25.86	1.5	0.976	0.12	1.7	0.999	0.03	0.3	1.15
Indo-methacin	0.333:0.222:0.444	0.998	2.32	0.5	0.977	11.47	1.4	0.995	0.04	0.8	0.999	0.01	0.3	1.09
	0.333:0.444:0.222	0.996	1.63	0.8	0.973	8.08	1.5	0.995	0.03	1.0	0.996	0.01	0.3	1.13
	0.666:0.111:0.222	0.999	2.59	0.1	0.985	12.90	1.2	0.998	0.05	0.5	0.999	0.02	0.3	1.03
	0.666:0.222:0.111	0.999	2.38	0.8	0.979	11.77	1.5	0.997	0.04	1.1	0.997	0.01	0.3	1.17

[a] Granulations containing HPC at high proportion and diclofenac sodium were not obtained due to extensive adhesivity during wet mixing.

The values of the release constants in Tables 1–4 are higher for the higher drug mass fraction, in general, and lower for the higher weight ratio of cellulosic–hydrophobic component, except for some formulations of diclofenac sodium. This means that the release rate decreases as the mass fraction of HPMC or HPC increases replacing either drug or hydrophobic Emvelop. Therefore, the decrease should be attributed to development of continuous barrier with increased thickness, surrounding the drug particles upon matrix hydration

Table 2
Results of kinetic model fitting (release rate constants k_i and exponent n, together with the correlation coefficients, R, and the lag times) for tableted wet granulations containing HPMC as cellulosic polymer

Drug	Mass fraction of Drug, HPMC and Emvelop	Zero order			Square root			Cube root			Power law			
		R	k_0 (h^{-1})	Lag time (h)	R	k_2 ($h^{-0.5}$)	Lag time (h)	R	k_3 (h^{-1})	Lag time (h)	R	k_p (h^{-n})	Lag time (h)	n
Diclofenac	0.333:0.222:0.444	0.997	6.99	−2.1	0.997	32.54	0.3	0.953	0.28	0.8	0.999	0.17	0.4	0.68
	0.333:0.444:0.222	0.994	7.08	−2.3	0.998	33.09	0.3	0.967	0.29	0.8	0.999	0.18	0.5	0.68
	0.666:0.111:0.222	0.994	9.36	−1.3	0.998	39.22	0.4	0.953	0.37	0.9	0.999	0.17	0.5	0.77
	0.666:0.222:0.111	0.999	8.26	−1.0	0.992	36.12	0.5	0.936	0.32	1.2	0.999	0.14	0.4	0.78
Ibuprofen	0.333:0.222:0.444	0.998	4.02	−1.5	0.994	20.22	0.6	0.999	0.09	−0.3	0.999	0.08	0.3	0.78
	0.333:0.444:0.222	0.996	3.76	−0.5	0.996	18.98	1.0	0.999	0.07	0.2	0.998	0.04	0.3	0.98
	0.666:0.111:0.222	0.996	5.78	−1.3	0.994	29.10	0.7	0.984	0.18	0.8	0.996	0.11	0.4	0.80
	0.666:0.222:0.111	0.998	5.58	−0.7	0.994	28.07	0.9	0.991	0.15	0.8	0.999	0.07	0.3	0.91
Naproxen	0.333:0.222:0.444	0.998	4.76	−0.5	0.991	23.85	0.9	0.998	0.11	0.5	0.999	0.06	0.3	0.91
	0.333:0.444:0.222	0.993	3.57	−1.4	0.996	18.04	0.7	0.998	0.07	−0.5	0.997	0.06	0.3	0.83
	0.666:0.111:0.222	0.998	7.74	−0.1	0.994	36.30	1.0	0.945	0.27	1.7	0.992	0.06	0.4	1.11
	0.666:0.222:0.111	0.996	6.17	−1.0	0.996	31.17	0.8	0.956	0.22	1.4	0.998	0.09	0.4	0.88
Indomethacin	0.333:0.222:0.444	0.999	4.31	0.2	0.982	21.35	1.2	0.993	0.09	0.9	0.998	0.04	0.3	0.99
	0.333:0.444:0.222	0.997	3.63	0.5	0.997	18.18	0.9	0.999	0.07	0.2	0.998	0.05	0.3	0.93
	0.666:0.111:0.222	0.988	4.68	−0.9	0.999	23.91	0.8	0.999	0.11	0.1	0.992	0.06	0.3	0.98
	0.666:0.222:0.111	0.997	3.92	−0.6	0.989	19.63	0.9	0.997	0.08	0.2	0.994	0.06	0.3	0.87

Table 3
Results of kinetic model fitting (release rate constants k_i and exponent n, together with the correlation coefficients, R, and the lag times) for tableted physical mixtures containing HPC as cellulosic polymer

Drug	Mass fraction of drug, HPC and Emvelop	Zero order			Square root			Cube root			Power law			
		R	k_0 (h^{-1})	Lag time (h)	R	k_2 ($h^{-0.5}$)	Lag time (h)	R	k_3 (h^{-1})	Lag time (h)	R	k_p (h^{-n})	Lag time (h)	n
Diclofenac	0.333:0.222:0.444	0.994	6.85	−2.0	0.998	32.4	0.4	0.958	0.27	0.8	0.999	0.16	0.4	0.72
	0.333:0.444:0.222[a]	–	–	–	–	–	–	–	–	–	–	–	–	–
	0.666:0.111:0.222	0.988	11.67	−1.4	0.998	45.3	0.3	0.982	0.36	0.6	0.995	0.23	0.6	0.74
	0.666:0.222:0.111	0.977	6.22	−2.6	0.993	31.7	0.3	0.978	0.28	1.0	0.996	0.16	0.4	0.71
Ibuprofen	0.333:0.222:0.444	0.997	2.60	0.2	0.993	13.1	1.2	0.999	0.05	0.5	0.994	0.02	0.3	1.20
	0.333:0.444:0.222	0.996	2.21	−0.8	0.975	10.9	0.8	0.993	0.04	−0.3	0.995	0.03	0.2	0.79
	0.666:0.111:0.222	0.998	3.01	−0.9	0.994	15.1	0.8	0.999	0.06	−0.2	0.997	0.04	0.3	0.93
	0.666:0.222:0.111	0.999	2.96	0.4	0.983	14.7	1.3	0.998	0.06	0.8	0.998	0.02	0.3	1.09
Naproxen	0.333:0.222:0.444	0.997	2.42	−0.8	0.985	12.1	0.8	0.997	0.04	−0.3	0.995	0.04	0.2	0.85
	0.333:0.444:0.222	0.997	2.44	0.7	0.970	11.9	1.4	0.993	0.04	1.0	0.996	0.02	0.3	1.08
	0.666:0.111:0.222	0.999	4.47	0.3	0.981	22.2	1.3	0.993	0.09	1.0	0.994	0.04	0.3	1.04
	0.666:0.222:0.111	0.996	3.54	1.0	0.971	17.4	1.6	0.987	0.07	1.4	0.994	0.02	0.3	1.27
Indomethacin	0.333:0.222:0.444	0.987	1.51	0.9	0.950	7.35	1.5	0.983	0.03	1.1	0.980	0.01	0.2	1.09
	0.333:0.444:0.222	0.997	1.39	0.8	0.971	6.85	1.5	0.995	0.02	0.9	0.995	0.01	0.2	1.11
	0.666:0.111:0.222	0.997	1.99	1.2	0.971	9.78	1.7	0.994	0.03	1.4	0.997	0.01	0.3	1.33
	0.666:0.222:0.111	0.993	1.89	1.6	0.960	9.24	1.9	0.990	0.03	1.8	0.990	0.01	0.3	1.39

[a] Physical mixtures containing HPC at high proportion and diclofenac sodium were not studied due to absence of corresponding wet granulations for comparison.

and/or erosion. The continuous barrier with increased thickness of cellulosic polymer should result in decreased diffusion rate of the dissolved drug and consequently in reduced release rate. Furthermore, the exception of the diclofenac sodium formulations indicates that the mass fraction of the cellulosic polymer although affects the release rate, it is not the controlling factor, as has been reported by other investigators [21–23]. Also the release rate constants in Tables 1–4 decrease in general, as the content of hydrophobic Emvelop increases replacing drug, except of the case of diclofenac sodium combined with HPC.

Table 4
Results of kinetic model fitting (release rate constants k_i and exponent n, together with the correlation coefficients, R, and the lag times) for tableted physical mixtures containing HPMC as cellulosic polymer

Drug	Mass fraction of drug, HPMC and Emvelop	Zero order			Square root			Cube root			Power law			
		R	k_0 (h^{-1})	Lag time (h)	R	k_2 ($h^{-0.5}$)	Lag time (h)	R	k_3 (h^{-1})	Lag time (h)	R	k_p (h^{-n})	Lag time (h)	n
Diclofenac	0.333:0.222:0.444	0.996	6.73	−2.4	0.997	31.6	0.3	0.952	0.27	0.7	0.999	0.18	0.4	0.66
	0.333:0.444:0.222	0.993	6.36	−2.4	0.998	30.5	0.3	0.981	0.22	0.4	0.999	0.16	0.4	0.68
	0.666:0.111:0.222	0.987	7.84	−2.3	0.999	34.9	0.2	0.963	0.32	0.6	0.996	0.19	0.5	0.70
	0.666:0.222:0.111	0.999	7.89	−1.0	0.993	35.1	0.6	0.938	0.30	1.2	0.999	0.14	0.4	0.79
Ibuprofen	0.333:0.222:0.444	0.998	3.63	−0.5	0.992	18.2	1.0	0.998	0.07	0.2	0.998	0.04	0.3	0.96
	0.333:0.444:0.222	0.997	3.26	−0.3	0.994	16.37	1.1	0.999	0.06	0.3	0.998	0.03	0.3	1.05
	0.666:0.111:0.222	0.994	5.35	−1.3	0.997	27.1	0.7	0.997	0.14	0.4	0.999	0.08	0.4	0.86
	0.666:0.222:0.111	0.999	4.89	−0.5	0.990	24.4	0.9	0.994	0.11	0.6	0.998	0.06	0.3	0.92
Naproxen	0.333:0.222:0.444	0.997	3.73	−0.8	0.995	18.8	0.9	0.999	0.08	0.1	0.998	0.05	0.3	0.97
	0.333:0.444:0.222	0.998	3.12	−1.2	0.990	15.6	0.7	0.999	0.06	−0.1	0.995	0.05	0.3	0.81
	0.666:0.111:0.222	0.999	6.27	0.4	0.989	31.3	1.3	0.978	0.18	1.7	0.995	0.04	0.4	1.23
	0.666:0.222:0.111	0.999	4.93	−0.5	0.989	24.6	0.9	0.992	0.12	0.7	0.996	0.06	0.3	0.94
Indomethacin	0.333:0.222:0.444	0.999	4.13	0.1	0.984	20.5	1.2	0.994	0.09	0.8	0.999	0.04	0.3	0.99
	0.333:0.444:0.222	0.998	4.18	−0.1	0.991	20.9	1.1	0.998	0.09	0.6	0.996	0.04	0.3	1.03
	0.666:0.111:0.222	0.995	4.64	−0.4	0.996	23.4	1.0	0.999	0.10	0.5	0.997	0.04	0.3	1.05
	0.666:0.222:0.111	0.996	4.52	−0.7	0.993	22.7	0.9	0.999	0.10	0.3	0.996	0.06	0.3	0.87

Table 5
Results of two-step fitting kinetic model [8], R is correlation coefficients and A and k_C are the release rate constants for tableted wet granulations and physical mixtures containing HPC as cellulosic polymer

Drug	Mass fraction of drug, HPC and Emvelop	Wet granulations					Physical mixtures				
		Initial part		Final part		Ratio, k_C/A ($\times 10^3$)	Initial part		Final part		Ratio, k_C/A ($\times 10^3$)
		R	A ($h^{-0.5}$)	R	k_C (h^{-1})		R	A ($h^{-0.5}$)	R	k_C (h^{-1})	
Diclofenac	0.333:0.222:0.444	0.991	27.9	0.999	0.066	2.36	0.998	24.95	0.997	0.085	3.40
	0.333:0.444:0.222[a]	–	–	–	–	–	–	–	–	–	–
	0.666:0.111:0.222	0.990	31.9	0.967	0.097	3.04	0.989	46.14	0.996	0.083	1.79
	0.666:0.222:0.111	0.998	23.6	0.973	0.031	1.30	0.997	21.38	0.972	0.034	1.57
Ibuprofen	0.333:0.222:0.444	0.994	12.9	0.989	0.065	5.03	0.979	7.917	0.988	0.137	17.33
	0.333:0.444:0.222	0.981	8.2	0.998	0.098	12.02	0.995	7.97	0.998	0.157	19.66
	0.666:0.111:0.222	0.997	13.4	0.997	0.107	8.00	0.999	9.98	0.998	0.114	11.39
	0.666:0.222:0.111	0.993	9.3	0.991	0.126	13.49	0.998	5.96	0.991	0.178	29.86
Naproxen	0.333:0.222:0.444	0.997	6.0	0.989	0.138	22.98	0.995	8.24	0.987	0.132	16.02
	0.333:0.444:0.222	0.978	3.6	0.997	0.169	47.85	0.999	3.62	0.995	0.207	57.18
	0.666:0.111:0.222	0.999	10.6	0.989	0.166	15.56	0.996	6.73	0.989	0.173	25.66
	0.666:0.222:0.111	0.996	6.7	0.995	0.206	30.58	0.990	4.56	0.996	0.216	47.43
Indomethacin	0.333:0.222:0.444	0.999	5.4	0.998	0.188	34.62	0.999	2.74	0.998	0.238	86.86
	0.333:0.444:0.222	0.989	3.1	0.985	0.192	62.95	0.989	3.02	0.995	0.186	61.72
	0.666:0.111:0.222	0.999	5.9	0.996	0.158	26.68	0.997	2.69	0.994	0.214	79.37
	0.666:0.222:0.111	0.959	3.6	0.991	0.184	51.11	0.987	1.20	0.986	0.248	206.42

[a] Granulations containing HPC at high proportion and diclofenac sodium were not obtained due to extensive adhesivity during wet mixing and therefore corresponding physical mixtures were not studied.

Concerning the effect of cellulosic polymer type or brand, in general, HPC results in lower release constants (Table 1–4), or in greater reduction of release rate than HPMC, with the exception of tablets containing diclofenac sodium as active ingredient. This greater reduction should result from retarded hydration and slower swelling and erosion of the matrix, since it vanishes for the case of the highly soluble diclofenac sodium. Dissolution of diclofenac sodium is very fast and may precede swelling of the cellulosic polymer; thus the release rate of diclofenac

Table 6
Results of two-step fitting kinetic model [8], R is correlation coefficients and A and k_C are the release rate constants for tableted wet granulations and physical mixtures containing HPMC as cellulosic polymer

Drug	Mass fraction of drug, HPC and Emvelop	Wet granulations					Physical mixtures				
		Initial part		Final part		Ratio, k_C/A ($\times 10^3$)	Initial part		Final part		Ratio, k_C/A ($\times 10^3$)
		R	A ($h^{-0.5}$)	R	k_C (h^{-1})		R	A ($h^{-0.5}$)	R	k_C (h^{-1})	
Diclofenac	0.333:0.222:0.444	0.999	24.6	0.999	0.090	3.64	0.997	24.6	0.999	0.076	3.09
	0.333:0.444:0.222	0.999	24.5	0.995	0.069	2.81	0.999	22.3	0.997	0.061	2.73
	0.666:0.111:0.222	0.996	30.7	0.996	0.097	3.16	0.996	36.4	0.999	0.053	1.47
	0.666:0.222:0.111	0.997	23.2	0.997	0.156	6.71	0.998	22.6	0.995	0.162	7.17
Ibuprofen	0.333:0.222:0.444	0.999	14.1	0.998	0.105	7.47	0.998	11.0	0.994	0.134	12.13
	0.333:0.444:0.222	0.990	11.5	0.990	0.120	10.41	0.990	10.4	0.990	0.133	12.76
	0.666:0.111:0.222	0.997	25.5	0.992	0.103	4.06	0.999	20.0	0.992	0.097	4.85
	0.666:0.222:0.111	0.997	17.1	0.994	0.123	7.18	0.993	13.1	0.995	0.138	10.51
Naproxen	0.333:0.222:0.444	0.991	11.9	0.993	0.124	10.4	0.999	12.7	0.994	0.118	9.28
	0.333:0.444:0.222	0.987	10.8	0.990	0.112	10.36	0.983	8.5	0.996	0.111	12.99
	0.666:0.111:0.222	0.996	26.5	0.994	0.166	6.27	0.998	18.3	0.990	0.162	8.86
	0.666:0.222:0.111	0.999	23.2	0.992	0.108	4.64	0.994	15.6	0.996	0.141	9.03
Indomethacin	0.333:0.222:0.444	0.991	9.6	0.992	0.171	17.85	0.999	9.4	0.994	0.166	17.61
	0.333:0.444:0.222	0.990	8.0	0.994	0.132	16.48	0.997	12.5	0.990	0.137	10.93
	0.666:0.111:0.222	0.995	17.1	0.990	0.080	4.65	0.998	14.6	0.989	0.111	7.59
	0.666:0.222:0.111	0.999	7.4	0.990	0.124	16.75	0.995	10.4	0.988	0.109	10.49

Table 7
ANOVA results for the main effects and 2-factor interactions of drug solubility, type of the cellulosic polymer, weight ratio of cellulosic–hydrophobic component, mixing method and drug mass fraction on the release rate and mechanism (constant k_p and exponent n of the power law kinetic model)

Effect	Release rate constant, k_p		Exponent, n	
	F	p	F	p
Drug solubility (1)	313.80	2.20×10^{-16}	29.81	7.28×10^{-10}
Cellulosic polymer type (2)	32.51	1.74×10^{-6}	7.82	0.008
Cellulosic–hydrophobic weight ratio (3)	10.74	0.002	0.01	0.934
Mixing method (4)	5.99	0.019	6.24	0.017
Drug mass fraction (5)	5.18	0.028	6.11	0.018
(1) × (2)	7.36	0.001	3.21	0.034
(1) × (3)	3.09	0.039	0.08	0.973
(1) × (4)	2.50	0.075	1.16	0.335
(1) × (5)	1.58	0.210	2.04	0.124
(2) × (3)	0.85	0.361	1.15	0.290
(2) × (4)	0.76	0.389	0.92	0.345
(2) × (5)	0.48	0.493	2.02	0.163
(3) × (4)	<0.01	0.978	0.05	0.818
(3) × (5)	1.52	0.226	0.13	0.721
(4) × (5)	0.30	0.584	0.04	0.843

sodium is independent of the mass fraction and the type or brand of the cellulosic polymer component.

Comparing the release between tablets prepared from granulations and physical mixtures, we can see that the rate constants in Tables 1–4 and plots in Figs. 1 and 2 change differently for the drugs under investigation. In the case of diclofenac sodium release is more or less similar, while for ibuprofen, release rate from tableted granulations is faster compared to that of physical mixtures. For naproxen, we similarly see higher release from tableted granulations (by 10–20% in 16 h), especially when HPMC is used as cellulosic constituent. For the case of indomethacin, the behavior is complex and depends on the type of the cellulosic polymer and the weight ratio of cellulosic–hydrophobic component. The granulations show higher cumulative release compared to physical mixtures, but only when contain cellulosic polymer (HPC and HPMC) at weight lower than that of the hydrophobic component (ratio 1:2). On the contrary granulations containing HPMC at weight (mass fraction) higher than the hydrophobic Emvelop show lower release compared to physical mixtures, by ca. 8% in 16 h (Figs. 1 and 2).

The differences of release between granules and physical mixtures cannot be attributed only to the hydration speed of the cellulosic polymer itself because they are related to the solubility of the drugs as well. Therefore, these differences should be explained on the basis of the effects of mixing procedure on the dispersion of the components and the subsequent influence on the hydration speed of the matrix tablet. In other words, the differences should be connected with alteration in the hydration of the cellulosic polymers due to the drug incorporated. The increase of release due to wet granulation for naproxen and ibuprofen should be a result of improved wetting by the dissolution liquid due to improved dispersion of the granulated powders. The different behavior of indomethacin, particularly with HPMC at mass fraction higher than that of hydrophobic Emvelop, may be attributed to its low solubility and different release mechanism. In that case, the improved dispersion reduces the erosion and therefore the release.

From the ANOVA results, Table 7, it is seen that the most significant effect on release rate constant, k_p, is that of drug solubility ($p = 2.2 \times 10^{-16}$) followed by those of type of cellulosic polymer ($p = 1.7 \times 10^{-6}$), weight ratio of cellulosic–hydrophobic component ($p = 0.002$), mixing method ($p = 0.019$) and drug mass fraction ($p = 0.028$). These mean that all main effects under investigation (nature, proportion and processing of the components) are significant. Also the ANOVA results show that significant, however, are the interaction effects of drug solubility with the type and proportion of the cellulosic polymer and the processing applied.

3.2. Release mechanism

Release mechanism can be elucidated indirectly either on basis of exponent n, in Eq. (4), or comparing fitting of the models of pure diffusion (Eq. (2)), of pure dissolution of drug particles after immediate and complete tablet erosion or disintegration (Eq. (3)) and of mixed simultaneous operation of them (Eq. (1)). Correlation coefficient closer to 1 and positive (realistic) lag time or closer to zero means better fitting. Alternatively, comparative evaluation of the ratio of erosion over diffusion kinetic constants of Eq. (5), listed in Tables 5 and 6, can provide direct evidence for the relative contribution of drug diffusion and matrix erosion processes.

From the results given in Tables 1–4, we can say the following. In all cases of tablets containing diclofenac sodium, both granulated and physically mixed, the best fitting is this of the pure diffusion model (Eq. (2)). Also, the pure diffusion model fits best to the release data of granulations containing ibuprofen but only in low mass fraction and combined with HPC as cellulosic polymer. For all the other ibuprofen formulations granulated and physically mixed the cube root or the model of pure drug particle dissolution provides the best fit. The n values for both diclofenac sodium and ibuprofen are between 0.66 and 0.84 for the best fitting of the pure diffusion model and between 0.79 and 1.20 for the best fitting of the cube root model. This means that both n values and comparison of model fitting lead to the same conclusion that the mechanism of release can be described as a mixed one involving Fickian and anomalous diffusion (matrix swelling and erosion), in proportion depending on the nature or the solubility of the drug. In other words, release is closer to

Fickian diffusion than to anomalous diffusion, for the case of highly soluble diclofenac sodium and well dispersed small amount of ibuprofen in highly hydrophilic HPC, probably because dissolution of drug particles precedes matrix swelling and erosion. Thus, the dissolved drug is transferred by diffusion through the water-filled pores to the surface of the tablet and the surrounding liquid. After the matrix swelling, release proceeds by diffusion through the gel barrier formed by the cellulosic polymer. The k_C/A ratio values (Tables 5 and 6) are in agreement to the above discussion, as lower ratio values correspond to cases where the diffusion model provides the best fit.

In the case of tablets containing naproxen, the models with the best fit are the zero order for compositions with high drug mass fraction, the cube root model for compositions with high weight ratio of hydrophobic Emvelop and the square root for tablets including HPMC in high weight ratio. Taking also into account the high n values (between 0.81 and 1.27), we can say that naproxen is released by anomalous diffusion, probably because of relatively quick matrix erosion. This is confirmed by the higher k_C/A values in the case of tablets containing HPC (from 15.6 to 57.2×10^{-3}) and lower values for HPMC tablets (from 4.6 to 12.9×10^{-3}). Matrix erosion may result because the stress developed due to hydration and swelling of the cellulosic polymer cannot be compensated. Then, depending on the mass fractions of naproxen and hydrophobic Emvelop, the cellulosic polymer forms a more or less disrupted or a continuous and thick gel barrier and the release proceeds more or less by direct dissolution of the drug particles or by diffusion though the continuous gel coating.

In the case of tablets containing indomethacin the fitting of the kinetic models seems to depend on the type of the cellulosic polymer and no effect of the granulation process can be observed. For tablets combining indomethacin and HPC best fitting is obtained with the zero order model, while for those containing HPMC with the cube root model, except if hydrophobic Emvelop is present in high mass fraction (0.444). Release fitting to the cube root model indicates extended erosion or development of insufficient gel barrier to maintain the diffusion process. The switch from cube root to zero order release kinetics is due to development of more sufficient gel barrier either because the hydrophobic Emvelop works as insulator (absolute barrier) reducing the surface available for drug release or because more HPMC is available for coating per particle of indomethacin. These both may result in increased transport by diffusion and reduced direct particle dissolution after the matrix erosion. Concerning the exponent, n, it has values between 0.87 and 1.39 in the case of indomethacin, and the ratio k_C/A has highest values in the case of tablets containing HPC (from 26.7 to 206.4×10^{-3}) and lowest in the case of tablets containing HPMC (from 4.7 to 17.9×10^{-3}).

Regarding the ANOVA results for exponent, n, Table 7, they show that significant are the main effects of all the experimental variables under investigation, except of the polymeric–hydrophobic weight ratio. This means that the presence of Emvelop does not affect the mechanism of drug release, but only the release rate (constant k_p). The most significant effect on release mechanism is that of drug solubility ($p = 7.2 \times 10^{-10}$), followed by the type of cellulosic polymer ($p = 0.008$) and those of mixing procedure ($p = 0.017$) and drug mass fraction ($p = 0.018$). Also, there is a significant interaction between drug solubility and type of cellulosic polymer. This means that the difference in the swelling between HPMC and HPC is affected by the drug solubility.

4. Conclusion

The study of drug release from tableted wet granulations and physical mixtures comprising cellulosic polymer and hydrophobic component revealed that for the release mechanism the most significant effect is that of drug solubility, followed by the type of cellulosic polymer, the mixing procedure and the drug mass fraction. Significant interaction between drug solubility and type of cellulosic polymer shows that alteration in the swelling of HPMC and HPC is caused by the drug solubility. Similarly, for the release rate, the most significant effect is that of drug solubility, followed by the type of the cellulosic polymer, the weight ratio of cellulosic–hydrophobic component, the mixing method and the drug mass fraction. Also significant are the interactions of drug solubility with the type and proportion of the cellulosic polymer and the processing applied. Presence of hydrophobic Emvelop affects the release rate without altering the release mechanism and wet granulation can increase or decrease the release rate, depending on the drug solubility and type of polymer present.

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