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Dissolution Profiles of Diclofenac Potassium Tablets from the Argentinean Market

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Abstract

In this study, the aim was to apply different comparison methods to dissolution profiles of immediate release commercial tablets of diclofenac potassium. Diclofenac potassium is classified as a class II drug as per the biopharmaceutical classification system. Dissolution testing was conducted using the USP monograph of diclofenac potassium tablets. All brands fulfil the specifications of dissolution test of USP comparison of dissolution profiles were carried out model independent approaches. Results show that there was no significant difference in dissolution efficiency and mean dissolution time between the reference product and Brands II, IV, V and VI. Using fit factors, only Brands I, II and V were similar.

Keywords: *Soil acidification; Nitrogen fertilizer; Aluminium*

Abbreviations: MDT: Mean Dissolution Time; DE: Dissolution Efficiency; SD: Standard Deviation; CV: Variation coefficient

Introduction

Diclofenac is commercially present as sodium and potassium salt in tablets for oral administration and as diethylamine for topical application. While extensive literature is available for sodium salt [1-3], little has been reported on the potassium salt [4].

Diclofenac potassium has excellent antipyretic, analgesic and anti-inflammatory properties. Diclofenac potassium is claimed to dissolve faster and hence absorbed faster than sodium salt. It is also indicated for the treatment of primary dysmenorrhea and mild to moderate pain [5].

Diclofenac potassium is classified as a class II drug as per the biopharmaceutical classification system (BCS) [5]. The poor dissolution rate of water-insoluble drugs is still a major problem confronting the pharmaceutical industry. Fini *et al.* [6] studied the dissolution efficiency of diclofenac salts prepared using alkaline metals hydroxide or organic aliphatic bases.

In recent years, more emphasis has been placed on dissolution testing within the pharmaceutical industry and correspondingly, by regulatory authorities. As a result FDA, EMA and WHO [7-9] provide recommendations to compare dissolution profiles. A dissolution profile is defined as the measured fraction (or percentage) of the labelled amount of drug that is released from a dosage unit (tablet or capsule) at a number of predetermined time points when tested in a dissolution apparatus, such as the US Pharmacopeia (USP) I or II dissolution systems. The FDA suggest some acceptable approaches for establishing similarity of dissolution profiles, such as the model-independent and model-dependent approaches, although any approach would be considered once it had been justified.

Although immediate release solid dosage forms are routinely subjected to test such as content uniformity, weight, hardness, friability and disintegration, the test that is most often associated with the assessment of *in vivo* performance is the dissolution test.

Methods for comparing *in vitro* dissolution profiles can be classified into three main groups: ANOVA-based statistical methods, model-independent and model-dependent approaches.

ANOVA-based methods do not rely on curve fitting procedures and the dissolution data are used in their native form or as a simple transform and the analysis is capable of showing differences between profiles in level and shape. The latter characteristic is especially important with respect to learning about differences in the dissolution mechanism. The characterization as model-dependent method or model-independent method depends on the values which are used to perform the calculation. A model-independent method uses the dissolution data in their native form. The model-dependent methods, however, are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters [10].

The aim of the present study was to evaluate and compare the dissolution profile of six commercial products containing Diclofenac potassium 50 mg. marketed in Argentina, based on their *in vitro* dissolution characteristics using USP Test, Apparatus 2 [11]. Each formulation was compared with the reference using model-independent methods: fit factors, mean dissolution time (MDT) and dissolution efficiency % (DE).

Materials and Methods

Reagents

Analytical grade monobasic potassium phosphate (Anedra, Argentine) and sodium hydroxide (Mallinckrodt, USA) were used. Diclofenac potassium was purchased in Saporiti, Argentina, 99.9% calculated with reference to the dried substance, origin India.

Materials

In our study, six commercial tablets containing Diclofenac potassium 50mg were purchased from pharmacies in Buenos Aires (Argentina). All tests were performed within products expiration dates.

Apparatus and procedure

All dissolution studies were performed using USP37, Apparatus 2 in a Sotax AT7 (Sotax AG, Basel Switzerland), which is a manual-sampling dissolution bath. The diclofenac potassium tablets test was performed at 50 ± 1 rpm. The dissolution medium simulated intestinal fluid (without enzyme) pH: 6.8, at 37 ± 0.5°C. The acceptance criterion set was Q = 75 in 60 min.

Dissolution media volume was 900 ml. In all experiments, 5 ml sample aliquots were withdrawn at 10, 15, 20, 30, 45 and 60 min using micropipettes. The withdrawn amounts were adjusted in the calculations. All samples were filtered through filter paper (Whatman 91;10.0 µm). The filter paper used was properly validated using the standard solution and comparing with membrane filters. The amount dissolved was determined spectrophotometrically in a UV-VIS Spectrophotometer Cary 1E Varian (Victoria, Australia). The standard solution was prepared at the same concentration and in the same Medium. Twelve tablets or capsules of each preparation were studied to obtain statistically significant results.

Comparative dissolution

Model-independent methods

Fit factors: A mathematical comparison was performed by applying f_1 and f_2. These fit factors directly compare the difference between the percent drug dissolved per unit time for a test and a reference formulation.

$$f1 = \left\{ \frac{[\Sigma |Rt\text{-}Tt|]}{[\Sigma [Rt]} \right\} \times 100 \text{ Where t=1 to n (1)}$$

$$f2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (Rt - Tt)^2 \right]^{-0.5} \times 100 \right\} \text{ (2)}$$

(1) Difference factor

(2) Similarity factor

Where n is the number of time points, R_t is the dissolution value of the reference formulation at time t and T_t is the dissolution value of the test formulation at time t.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the curves. Values of f_1 between 0 and 15 and values of f_2 between 50 and 100 are used to define equivalence of two dissolution profiles, which means an average difference of no more than 10% at the sample time points.

Dissolution efficiency: This concept was proposed by Khan and Rhodes [12] in 1975 and is defined as follows:

$$DE\% = \frac{AUC_0^T}{Q_{100.T}} \times 100 \quad (3)$$

Where Q_{100} is the percentage of dissolved product, DE is then the area under the dissolution curve between time points 0 and T expressed as a percentage of the curve at maximum dissolution, Q_{100}, over the same time period.

Mean dissolution time: The mean dissolution time is calculated from the accumulative curves of dissolved product depending on the time [13].

$$MDT = \frac{\Sigma[ti.\Delta Qi]}{Q_\infty} \quad (4)$$

Where t_i is intermediate time of the intervals of time sampled, ΔQ_i is the increase of the quantities of product dissolved in every interval of t considered and Q_∞ is the maximum of product dissolved.

The results of DE and MDT of the different Brands of Diclofenac potassium tablets were compared with the reference using a two-variable *t test* as follows:

$$t = \frac{|\bar{X}_R - \bar{X}_T|}{S_d} \sqrt{\frac{1}{n_R} + \frac{1}{n_T}} \quad (5)$$

Where $\bar{X}_R$ and $\bar{X}_T$ are means of the model parameters of the reference and test products, respectively, n_R and n_T are the number of measurements for the mean $\bar{X}_R$ and $\bar{X}_T$, and S_d is the weighted average standard deviation as shown below

$$S_d = \sqrt{\frac{(n_R - 1)S_R^2 + (n_T - 1)S_T^2}{n_R + n_T - 2}} \quad (6)$$

Where S_R and S_T are the standard deviations of model parameters for the reference and test products. If the calculated *t* values is less than the critical value of t (1- α/2, n_R+n_T-2), the two means $\bar{X}_R$ and $\bar{X}_T$ differ only randomly at risk level α.

Results and Discussion

Dissolution of drug from oral solid dosage forms is a necessary criterion for drug bioavailability (i.e., the drug must be solubilized in the aqueous environment of the gastrointestinal tract to be absorbed). For this reason, dissolution testing of solid oral drug products has emerged as one of the most important performance test for assuring product uniformity and batch to batch equivalence. Variations of the pharmacopeia limits indicate unacceptable products.

Brand	Other Ingredients	Appearance
I	Tricalciumphosphate, sodiumstarchglycolate, colloidalsilicondioxide, maizestarchmagnesiumstearate, povidone K-30, microcrystallinecellulose, cellacefate, diethylphthalate, titaniumdioxide, amaranth red aluminiunlake, tartrazinealuminiumlakeand talc	Brown, circular
II	Lactose, cross-linked carboxymethylcellulose, silicon dioxide, magnesium stearate, sunset yellow aluminum lake, titanium dioxide, dextrose, lecithin, potassium aluminum silicate, microcrystalline cellulose	Orange, circular, with indented line in center
III	Coprocessed lactose and microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, silicon dioxide, talc, Poly(methacrylic acid-co-ethyl acrylate) 1:1, polyethilene glycol 6000, polysorbate 80, triethyl citrate, titanium dioxide, talc, iron (III) oxide yellow.	Yellow, circular
IV	Lactose, coprocessed lactose and microcrystalline cellulose, sodium starch glycolate, magnesium stearate, cellulose aceto phthalate, polyvinylpyrrolidone-vinyl acetate copolymer, polysorbate 80, titanium dioxide, diethyl phthalate	White, circular
V	Lactose monohydrate, coprocessed lactose and microcrystalline cellulose, sodium croscarmellose, magnesium stearate, hydroxypropyl methylcellulose, propylene glycol, titanium dioxide, talc, brilliant blue lake.	Light blue, circular
VI	Magnesium stearate, sodium starch glycolate, coprocessed lactose and microcrystalline cellulose, distilled water, hydroxypropyl methylcellulose, polyethilene glycol 6000, talc, iron (III) oxide brown, iron (III) oxide red, titanium dioxide	Brown, circular

Table 1: *Formulation Compositions.*

Table 1 summarizes the characteristics of the six products. The products were purchased from pharmacies in Buenos Aires (Argentina). All tests were performed within products expiration dates, which were similar among brands. In this study we defined Brand I as the reference product.

Time (min)	Brand	Mean%	RSD	Lower Limit	Upper Limit
10	I	56.3	26.0	29.9	81.3
	II	55.4	11.3	53.8	65.1
	III	12.6	21.1	10.6	16.4
	IV	19.0	36.7	11.1	30.8
	V	48.3	15.4	42.5	63.2
	VI	50.8	18.1	34.5	62.1
15	I	90.3	8.8	83.0	102.8
	II	79.0	10.1	77.0	89.1
	III	23.6	18.0	19.4	30.5
	IV	29.9	23.5	22.4	41.3
	V	84.5	8.0	73.9	91.6
	VI	67.4	14.0	51.6	80.2
20	I	96.8	3.1	93.6	100.5
	II	93.9	11.2	80.3	101.8
	III	46.7	13.4	39.8	56.2
	IV	59.3	30.2	36.0	82.4
	V	88.3	3.5	84.1	92.7

Time (min)	Brand	Mean%	RSD	Lower Limit	Upper Limit
	VI	82.7	11.3	67.8	95.9
30	I	97.7	2.2	94.1	99.9
	II	103.2	4.6	95.9	109.9
	III	80.1	15.1	67.6	98.6
	IV	82.6	14.2	64.8	96.3
	V	95.4	2.0	92.8	98.1
	VI	96.1	4.2	91.8	103.5
45	I	98.4	2.5	95.8	101.6
	II	105.0	2.5	101.7	108.3
	III	102.9	6.6	92.0	109.8
	IV	101.0	4.1	95.0	106.9
	V	102.3	4.5	98.2	110.6
	VI	101.1	3.8	96.5	107.5
60	I	99.4	6.0	95.0	111.1
	II	104.2	3.7	99.2	109.4
	III	107.2	4.1	100.9	114.0
	IV	104.5	4.4	99.7	113.2
	V	102.5	1.7	100.4	104.9
	VI	100.2	4.6	96.4	108.2

Table 2: *Dissolution data and descriptive statistics of six brands of diclofenac potassium tablets.*

In the dissolution test for diclofenac potassium tablets described in the American Pharmacopeia (United States Pharmacopeia 37) no less than 80% (Q+5%) should be dissolved in 60 minutes. Table 2 summarizes the mean percent dissolved at each time point, the relative standard deviation (RSD), and the upper and lower limits.

Brand	M	SD	CV	t_{ex}
I	84.4	4.2	5.0	
II	82.6	2.7	3.2	0.2198
III	60.8	3.8	6.2	2.4326
IV	64.9	5.8	9.0	1.5781
V	80.4	0.8	1.0	0.5540
VI	79.3	4.4	5.5	0.4928

Table 3: *Average (M), Standard Deviation (SD), Variation Coefficient (CV) and t experimental (t_{ex}) of Dissolution Efficiency % (ED).*

Brand	M	SD	CV	t_{ex}
I	13.6	2.6	19.0	
II	14.6	1.8	12.5	0.1838
III	28.4	2.6	9.1	2.3422
IV	25.6	4.0	15.5	1.4694
V	16.0	0.5	2.9	0.5357
VI	16.8	2.7	16.1	0.4970

Table 4: *Average (M), Standard Deviation (SD), Variation Coefficient (CV) and t experimental (t_{ex}) of Mean Dissolution Time (MDT).*

The DE and the MDT values are a useful way to reduce each curve to a single number, which may be related to the dissolution rate constant. The average, the standard deviation (SD), the variation coefficient (CV) and t_{ex} of the DE data are presented in Table 3 and the MDT data are presented in Table 4. Test "*t*" with 95% confidence for 22 degrees of freedom was ($t_{n-2,\ \alpha:\ 0.05}$) = 2.0739. There is no significant difference among the reference product and Brands II, IV, V and VI for both determinations.

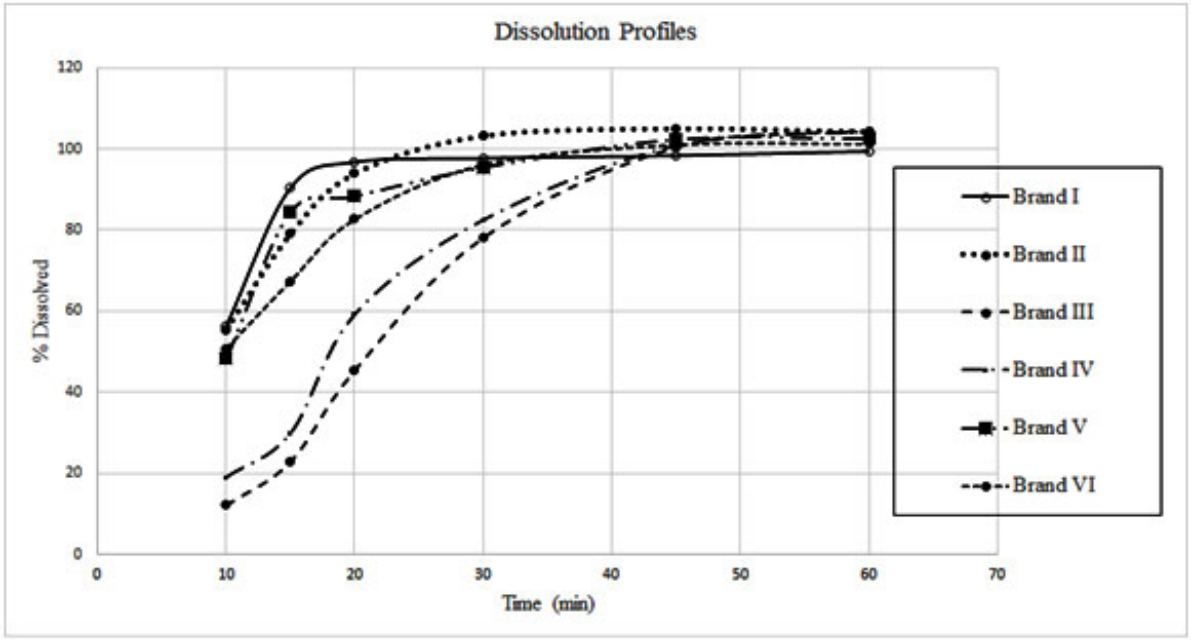

Figure 1: *Dissolution profiles of diclofenac potassium tablets.*

Fit factors are important quantitative methods that have been recommended by FDA, EMA and WHO guidelines for industry for comparison of dissolution profiles (Figure 1). Results obtained from the test using Brand I as the reference are shown in Table 5. The similarity factor f_2 is more sensitive in finding dissimilarity between dissolution curves than the difference factor f_1, and the values of fit factors are dependent on the number of sampling time point chosen. According to FDA f_1 values up to 15 and f_2 values greater than 50 should ensure equivalence of the dissolution curves, indicating an average difference of no more than 10% at the sample time points. Based on this guideline, only Brand II and V seem to show a dissolution curve similar with the reference.

Brand	Fit Factor	
	f_1	f_2
I/II	6	58
I/III	35	18
I/IV	29	22
I/V	6	60
I/VI	9	45

Table 5: *Fit Factors for the six brands of diclofenac potassium tablets based on the average of twelve tablets.*

Conclusion

This study found variations in the dissolution profiles of diclofenac potassium tablets commonly available in Argentina. The analyzed products presented very distinct dissolution profiles, showing that the dissolution test may be formulation dependent. All Brands fulfil the specifications of dissolution test of USP 37, Q = 75 in 60 min. There is no significant difference (p = 0.05) among the reference product and Brands II, IV, V and VI for DE and MDT. Using fit factors, only Brands I, II and V were similar.

In conclusion, significant differences were seen between the *in vitro* dissolution profiles of diclofenac potassium tablets from various commercial preparations. Nevertheless, the potential impact of these results on the *in vivo* bioavailability would require further investigation.

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