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Note

Mathematical evaluation of in vitro release profiles of hydroxypropylmethylcellulose matrix tablets containing carbamazepine associated to β-cyclodextrin

Letícia S. Koester, George G. Ortega, Paulo Mayorga, Valquiria L. Bassani*

Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

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Abstract

The release kinetics of carbamazepine (CBZ) either complexed or physically mixed with β-cyclodextrin (βCD) from hydroxypropylmethylcellulose (HPMC) matrix tablets was investigated using different mathematical equations. The model-dependent approach was compared to the utilization of fit factors. Notwithstanding difference (f_1) and similarity (f_2) factors allowed the differentiation of the formulations containing CBZ complexed with βCD from the one containing a simple physical mixture of CBZ and βCD. The Weibull model was more useful for comparing the release profiles. Weibull parameters were more sensitive to the differences between the two release kinetic data.

Keywords: Carbamazepine; β-Cyclodextrin; Hydroxypropylmethylcellulose; Fit factors; Zero-order; First-order; Higuchi; Weibull

1. Introduction

In a previous work [1] we described the preparation of carbamazepine/β-cyclodextrin (CBZ/βCD) complexes in solid state by spray-drying and freeze-drying. The complexes were incorporated in hydroxypropylmethylcellulose (HPMC) tablets. It was observed that the 30% HPMC matrix tablets containing CBZ previously complexed with βCD released the drug faster, compared to the formulation containing a physical mixture (PM) of both substances, regardless of the drying method employed. The matrices containing 30% HPMC associated to CBZ/βCD complex were considered more promising dosage forms for modulating CBZ release from a controlled release system. However, the graphical analysis performed formerly allowed us to conclude that formulations containing the spray-dried and freeze-dried complexes were qualitatively equivalent to each other and that the release of CBZ from the PM was slower compared to them.

In order to analyze dissolution data equivalence, FDA guidance documents [2] consider some approaches such as a model-independent approach based on the calculation of difference (f_1) and similarity (f_2) factors [3], which is currently applied [4,5]. The main advantage of the f_1 and f_2 equations is to provide a simple way to describe the comparison of the data [6]. Nevertheless, both equations do not take into account the variability or correlation structure of the data, are sensitive to the number of points used [6] and, from a statistical point of view, this method seems to be less discriminating than other methods such as ANOVA-based and model-dependent methods [5]. Although ANOVA methods take the variability in the dissolution profile into account, this method has been also questioned for ignoring the correlation between the dissolution time points, namely, for treating each time point as if it were independent of the others [6]. According to Costa and Lobo [7], release models with major applicability and that best describe drug release phenomena are Weibull [8] along with Higuchi, zero-order and Korsmeyer-Peppas.

In this context, the purpose of the present work is to compare the 30% HPMC formulation containing CBZ complexed with βCD with the one containing CBZ physically mixed with βCD and demonstrate the effect of

* Corresponding author. Address: Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Av. Ipiranga, 2752, 90610-000 Porto Alegre, RS, Brazil. Tel.: +55-51-3316-5090; fax: +55-51-3316-5437.

E-mail address: valqui@farmacia.ufrgs.br (V.L. Bassani).

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CBZ/βCD complexation on drug release rate, using some model-dependent methods (zero-order, first-order, Higuchi and Weibull). Additionally, data analysis by fit factors is considered and compared to the approach performed using the referred models.

2. Materials and methods

2.1. Materials

The matrices were constituted by 12 mm tablets containing 30% HPMC along with either PM or solid complexes of CBZ/βCD. The formulations containing spray-dried and freeze-dried complexes were named SD and FD, respectively. The tablet hardness was kept constant at 61.7 ± 3.4 N. The dissolution tests had been performed in a Pharma Test dissolution tester coupled to a HP 8452A spectrophotometer, and the overall conditions were as follows: 75 rpm; distilled water as dissolution medium; 37 °C; six replicates. The tablets were placed in baskets at the bottom of the vessels in order to avoid floating.

2.2. Dissolution data analysis

A mathematical comparison was performed by applying f_1 [Eq. (1)], and f_2 [Eq. (2)]. According to the FDA guidance [2], values of f_1 between zero and 15 and of f_2 between 50 and 100 ensure sameness or equivalence of the two dissolution profiles. In both equations, R and T represent the dissolution measurements at P time points of the reference and test, respectively:

$$f_1 = \left\{\left[\sum_{i=1}^{P} |R - T|\right] \Big/ \left[\sum_{i=1}^{P} R\right]\right\} \times 100 \quad (1)$$

$$f_2 = 50 \log\left\{\left[1 + \left(\frac{1}{P}\right)\sum_{i=1}^{P}(R - T)^2\right]^{-1/2} \times 100\right\} \quad (2)$$

CBZ release kinetics was analyzed by various mathematical models, which were applied considering the amounts of drug released from 30 min to 5 h. Table 1 presents the models tested [8–10]. A simplified Higuchi model was adopted [7,11].

Table 1
Applied dissolution models

Model	Equation
Zero-order	$Q_t = Q_0 + k_0 t$
First-order	$\ln Q_t = \ln Q_0 - k_1 t$
Higuchi	$Q_t = k_H t^{1/2}$
Weibull	$\mathrm{Log}[-\ln(1 - m)] = \beta \log(t - \mathrm{Ti}) - \log a$

Q_t, amount of drug released in time t; Q_0, initial amount of drug in the tablet; k_0, k_1, k_H, release rate constants; m, accumulated fraction of the drug; β, shape parameter; a, scale parameter; Ti, location parameter.

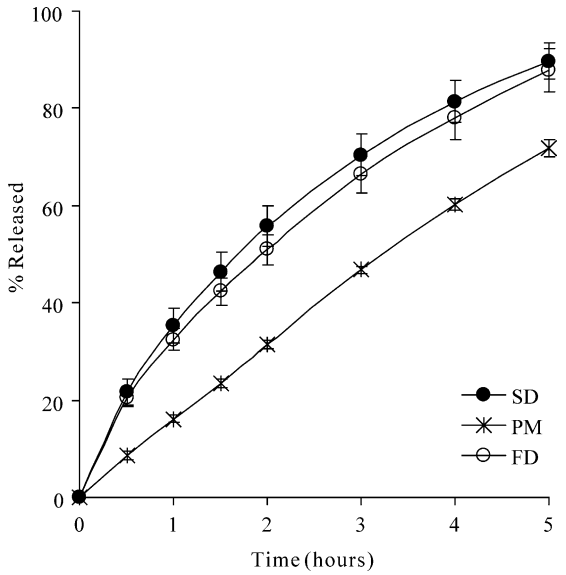

Fig. 1. In vitro dissolution profiles of CBZ from SD, FD and PM formulations.

3. Results and discussion

The cumulative % CBZ released versus time plots from PM, SD and FD matrix tablets are presented in Fig. 1. The values of f_1 and f_2 for formulations SD, FD and PM were calculated from the means of percent dissolved at each time point (Table 2). The number of points was limited to not more than one after 85% dissolution, as recommended by Shah and co-workers [12]. As one can observe, the dissolution profiles of SD and FD can be considered equivalent to each other. On the other hand, the formulation containing the PM of CBZ and βCD is neither similar to SD nor to FD. Although fit factors are easy to calculate, they lack further information about the kinetics of drug release from these tablets. In this way, the linearization of CBZ dissolution profiles by using the equations presented in Table 1 would better characterize the differences found between the systems containing complexes or a PM of CBZ/βCD. The parameters calculated by these models and the determination coefficients (R^2) obtained are summarized in Table 3. Considering the R^2 values, the calculated first-order model failed to fit FD and PM, whereas it could fit SD ($R^2 = 0.993$). Higuchi model was able to fit SD and FD but not PM. This can be an indication that the release kinetics of CBZ complexed with βCD may be square root time dependent, as in the Higuchi

Table 2
f_1 and f_2 values for each comparison

Comparisons	f_1 [a]	f_2
SD × FD	5.5 or 5.8	74.0
SD × PM	28.4 or 39.6	36.8
FD × PM	25.2 or 33.8	40.4

[a] The first f_1 value is obtained when the first formulation on the left column is set as reference.

Table 3
Parameters and determination coefficients of the linearization of CBZ release from SD, FD and PM formulations

Dissolution models		SD	FD	PM
Zero-order	k_0	3.38	3.32	2.90
	R^2	0.963	0.979	0.998
First-order	k_1	0.44	0.40	0.25
	R^2	0.993	0.987	0.988
Higuchi	k_H	9.04	8.95	8.50
	R^2	0.997	0.999	0.987
Weibull	β	0.92	0.95	1.15
	R^2	0.999	0.994	0.997
	Td	2.58	2.60	4.42
	a	−0.38	−0.40	−0.74

k_0, k_1 and k_H, release rate constants; β, shape parameter; Td, time interval necessary to release 63.2% of the drug; a, scale parameter; R^2, determination coefficient.

model, which can describe the drug dissolution from several types of modified release systems, e.g. plastic and wax matrices [7,13]. The zero-order model as well as the Weibull model were the ones which seem to adequately fit to the dissolution data of PM. Zero-order did not fit either SD or FD, which suggests that the release kinetics of CBZ from these formulations are different from the one observed in PM. Nevertheless, the Weibull equation was found to fit SD and FD dissolution data as well as PM, what corroborates the theory that this equation can be successfully applied to almost all kinds of dissolution curves [7].

Although Weibull distribution cannot adequately characterize the dissolution kinetic properties of the drug, it can describe the dissolution curve in terms of applicable parameters. The linearity of the Weibull plots can be observed in Fig. 2. The shape parameter, β, characterizes the curve as either exponential ($\beta = 1$), S-shaped with upward curvature followed by a turning point ($\beta > 1$), or as one with steeper initial slope than consistent with the exponential ($\beta < 1$) [8].

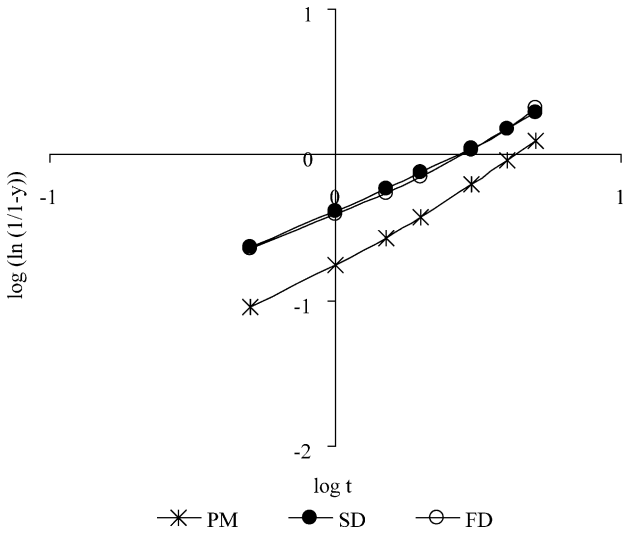

Fig. 2. Weibull plot for formulations SD, FD and PM.

Weibull β parameter was < 1 for SD and FD, and > 1 for PM (Table 3), suggesting that the dissolution curve shapes of formulations containing CBZ complexed with βCD are different from the curve shape of the PM. The time parameter, Td, can be calculated from a and β parameters ($a = (T_d)^{\beta}$) and represents the time interval necessary to dissolve 63.2% of the drug [8]. T_d was approximately 1.7 times higher for PM than for the other two formulations. Taken together, the analysis performed by the Weibull model suggests that the kinetics of CBZ release from formulations containing CBZ/βCD complexes are different from the kinetics observed in the formulation containing CBZ and βCD in a simple PM. Among the studied models, Weibull was considered a good model once it possesses parameters that are sensitive to the ranges of dissolution profiles.

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