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In vitro evaluation of sustained released matrix tablets containing ibuprofen: a model poorly water-soluble drug

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A matrix system was developed that releases ibuprofen (IB) over a 12-hour period and the influence of the polymer type and concentration on the release rate of the drug was evaluated. Tablets containing different concentrations of Carbopol (CP), hydroxypropyl methylcellulose (HPMC), or ethyl cellulose (EC) were prepared using direct compression and the drug content, content uniformity, hardness, friability, dissolution performance, and *in vitro* release kinetics were examined. Formulated tablets were found to be within acceptable limits for physical and chemical parameters. The release kinetics of the Carbopol®971P 8% formulation showed the best linearity (r^2 =0.977) in fitting zero-order kinetics, suggesting the release rate was time independent. The drug release from tablets containing 8% CP was extended over approximately 18 hours and the release kinetics were nearly linear, suggesting that this system has the potential to maintain constant plasma drug concentrations over 12 hours, which could reduce the frequency of administration and the occurrence of adverse effects associated with repeated administration of conventional IB tablets.

Uniterms: Ibuprofen/study. Ibuprofen/sustained release tablets. Ibuprofen/formulation/carbopol. Ibuprofen/formulation/hydroxypropyl methylcellulose. Ibuprofen/formulations/ethyl cellulose. Ibuprofen/formulations/release kinetics.

INTRODUCTION

Oral administration of drugs is generally preferred, especially over parenteral administration. Oral products are produced in a more cost-effective manner in comparison with parenteral products, and account for approximately 60% of all prescription products worldwide (Advanced oral, 2011).

Sustained-release oral drug products are designed to slowly release the active ingredient over an extended time following administration, and offer significant advantages over conventional orally administered products, including reduced dosing frequency and decreased drug plasma-concentration fluctuations (Charman *et al*., 2002; Moodley *et al*., 2012). Matrix formulations of hydrophilic and/or hydrophobic polymers have been used to control the release of drugs (Malmsten, 2002; Qiu, Bae, 2006) and can be produced using conventional processing equipment.

Hydrophilic matrices hydrate following oral administration and form a gelatinous layer that acts as a barrier to control the rate of drug release (Rabasco, 1999; Bernard *et al*., 2004; Rajabi, Rane, Felton, 2013). Hydroxypropyl methylcellulose (HPMC) is one of the most common hydrophilic polymers used in matrix systems (Tiwari, Rajabi-Siahboomi, 2008). High molecular weight Carbopol (CP) polymers at relatively low levels (3–30%) have also been employed (Lubrizol Advanced Materials, 2008). Ethyl cellulose (EC) hydrophobic polymer control drug release predominately through the formation of a network of capillaries or channels.

The objective of this study was to investigate the influence of the polymer type and concentration on the release rate of ibuprofen (IB), a first-line nonsteroidal anti-

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inflammatory drug (NSAID) that is used in the treatment of rheumatic diseases to reduce the symptoms of chronic inflammation and pain. IB has poor water solubility and is a good candidate for formulation into a modified release system because of its short half-life (approximately2 hours) (Burke, Smyth, Fitzgerald, 2007; Furst, Ulrich, Varkey, 2009; Raffa, 2005; Sweetman, 2007). The overall goal was to develop a matrix system that will release the drug over a 12-hour period. The release kinetics were also studied to better understand the influence of polymer composition on the mechanism of drug release from the matrices.

MATERIAL AND METHODS

IB was obtained from Astroquim, S.A. de C.V. (Ecatepec, México) and IB standard from Sigma-Aldrich. Carbopol® 971P was a gift from Lubrizol Advanced Materials (Cleveland OH, USA). ETHOCEL N-50 and METHOCEL E4M were gifts from Gylsa and manufactured by Dow Chemical Company (Midland MI, USA). Microcrystalline cellulose (MCC), magnesium stearate, talc, colloidal silicon dioxide, and sodium lauryl sulfate were from Desarrollo de Especialidades Químicas, S.A. de C.V. (Monterrey, México).

The compositions of the formulations are shown in Table I. Experimental batches of 0.5 kg of each formulation were prepared. The amounts of the excipients in the formulations were determined from preliminary studies based on the powder mixtures during the manufacturing process and the percentage of each polymer that gave the best flow characteristics and non-stick properties was selected. The type and amount of formulation components in the mixture were selected to allow for manufacturing by direct compression. For comparison, commercially available immediate-release IB tablets (Productos Farmacéuticos Collins, S.A. de C.V., Jalisco, México) were obtained from a local pharmacy.

IB, polymers, MCC, and sodium lauryl sulfate were sieved through a #25 sieve and blended for 15 min in a polyethylene bag. Talc and magnesium stearate were sieved, added to the drug/polymer blend, and mixed for three minutes. Final powder blends were compressed using 16 mm punches on a 10-station rotary tablet press (ADEPT 10D mini-press, Mumbai, India).

Physical properties of the tablets

Ten tablets were taken at random from each batch and subjected to tablet hardness testing using a Vankel 200 hardness tester (Cary N.C., USA). Standard deviations (SD) and relative standard deviations (RSD) were calculated from the data. An additional ten tablets were randomly selected from each batch for friability testing. Tablets were weighed, placed in the friabilator (Vankel 41-1200), and subjected to 25 rotations per minute for 4 minutes. Loose powder was removed and the remaining tablets were reweighed to determine a weight loss percentage, following the U.S. Pharmacopeia method (USP, 2015).

Content and content uniformity

Ten tablets from each batch were randomly selected for drug content analysis. Tablets were weighed then ground to a fine powder. An amount equivalent to 100 mg of IB powder based on theoretical loading was weighed and transferred to a 100 mL volumetric flask, 50 mL of phosphate buffer pH 7.2 was added. The flask was subjected to ultrasonication for 60 min and the volume was completed with the same buffer solution. The resulting

TABLE I - Composition of matrix tablets of IB used in this study

	C1	C2	C3	H1	H2	H3	E1	E2
IB	60.50	59.00	57.50	44.50	49.50	54.50	44.50	44.50
Carbopol®971P	5	6.50	8	1	1	1	1	1
Hydroxypropylmethylcellulose	-	-	-	30	15	10	-	-
Ethylcellulose	-	-	-	-	-	-	30	20
Microcrystaline cellulose	30	30	30	20	30	30	20	30
Colloidal silicon dioxide	1	1	1	1	1	1	1	1
Talc	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Sodium lauryl sulfate	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Magnesium stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Percentage	100	100	100	100	100	100	100	100

solution was filtered and the first few milliliters of the filtrate were discarded. The filtered solution was analyzed using a UV Spectrophotometer at 265 nm (Varian Inc. Cary 50; California, USA). The absorbance obtained was then converted to the amount of IB using a standard calibration curve prepared with an IB standard of 1 mg mL^{-1} in the same medium.

In vitro dissolution

In vitro dissolution studies were carried out according to the USP paddle method. The dissolution medium was 900 mL of phosphate buffer (pH 7.2) previously degassed, at 37.0 ± 0.5 °C, and a stirring speed of 50 rpm was used. A six-vessel dissolution apparatus (Vankel VK 7000, Cary, N.C., USA) was used and six randomly selected tablets from each batch were tested**.** Drug release was monitored at intervals of 2 hours; samples were filtered with hydrophilic polyvinylidene fluoride (PVDF) acrodiscs of 0.45 µm prior to UV-VIS spectrophotometric analysis at 265 nm (spectrophotometer Varian Inc. Cary 50) using a previously validated method of quantification (linearity, precision, and accuracy were assessed). Data were graphed as cumulative percentage drug release (calculated from the total amount of IB in each formulation) versus time. The f_2 similarity factor, calculated from Eq. 1, was then used to compare the dissolution data (Shah *et al*., 1998).

$$f_2 = 50 \times \log\left\{\left[1+\left(\frac{1}{n}\sum (R_t - T_t)^2\right)\right]^{-0.5} \times 100\right\}$$

Analysis of the *in vitro* release kinetics

The following kinetic models were used to evaluate the *in vitro* drug release: zero order (Eq. 2), first order (Eq. 3), Higuchi (Eq. 4), and Korsmeyer-Peppas (Eq. 5).

$$Q_t = Q_0 + k_0 t \tag{2}$$

$$\log Q_t = \log Q_0 - k_1 t / 2.303 \tag{3}$$

$$Q_t = k_H t^{1/2} \tag{4}$$

$$M_t / M_\infty = kt^n \tag{5}$$

where: Q_t is the amount of drug dissolved over time t, Q_0 is the initial amount of drug in solution (equal to zero), k_0 is the zero order release constant (expressed as concentration/time), the constant k_1 is first order (expressed in time units, h^{-1}), $k_H t^{1/2}$ is the dissolution constant of the Higuchi equation (expressed in time units, $h^{1/2}$), M_t is the amount of drug released at time t, M_∞ is the total amount of drug released at infinite time, k is the release rate constant (expressed as h^{-n}) and n is the release exponent which indicates the type of release mechanism.

Validation of the analytical method

NORMA Oficial Mexicana NOM-177-SSA1-2013, (NOM 177, 2013) was used to demonstrate whether the dissolution test method was adequate. The test was validated following assessment of linearity, precision (repeatability and intermediate precision), and accuracy.

Linearity was obtained from the correlation coefficient of three standard curves using five different buffered solutions with concentrations of 0.06-0.6 mg mL^{-1} of IB. A stock solution of IB (1 mg mL^{-1}) was prepared by dissolution in pH 7.2 buffer solution. Solutions with concentrations of 0.06, 0.1, 0.2, 0.4, and 0.6 mg mL^{-1} were prepared for triplicate studies of precision and accuracy; absorbance was determined at 265 nm. Linearity was evaluated by linear regression analysis using the least squares regression method (a regression coefficient > 0.99 is required).

The repeatability (intra-assay precision) and intermediate precision (interday precision) were calculated by analysis of two known standard solutions of IB on different days. Each solution was prepared and analyzed in triplicate in a UV-VIS spectrophotometer on two consecutive days, in the same spectrophotometer, by the same operator. Relative standard deviation (RSD) was used to calculate the precision of the method (<3% RSD is required).

The accuracy was expressed as the agreement between the set reference value and the measured value of each concentration. IB concentrations of 0.6, 0.1, 0.2, 0.4, and 0.6 mg mL^{-1} were analyzed in triplicate in a UV-VIS spectrophotometer (<3% RSD on each point is required).

RESULTS AND DISCUSSION

To assess the linearity of the method, calibration curves of IB concentration versus absorbance were plotted, giving a correlation coefficient of approximately 0.9997 over the concentration range studied (0.06–0.6 mg mL^{-1}). The representative linear equation was $y = 1.786x + 0.012$. IB concentration measurement accuracy was determined by same- (intraday) and alternate-day (interday) spectrophotometry in dissolution test standardized conditions. The average recovery was 98.60–101.79%. The RSD values were less than 3%, indicating that the precision of the dissolution procedure and analysis method was acceptable (México, 2013).

Direct compression tableting is a very cost-effective method to produce tablets. Benefits include reduced processing times, fewer manufacturing steps, decreased labor costs, and less power consumption. In contrast, wet granulation is considered to be a relatively laborious process, despite its other advantages, and involves considerable material handling, additional processing steps, and energy costs (Niazi, 2009; Summers, Aulton, 2007). The current study uses a direct compression technique to produce matrix tablets to investigate the influence of polymer type and concentration on the release rate of a model poorly water-soluble drug. The model drug, IB, also has poor powder flow properties (Costa, Sousa, 2001). The addition of excipients, such as talc and colloidal silicon dioxide, also called "flow promoters", helps to improve the flowability of powder blends, reducing the phenomena of adhesion and cohesion between particles. The sliding effect of colloidal silicon dioxide is because of its very small particle size, which allows attachment to the surface of other ingredients to reduce interparticle friction; however, talc exerts its sliding effect by reducing adhesive force between the surface-IB particles (Liu *et al.*, 2008; Staniforth, Aulton, 2007). In the current study, both of these excipients were employed to improve the flowability of the powder blend. The percentage of colloidal silicon dioxide used (1%)was within the recommended limits specified in the Handbook of Excipients (Rowe, Sheskey, Quinn, 2009) for use as a glidant. The amount of talc in the formulations was maintained at 2.5%, a concentration high enough to show the desired effect on powder adhesion, but low enough not to cause segregation from the powder mixture. Microcrystalline cellulose, at concentrations of 20% and 30%, was used to improve the compressibility of the powder blends. Note that although the total tablet weight varied, the target of 400 mg of drug per tablet was held constant.

Table II shows the results of the physical evaluation of the tablets from the different formulation batches. All tablets investigated in the study exhibited a hardness of >15 kp. Although there is not a USP specification for hardness, a minimum hardness of 4 kp is considered sufficient to obtain physically stable tablets that are not likely to break during routine handling. The friability of all tablets was less than 1%, indicating that the tablets would have sufficient physical stability during packing, transportation, and handling (USP, 2015). IB is known to exhibit poor tableting behavior because of its hydrophobic structure, low flowability, and tendency to stick to the tablet punches, all of which have been shown to lead to variations in tablet weight (Bushra *et al.*, 2008). In the current study, the drug content ranged from approximately 99% to 104% of theoretical. In addition, the RSD ranged from 0.48 to 1.33 and were well within the USP acceptance criteria (<6% RSD) for content uniformity for all tablet formulations.

Figure 1 shows the release profiles of the formulations containing HPMC as the primary rate-controlling polymer in comparison with an immediate-release formulation IR. The tablets containing up to 30% HPMC showed very slow and incomplete drug release from the matrix over the time of the study. An f_2 similarity evaluation confirmed that these formulations did not have similar release profiles, with values of less than 50.The H3 formulation (10% HPMC) released the largest amount of drug, but the percentage of drug dissolved was less than 60%, meaning that at the end of the release profile study (12 hours) 40% of the drug remained in the tablet. In contrast, drug release was rapid and complete from the immediate-release formulation.

Drug release from hydrophilic matrices generally occurs by diffusion through the gelatinous layer, erosion of the matrix (i.e. dissolution of the polymer), or a

TABLE II - Physical evaluation of tablets from the different formulations

Formulation	Weight (mg) Mean±S.D. n=10	Hardness (kp) Mean±S.D. n=10	Friability (%) weigth loss n=10	Drug content (%) IB±S.D. n=10	RSD Content uniformity
C1	644.57±6.54	17.68±0.55	0.24	102.56±1.36	1.33
C2	671.97±6.37	19.06±0.55	0.15	98.90±0.81	0.83
C3	693.97±8.36	21.66±1.08	0.17	104.71±1.10	1.06
H1	885.92±5.58	16.22±0.45	0.48	101.62±0.68	0.68
H2	806.81±6.80	18.95±0.57	0.26	101.23±0.55	0.55
H3	730.56±3.17	16.58±0.47	0.24	101.48±0.51	0.48
E1	889.20±9.40	23.17±0.79	0.35	101.07±0.79	0.79
E2	892.44±6.64	26.77±1.23	0.23	101.45±0.61	0.60

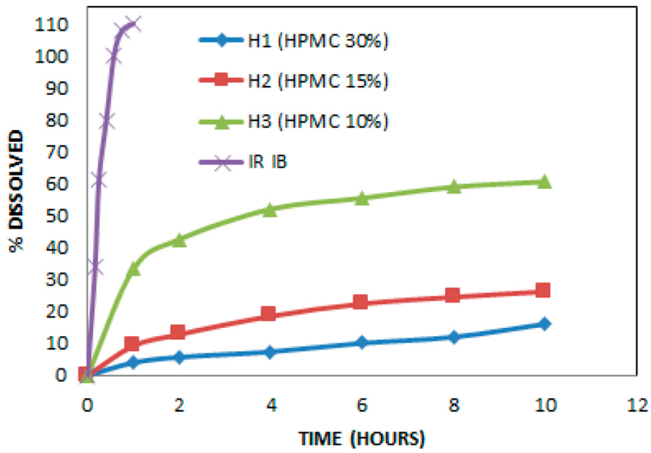

FIGURE 1 – *In vitro* release of tablets containing IB IR and HPMC as the main rate-controlling polymer. (X) IB IR; (Δ) 10% HPMC; (×) 15% HPMC; (♦) 30% HPMC.

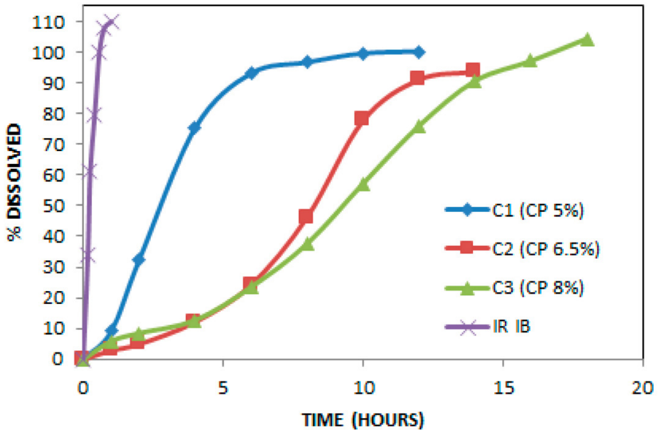

FIGURE 2 – *In vitro* release of tablets containing IB IR and Carbopol®971P as the rate-controlling polymer. (X) IB IR; (♦) 5% CP; (×) 6.5% CP; (Δ) 8% CP.

combination of the two, depending on the solubility of the drug (Harris *et al.*, 2006). Because IB is poorly water soluble, drug release from the HPMC matrix system is likely to be predominately controlled by the dissolution rate of the polymer. Note that the grade of HPMC used in the developed formulations was METHOCELE 4M, a relatively high molecular weight polymer with a high viscosity (about 4000 cps for a 2% solution) (Rowe, Sheskey, Quinn, 2009). A lower molecular weight grade of the same polymer (e.g. K100LVCR or METHOCELE 50LV, with viscosities of approximately 100 and 50 cP, respectively) may be used to achieve a faster erosion (dissolution of the polymer matrix) rate and thus a faster drug release rate (Rowe, Sheskey, Quinn, 2009; Tiwari, Dinunzio, Rajabi, 2011).

The dissolution results of the matrix formulations containing CP as the primary rate-controlling polymer are shown in Figure 2.

CP is a cross-linked acrylic acid polymer that differs structurally from linear polymers such as HPMC, and is capable of forming gels at lower concentrations (Lubrizol Advanced Materials, 2008). The formulations with CP showed rapid gel formation in the dissolution media due to ionization of the carboxylic acid functional groups (Nizar, Hatim, Wasfy, 2011). This rapid gelation, as evidenced by less than 6% of drug being released within the first hour of the dissolution test, minimizes the burst effect common with HPMC matrices. When 5% CP was used, approximately 90% of the IB was released over a 6-hour period. However, when the polymer concentration was increased to 6.5% and 8% (C2 and C3, respectively), the release of IB was much slower and extended for over 12 hours. An f_2 similarity evaluation confirmed that these formulations did not have similar profiles ($f_2 < 50$).

It should be noted that CP used in low concentrations (<3%) also improved the physical characteristics of the tablets, giving increases in tablet hardness and lower friability at lower compression forces. A minor tendency to stick on the punch faces was observed when this polymer was included in the EC and HPMC formulations. The CP levels in all tablet formulations were kept low to avoid effects on the dissolution; thus, the release of IB was predominantly dependent on the main (highest concentration) polymers used (Lubrizol Advanced Materials, 2011).

Figure 3 shows the dissolution profiles of matrix formulations containing 20% and 30% EC as the primary rate-controlling polymer.

The EC matrix tablets showed similar dissolution profiles ($f_2 = 89$), irrespective of the concentration of the

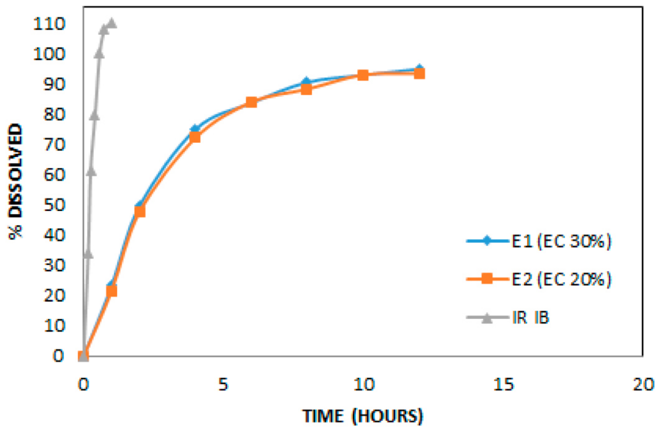

FIGURE 3 - *In vitro* release of tablets containing IB IR and EC as the main rate-controlling polymer. (X) IB IR; (Δ) 20% EC; (♦) 30% EC.

polymer, with approximately 90% of the drug released after 8 hours. It should be noted that the dissolution profiles of the EC-based formulations were different to the profiles of the matrices containing either HPMC or CP, as evidenced by f_2 values of less than 50. Interestingly, drug release from the EC matrix exhibited bimodal behavior: the first 4 hours showed a relatively fast release of IB (75% of the drug released at hour four), then a slow release phase. However, the E1 formulation contained a higher amount of MCC (30%), which when tableted produced slightly harder tablets (23.17 kp) compared with the E2 formulation (average hardness of 26.77 kp). Tablet hardness can influence the rate at which water permeates into the tablet and thus how quickly the drug releases from the system. The amount of MCC incorporated in the matrix tablets may have an effect on the deformation of the polymer particles (average particle size of 305 µm) during compression and therefore affect the porosity of the tablet, with higher MCC concentrations creating a less porous matrix (Tiwari, Dinunzio, Rajabi, 2011). The type of the polymers and the nature of excipients, such as MCC; as well as the physical properties of the granules, such as the specific surface area, shape, and hardness, can significantly affect the rate of dissolution of drugs contained in a formulation (Reddy, Mutalik, Reddy, 2003). In this study, the hardness of all the tablets investigated had no direct effect on drug release. Although the EC tablets had the highest hardness values they showed faster IB release than the other formulations. Table III shows the dissolution similarity factor values for the different formulations; in all cases, there was no similarity to the reference formulation.

TABLE III - f2 Values from the different formulations

Formulation	F2 value
C1	25.5
C2	48.4
C3	44.8
H1	24.7
H2	31.8
H3	37.3
E1	25.5
E2	25.5

In modified-release systems, understanding the drug-release mechanisms of different dosage forms is necessary to optimize the tablet design (Bernard *et al.*, 2004; Dash *et al.*, 2010). Table IV shows the values of r^2 and the rate constants obtained for the different kinetic models of all of the formulations investigated in this study. Figures 4-7 show analysis of the linear regression graphs corresponding to different kinetic models from the dissolution profile of C3, the formulation containing the highest level of Carbopol. The slopes of the lines correspond to the release rate constants (k) in the zero-order and Higuchi models, while the value for k in the first-order model was obtained from the equation: slope = –k/2.303.The value of the release exponent *(n)* is related to the slope of the line in the Korsmeyer-Peppas model.

The release kinetics of the C3 formulation showed the best linearity (r^2 =0.977) in fitting zero-order kinetics, suggesting the release rate was time independent. As

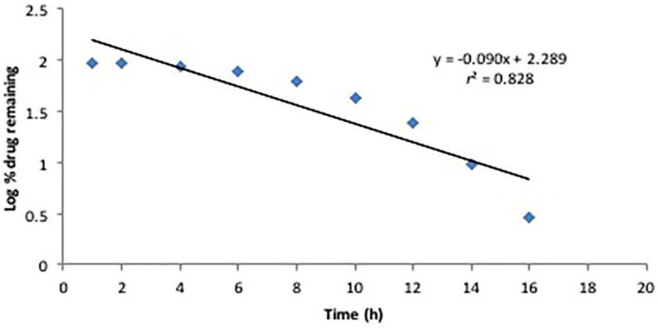

FIGURE 4 - First-order release model of C3.

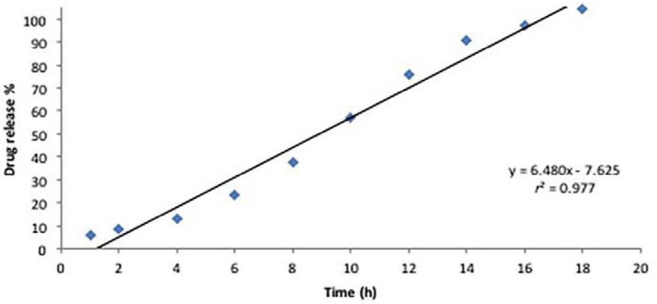

FIGURE 5 - Zero-order release model of C3.

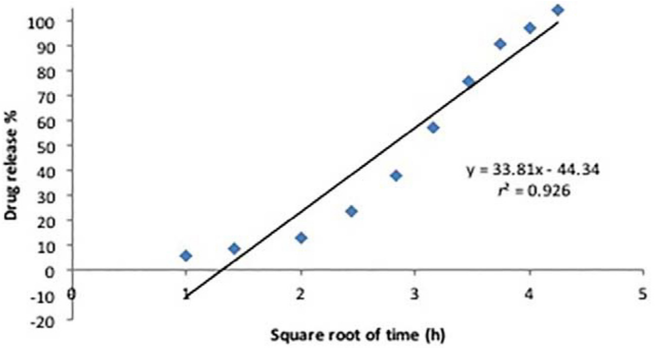

FIGURE 6 - Higuchi release model of C3.

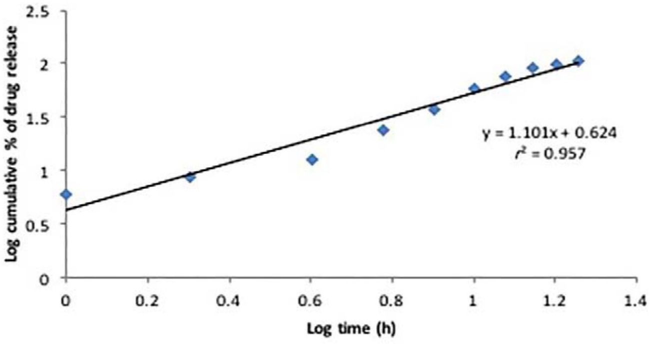

FIGURE 7 -Korsmeyer-Peppas model for the mechanism of drug release.

reported (Varelas, Dicon, Stediner, 1995), these models fit hydrophilic matrix systems containing poorly water-soluble drugs. In addition, the value of the release exponent *n* in the Korsmeyer-Peppas model approached a value of one, which corresponds to a case II transport mechanism, where drug release is predominately controlled by polymer relaxation and erosion. It is interesting to note that the formulations containing less CP (C1 and C2) had lower r^2 values in the zero-order release model, suggesting that higher levels of this polymer are necessary to achieve time-independent drug release. These results are in agreement with previously published data (Lubrizol Advanced Materials, 2011).

In contrast to the CP formulations, the formulations containing the hydrophobic EC (E1 and E2) showed a best fit to first-order kinetics (r^2 =0.961 and 0.973, respectively) and the exponent value *n* from the Korsmeyer-Peppas model ranged between 0.5 and 1, indicating a combination of diffusion and erosion mechanisms. This so-called anomalous diffusion (non Fickian) was likely due to swelling and relaxation of the EC in the dissolution media. A study using matrix tablets of IB and EC found that diffusion was the predominant mechanism of drug release (Chandran, Asghar, Mantha, 2008; Lopes, Sousa, Costa, 2006).

The value of the diffusional exponent *n* for the H3formulation indicates a Fickian diffusion–type release mechanism for the IB. Fickian diffusional release shows a rapid initial release, followed by a decrease in release owing to a chemical potential gradient (Bernard *et al.*, 2004; Harris *et al.*, 2006; Singh *et al.*, 2012). These findings are in agreement with previous reports that have shown that poorly soluble drugs are released mainly by attrition mechanisms from hydrophilic and swellable polymeric matrices (Vueba *et al.*, 2005).Table IV shows the values of r^2 and the rate constants obtained from the different kinetic models for the formulations investigated in this study.

CONCLUSIONS

Matrix tablets containing a model poorly water-soluble compound IB formulated with a hydrophilic, rate-controlling polymer (CP®971P) at concentrations above 6.5% could be prepared by direct compression. These tablets showed drug release over a 12-hour time period. The rapid gelation of the CP polymer prevented the initial burst effect commonly observed with HPMC and EC matrices. Moreover, at the highest Carbopol concentration (8%), drug release generally followed zero-order kinetics, suggesting that this system has the potential to maintain a constant plasma concentration of IB over 12hours, which could reduce the frequency of administration and the occurrence of adverse effects associated with repeated administration of conventional IB tablets. Further research, however, is needed to investigate whether such a system will follow zero-order kinetics *in vivo*.

TABLE IV - Kinetics parameters calculated

Formulation	Zero Order		First Order		Higuchi		Korsmeyer-Peppas		
	r^2	k_0 (h^{-1})	r^2	k_1 (h^{-1})	r^2	k_H ($h^{-1/2}$)	r^2N		k_{KP} (h^{-n})
C1	0.769	7.88	0.973	0.5803	0.880	38.07	0.908	1.031	0.0773
C2	0.956	8.02	0.89	0.2210	0.901	37.49	0.966	1.437	0.0211
C3	0.977	6.48	0.828	0.2072	0.926	33.81	0.957	1.101	0.0433
H1	0.983	1.26	0.979	0.0138	0.945	5.19	0.970	0.569	0.0434
H2	0.940	1.87	0.951	0.0230	0.988	8.07	0.994	0.466	0.0895
H3	0.867	2.82	0.909	0.0552	0.946	12.37	0.976	0.259	0.3332
E1	0.784	5.78	0.973	0.2395	0.893	27.83	0.918	0.583	0.2224
E2	0.789	5.87	0.961	0.2256	0.898	28.26	0.922	0.612	0.2036

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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