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The Influence of Formulation on the Dissolution Profile of Diclofenac Sodium Tablets

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ABSTRACT In attempts to design delayed-release tablets of diclofenac sodium, seven experimental batches were produced. The influence of superdisintegrant croscarmellose sodium (CCS), the granulation process, and the thickness of Eudragit® L 100 coating film were evaluated. The values of dissolution efficiency and the similarity factor were used to compare the dissolution profiles of each experimental batch and the reference Voltaren®. Both methods appear to be applicable and useful in comparing dissolution profiles. Based on such values four batches were considered similar when contrasted with the reference. The results suggest an optimal relationship between the amount of CCS and the thickness of the coating film, which provides appropriate dissolution rate of diclofenac sodium from the dosage forms.

KEYWORDS Diclofenac sodium, Dissolution profile, Croscarmellose sodium, Eudragit® L 100

INTRODUCTION

The development of a pharmaceutical dosage form involves several steps, with the purpose to create a physical system containing the active substance and requisites of quality that assure its efficacy and safety (Prista et al., 1996). Although most prescription drugs are administered in solid oral dosage forms due to convenience and stability, issues of low bioavailability are common (Blanchard, 1978). The efficiency of a solid oral dosage form depends on its ability to release the drug-involving phenomena such as disintegration, dissolution, and diffusion (Flynn et al., 1974; Blanchard, 1978).

Since the drug should be dissolved to be absorbed, suitable dissolution characteristics are important to ensure that the drug product will exert the desired therapeutic effects (Chow & Ki, 1997). Among the factors with a potential to influence the bioavailability are the physical-chemical characteristics of the drug molecules (i.e., partition coefficient, ionization constant, solubility, polymorphism, particle size and particle shape distribution, stability at various pH values and against gastrointestinal enzymes), the pH and physiological conditions of the absorption site, and the manufacturing factors such as excipients and equipments (Blanchard, 1978; Giunchedi et al., 1990; Johnson et al. 1991).

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The adjustment of the pharmaceutical parameters is the major challenger during the development of a generic formulation to become bioequivalent to the reference product. After oral administration of a solid dosage form, the absorption of the drug substance depends on its dissolution in the gastrointestinal tract. In case of a lower dissolution rate than absorption rate, the release of the drug will be a limiting step of absorption and will modify its kinetic and bioavailability (Brossard & Wouessidjewe, 1990).

Throughout formulation studies, dissolution profiles obtained from the reference and the test products generally are compared with the purpose of maximizing the chances of success during the bioequivalence tests (Moore & Flanner, 1996; Gohel & Panchal, 2000).

Dissolution profiles are obtained by plotting the cumulative percentage of drug released versus sampling time point. It is considered an important tool to detect the influence of critical manufacturing variables, such as the method of compression and the granulation procedure (Gozáles et al. 1995), the mode of incorporating the diluents (Holgado et al., 1995), the type of disintegrant (Bolhuis et al., 1982; Giunchedi et al., 1990), and the coating parameters (Sielpmann et al., 1999). Moreover, comparative studies of different formulations (Ferraz et al., 1998; Pinho & Storpitis, 1999; Villanova et al., 1999), in vitro–in vivo correlations (Liu et al., 1995), and interactions between components of the dosage form (Lorenzo-Lamoza et al., 1998; Khalil & Sallam, 1999) can be evaluated using dissolution profiles. Therefore, based on such information it is possible to select the appropriate manufacturing process and excipients that allow the candidate drug to reach the bioequivalence of the reference product.

Several methods have been described for the comparison of dissolution profiles including the dissolution efficiency (DE%) and the similarity factor (f_2) (Polli et al., 1997; Shah et al., 1998). The DE% is defined as the area under the dissolution curve (AUC) between different time points, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975). This method enables comparison of several formulations simultaneously and theoretically can be related to the the mean plasma concentration time curve obtained after deconvolution of the in vivo data (Vaughan & Tucker, 1976; Andrade et al., 2002; Corrigan et al., 2003). The similarity factor (f_2), proposed by Moore and Flanner (1996), is recommended by the US Food and Drug Administration (FDA) to compare dissolution profiles (USHHS, 1997). The f_2 equation is a logarithmic transformation of the average of the squared vertical distances between the test and reference mean dissolution values at each dissolution time point, multiplied by an appropriate weighting (O'Hara et al., 1998). The test product is considered similar to the reference when its f_2 value is higher than 50%, which means that the average difference between both dissolution profiles is less than 10% at all sampling points (Shah et al., 1998). In addition, to use this method, the within-batch variability, in terms of the coefficient of variation, should be less than 15%; and when using the mean data, the coefficient of variation at earlier time points should not be more than 20% and not exceed 10% at later time points (O'Hara et al., 1998).

The objective of this study was to develop controlled-release tablets of diclofenac sodium 50 mg, a nonsteroidal anti-inflammatory and analgesic drug, which presents an in vitro dissolution profile equivalent to the reference (Voltaren® 50 mg) by using the concepts of DE% and f_2.

The formulation factors considered in this work were: (1) percentage of super-disintegranting (croscarmellose sodium), (2) granulation technology (ribbon blender or high-shear mixer), (3) drying technology (stove or fluid bed dryer processor), (4) thickness of coating film (TCF), and (5) rotational speed of coating pan (RSP).

MATERIALS AND METHODS

Chemicals

Diclofenac sodium reference standard (lot H) and 1-(2,6-dichlorophenyl)indolin-2-one (lot G) were obtained from United States Pharmacopeia (Rockville, MD, USA). Diclofenac sodium raw material (Nortec S.A., Duque de Caxias, Brazil), croscarmellose sodium (CCS) and microcrystalline cellulose (MC 101) (Blanver Farmoquímica Ltda, Cotia, Brazil), cornstarch (Corn Products, Balsa Nova, Brazil), manitol (Getec, Rio de Janeiro, Brazil), sodium lauryl sulfate (Vetec, Rio de Janeiro, Brazil), magnesium stearate (F. M. Indústria e Comércio de Produtos Químicos Ltda., Cotia, Brazil), polymethacrylate (Eudragit® L 100; Rhon Pharma, Darmstadt, Germany), titanium oxide (Millenium Inorganic Chemicals S.A., Camaçari, Brazil), polyethylene glycol 6000 (ForLAB, Rio de Janeiro, Brazil), talc (Magnesita S.A., Contagem, Brazil), isopropanol (Rhodia S.A., São Paulo, Brazil), dibutyl phthalate (Riedel de Haën, Buchs, Switzerland), and pigments (Basf S.A., São Bernardo do Campo, Brazil) were used to produce the controlled-release tablets of diclofenac sodium. All the other chemicals were either analytical or HPLC grade.

Manufacturing of Cores

The cores of diclofenac sodium 50 mg (2 kg) were prepared by the wet granulation method using two processes, (1) high-shear mixer, model Pharma Matrix PMA 1 (Niro Inc., Columbia, MD, USA) and (2) ribbon blender (Lawes, São Bernardo do Campo, Brazil).

The cores consisted of diclofenac sodium (32.57%), microcrystalline cellulose (19%), sodium lauryl sulfate (0.2%), and magnesium stearate (1.95%). In addition, the amounts of cornstarch and CCS on each core were 16.28% and 0% (core C1), 15.78% and 0.5% (core C2), 14.28% and 2% (core C3), and 13.78% and 2.5% (core C4), respectively.

The powders were passed previously through a No. 20 mesh sieve, except the magnesium stearate, which was passed through a No. 45 mesh sieve.

In the first process, the materials, except the lubricant and disintegrant, were placed into the high-shear mixer and homogenized for 2 min at 400 rpm. Afterward, the powders were humidified with a suspension containing 13% of cornstarch in purified water (320 mL/kg of core) and mixed 2 min at 400 rpm. In addition, the resulting mixture was granulated for 2 min with the impeller motor at 400 rpm and chopper motor at 1500 rpm, and for 30 sec, the speed of the chopper motor was increased to 3000 rpm. In the second method, the powders were mixed for 25 min in a ribbon blender and the same proportion of the humectant was applied.

The granules from the high-shear mixer were dried into a fluid bed dryer model GPCG1 (GLATT, Binzen, Germany) at 60°C until 3% of humidity was reached, then passed through a No. 1.5 mesh sieve. Those granules obtained from the ribbon mixer were dried in a pharmaceutical stove (Lawes, São Bernardo do Campo, Brazil) at the same conditions and were passed once through a No. 1.5 mesh sieve and twice through a No. 2 mesh sieve.

The granules and the disintegrant (croscarmellose sodium) were placed into a cubic mixer, attached to a motor drive model AR 402 (Erweka, Düsseldorf, Germany), and mixed for 5 min at 120 rpm. The same procedure was performed adding lubricant (magnesium stearate). A minirotary tablet press machine Picolla, model B-2/10 (Riva, Buenos Aires, Argentina), equipped with 7-mm biconcave punches was used to produce the cores.

Preparation of Eudragit® L Film

Suspensions of Eudragit® L 100 were prepared according to the thickness of the film used to coat the diclofenac sodium cores (3.3, 3.5, 4, and 4.5 mg/cm^2) (Table 1). In brief, in a mixing vessel containing isopropyl alcohol (66%), weighed quantities of talc (14%), magnesium stearate (2%), titanium oxide (6%), and pigments (6%) were added one after the other under stirring. The suspension was dispersed in an ultra-turrax model T 50 (IKA® Werke GmbH & Co., Staufen, Germany) and polyethylene glycol 6000 (2%) dissolved in water (4%) was added and homogenized. This 30% pigment suspension was let to stand overnight.

A base coat solution was prepared at room temperature with stirring by adding 13 parts by weight of Eudragit® L 100 (= 12.5% dry polymer substance) into a mixture of 82 wt. parts isopropyl alcohol and 5 wt. parts water containing 50% of dibutyl phthalate.

Before the coating process both mixtures were combined, diluted when necessary with isopropyl alcohol to a concentration of 8% to 10% of total solids, and homogenized for 15 min in a cone mill model MKO 2000 (IKA® Werke GmbH & Co., Staufen, Germany) to facilitate spraying, reduce the tendency to sticking, and to ensure more uniform distribution.

TABLE 1 **Technological Parameters of Experimental Batches of Delayed-Released Diclofenac Sodium Tablets**

Pilot	%CCS	TCF	RSP
A	0.5%	4.5 mg/cm^2	200 rpm
B	0.5%	4.5 mg/cm^2	400 rpm
C	2%	4.5 mg/cm^2	200 rpm
D	0%	3.3 mg/cm^2	200 rpm
E	0.5%	3.5 mg/cm^2	200 rpm
F	2%	4 mg/cm^2	200 rpm
G	2%	3.3 mg/cm^2	200 rpm

CCS = Croscarmellose sodium; TCF = thickness of coating film; RSP = rotational speed of coating pan.

Coating Procedure

The cores were placed into a stainless steel coating pan (9.5 L, 275 mm i.d.; Erweka, Düsseldorf, Germany), prewarmed, and coated at 40°C using a pneumatic spray gun (1.2 mm of nozzle diameter). To test the effect of rotational speed of the coating pan, tablets were coated at 200 and 400 rpm.

The distance between the nozzle and the tablets was set at 250 mm, the angle of inclination of the coating unit was 35°, the inlet air rate was 1 m^3/min, the spray rate was set at 10 g/min, and the atomizing air pressure was 0.5 bar. During spray application, the coating suspension was mixed continuously. The percent mass increase of the tablets upon coating was taken as indicative of the coat thickness.

Dissolution Profiles

The dissolution profiles of the experimental batches and five lots of the reference (Voltaren® 50 mg) on acid (HCl 0.1 N, 900 mL) and buffer (pH 6.8, 900 mL) stages were performed according to the dissolution test conditions specified in the Brazilian Pharmacopeia (*Farmacopéia brasileira,* 2003).

The tablets were first exposed to HCl (0.1 N) and transferred into the phosphate buffer. Samples (10 mL) were collected after 30, 60, and 120 min during the acid phase and after 5, 10, 20, 30, 45, and 60 min during the buffer phase. The same volume was replaced with fresh dissolution medium at 37°C. After appropriate dilution, the samples were analyzed for diclofenac sodium at 276 nm using a U-2001 spectrophotometer (Hitachi, Tokyo, Japan). Cumulative percentage of drug released at each time point was calculated and the mean values of 12 tablets were used to perform the dissolution profiles and to determine the f_2 and DE%. The time interval equivalent to 70–90% dissolution was chosen to determine the DE% to ensure that most of the dissolution pattern was taken into account (Anderson et al., 1998), and only one time point after reach 85% of dissolution was used to calculate f_2 to avoid bias in the similarity assessment (Shah et al., 1998).

RESULTS AND DISCUSSION

Studies of Dissolution Profiles

The dissolution profiles in this study were derived from the mean of 12 tablets, and in all cases, the coefficient of variation (CV) within each time point varied from 2.1 to 10.8%.

The dissolution profiles of the cores C1, C2, C3, and C4 of diclofenac sodium produced using a high-shear mixer and fluid bed dryer were compared (Fig. 1). The lowest dissolution rates were observed for the cores without the super-disintegrant croscarmellose sodium (CCS) (C1) and with 2.5% of CCS (C4). The profiles of the cores C2 and C3 containing 0.5% and 2% of CCS, respectively, were similar and exhibited the highest dissolution rates.

The ethers of cellulose, like CCS, present gelling properties in contact with the aqueous medium, creating a hydrophilic barrier when used at high concentrations, which can retard the drug release (Zuleger & Lippold, 2001). Such a property is compatible with the behavior observed for core C4 containing the highest percentage of CCS (2.5%), but a profile similar to the core without any desintegrant (C1).

The core C5 showed the lowest dissolution rate contrasted to those manufactured using a high-shear mixer and fluid bed dryer (Fig. 1). The higher compactness of the granules produced by the ribbon mixer and dried in a pharmaceutical stove might have delayed the diffusion of dissolution medium into the pores of the core and compromised the release of diclofenac sodium (Sunada et al., 1998).

Based on these results, the cores with 0%, 0.5%, and 2% of CCS produced using a high-shear mixer and fluid bed dryer were selected to be coated. After coating, the tablets were submitted to the dissolution test, and, as expected, no significant release (<1%) of drug was observed after 2 h in contact with HCl 0.1 N.

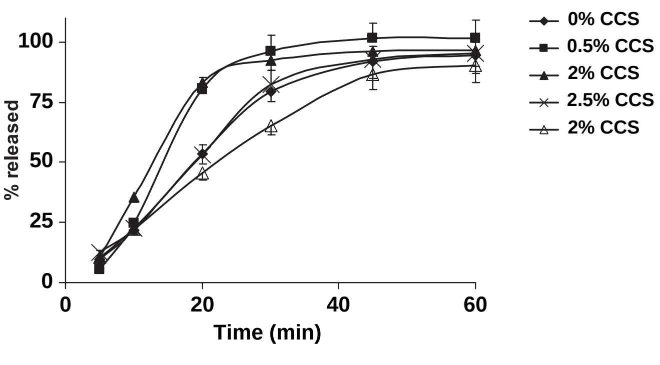

FIGURE 1 Dissolution Profiles on Buffer Stage (pH 6.8) of the Cores of Diclofenac Sodium (Mean ± SD) Containing Different Concentrations of Croscarmellose Sodium (CCS) and Produced Using High-Shear Mixer: (◆) Core C1; (■) Core C2; (▲) Core C3; (×) Core C4, or Ribbon Mixer; (△) Core C5 (*n* = 12).

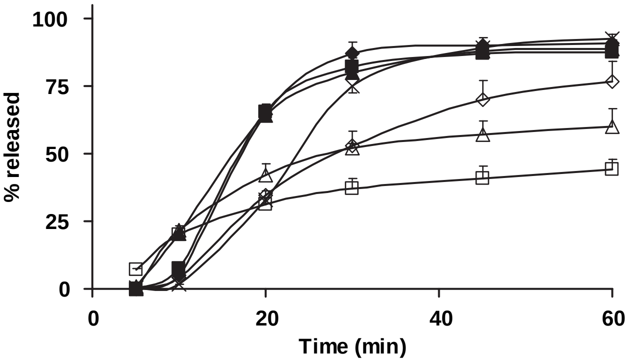

FIGURE 2 Dissolution Profiles on Buffer Stage (pH 6.8) of the Pilots of Diclofenac Sodium (Mean ± SD) With Different Concentrations of CCS and Thickness of Polymeric Film Varying of 3.3 to 4.5 mg/cm^2: (♦) Pilot A (0.5% CCS; 4.5 mg/cm^2); (■) Pilot B (0.5% CCS; 4.5 mg/cm^2); (▲) Pilot C (2% of CCS; 4.5 mg/cm^2); (×) Pilot D (0% CCS; 3.3 mg/cm^2); (◇) Pilot E (0.5% CCS; 3.3 mg/cm^2); (□) Pilot F (2% CCS; 4 mg/cm^2); (△) Pilot G (2% CCS; 3.3 mg/cm^2). The Rotational Speed of the Coating Pan Was Set at 200 rpm, Except for Pilot B (400 rpm) (*n* = 12).

The same tablets were tested in buffer pH 6.8 and their dissolution profiles of the pilots were compared (Fig. 2).

The tablets with lower thickness of coating film (pilots F and G) and 2% of CCS had their dissolution rate compromised when compared with the pilots D and C. These results suggest that a lower thickness of the coating film associated with the presence of the super-disintegrant in the core are less effective in protecting the dosage form against an acid environment such as gastric fluid. This combination may have privileged to some extent the diffusion of the acidic solution into the core during the first stage of dissolution test, which may have impaired the dissolution rate of diclofenac sodium during the subsequent buffer stage.

To assess such a phenomenon, a qualitative experiment was performed. In brief, 500 mg of diclofenac sodium was added into the dissolution vessel containing 900 mL of HCl 0.1 N (37°C). After 2 h under continue agitation (50 rpm), the residue was removed and dried under vacuum until attaining constant weight. The same residue was subjected to the buffer condition of the dissolution test and again the remainder was dried as mentioned here. The pure drug and both residues were dispersed in potassium bromide and their infrared spectra were recorded using a Perkin Elmer FT-IR spectrophotometer (Spectrum 1000, Boston, MA, USA). The FT-IR spectra of the raw drug have revealed two typical bands at around 1574 and 1399 cm^{-1}, attributed to the symmetrical and asymmetrical stretching of the caboxylate anion, respectively (Silverstein & Bassler, 1967). However, the spectra of both residues were similar but different from the pure drug and presented four distinct bands typically due to stretching of the O–H group of carboxylic acid (3000 and 2500 cm^{-1}), stretching of the C=O group of aliphatic carboxylic acid (1694 cm^{-1}), and bending vibration of the O–H moiety of carboxilic acids (938 cm^{-1}) (Silverstein & Bassler, 1967). These results support the conversion of the diclofenac sodium into its acid form in the presence of HCl 0.1 N and, in addition, suggest that the buffer pH 6.8 was not able to promote complete solubilization of the free acid formed. When the diclofenac sodium (500 mg) was direct tested under buffer conditions without any previous contact with the acidic medium, a complete solubilization was observed after 45 min.

Lowering the pH of a suspension of diclofenac sodium (pKa = 4) (Sallman, 1986) with HCl 0.1 N resulted, initially, in a slight increase (3%) followed by an abrupt drop of its solubility and consequent precipitation of the free acid (Ledwidge & Corrigan, 1998).

The effect of a previous contact of a solution of HCl 0.1 N on the dissolution rate of diclofenac sodium-containing tablets in buffer pH 6.8 was also observed by others (Sheu et al., 1992; Ho et al., 1997). The decrease on the release of diclofenac sodium from the dosage forms during the buffer stage was related inversely to the time the tablets remained in the acidic solution. Such behavior was attributed to a deposition of an insoluble layer of the free acid on the core surface, which has lower solubility in pH 6.8 than the salt form.

In this study, the dissolution profiles of the pilots with 0.5% of CCS (pilot A, B, and E) (Fig. 2) support these observations. Pilot E, with the thinnest coating film, demonstrated lower release of the diclofenac sodium when compared with pilots A and B, but it was higher than the pilots F and G, which have coating films of 3.3 mg/cm^2 and 4.0 mg/cm^2 thickness, respectively, but a higher percentage of super-disintegrant (2%). The rotational speed of the coating pan did not influence the drug release, since pilots A and B presented similar dissolution profiles (Fig. 2).

The dissolution profiles of five lots of Voltaren® in buffer stage demonstrated a homogenous shape of the curves and a lower variability (<5%) in each time

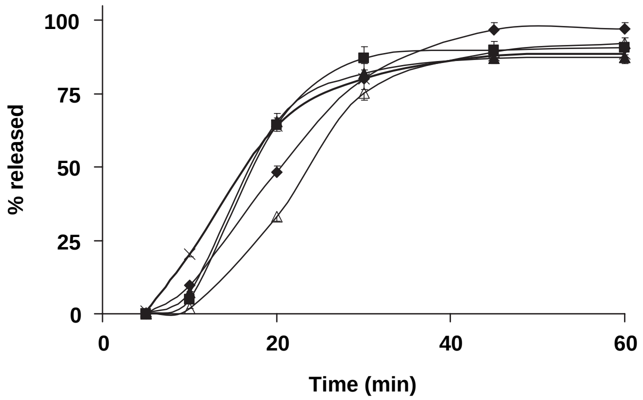

FIGURE 3 Dissolution Profiles on Buffer Stage (pH 6.8) of the Pilots A (■), B (▲), C (×), D (△), and the Reference (Voltaren®) (◆) (Mean ± SD) ($n = 12$).

point (data not shown). Therefore, for further comparisons only one lot of the reference was used.

Pilots A, B, and C with highest thickness of coating film (4.5 mg/cm^2) and containing the super-desintegrant CCS (0.5% or 2%), and pilot D with the lowest thickness of Eudragit® (3.3 mg/cm^2) but without CCS, showed a similar dissolution profile in pH 6.8 when compared to the reference (Voltaren® 50 mg) (Fig. 3).

Fit Factors and Dissolution Efficiency

The mean values of DE% ($n = 12$) were analyzed by one-way-analysis of variance (ANOVA) using Prism® software version 4.00 for Windows® (GraphPad Software Inc., San Diego, CA, USA). The mean DE% of the experimental batches were further compared with the reference by using the Dunnett's multiple comparison test ($p = 0.05$). The results indicated that only the experimental batches A (DE: 68.88 ± 10.7%; f_2: 53.67%), B (DE: 67.21 ± 18.5%; f_2: 51.79%), C (DE: 68.73 ± 9.1%; f_2: 51.73%), and D (DE: 60.25 ± 7.8%; f_2: 54.35%) were similar to the Voltaren® (DE: 67.94 ± 8.2%), since their DE% did not differ significantly from the reference, and the values of f_2 were higher than 50% as recommended by FDA (SUPAC-MR, 1997). Conversely, the DE% values of pilots E (48.41 ± 17.1%), F (46.35 ± 14.7%), and G (34.26 ± 20.1%) differed significantly from the reference ($p < 0.01$) and their f_2 values were 36.37%, 29.74%, and 10.34%, respectively.

The experimental batches A (0.5% CCS), B (0.5% CCS), and C (2% CCS) were coated with 4.5 mg/cm^2 of polymeric film, while pilot D, without super-disintegrant, was coated with 3.3 mg/cm^2. Pilots E (0.5 % CCS), F (2% CCS), and G (2% CCS), which did not show similarity with the reference, were coated with 3.5, 3.3, and 4 mg/cm^2 of polymeric film, respectively.

These results demonstrated that the ratio of CCS and the thickness of Eudragit® L 100 coating film have a direct influence on the dissolution rate of diclofenac sodium and should be adjusted during the development stage to obtain tablets with similar profile to the reference product (Voltaren®).

CONCLUSIONS

The dissolution efficiency (DE%) and the similarity factor (f_2) models showed to be applicable and useful tools to compare dissolution profiles. Based on these values, four different formulations of controlled-release tablets of diclofenac sodium 50 mg with in vitro profiles similar to the reference (Voltaren®) were obtained. In addition, this work demonstrated that the ratio between the proportion of super-disintegrant, croscarmellose sodium, and the thickness of the Eudragit® L 100 coating film was a crucial factor to adjust the dissolution rate of the diclofenac sodium in the experimental batches of controlled-release tablets.

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