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Original Article

IN VITRO EQUIVALENCE STUDY OF DIFFERENT DOSES OF CARBAMAZEPINE REFERENCE TABLETS USING USP APPARATUSES 2 AND 4

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ABSTRACT

Objective: To perform an *in vitro* equivalence study of two doses of carbamazepine reference tablets sold in the local market under hydrodynamic conditions of USP Apparatus 4, a dissolution apparatus that better simulates the human gastrointestinal tract. Results were compared with dissolution official conditions using USP Apparatus 2.

Methods: Dissolution profiles of both formulations were carried out with an automated USP Apparatus 2 at 75 rpm and 900 ml of dissolution medium. USP Apparatus 4 with laminar flow at 16 ml/min and 22.6 mm cells were used. 1% lauryl sulfate aqueous solution at 37.0±0.5 °C was used as dissolution medium. Spectrophotometric determination of drug at 285 nm was carried out during 60 min. Dissolution profiles were compared with model-independent and-dependent approaches.

Results: When comparing dissolution profiles of low *vs*. high dose similar profiles were found (f_2>50) in each dissolution apparatus, however, when the same dose was compared, USP 2 *vs*. USP 4, opposite results were obtained. Comparison of mean dissolution time and dissolution efficiency data corroborates these results. Weibull function was the best mathematical model that described the *in vitro* dissolution performance of carbamazepine. No significant differences were found in *Td* values (low *vs*. high dose) but opposite results were also found with USP 2 *vs*. USP 4.

Conclusion: Equivalent dissolution performance of two doses of carbamazepine reference tablets were found in each USP dissolution apparatus. The main problem identified in this comparative study is the low dissolution rate and extent found with USP Apparatus 4. More research on this field is necessary for all available doses of reference drug products since the quality of generic formulations depends on the quality of references.

Keywords: Carbamazepine, Flow-through cell method, Reference drug products, USP Apparatus 4

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INTRODUCTION

Dissolution test is an important tool to ensure lot-to-lot good quality and after some manufacture, changes as well as for determination of interchangeability among generic formulations. These formulations have the same pharmacological effect with the benefit of lower costs for patients and hospitals. Generic drug products should demonstrate the same *in vitro* dissolution performance of reference drug products so, quality of generic drug products depends of the quality of references. Due to the high cost of bioequivalence studies and information of Biopharmaceutics Classification System (BCS) about solubility and permeability of some drugs, Guidelines for Industry-based on BCS have established criteria by which bioequivalence studies can be replaced by *in vitro* dissolution studies [1]. This waiver is based mainly on the fulfillment of f_2 similarity factor between dissolution profiles of test and reference (f_2>50) using dissolution media with pH of physiological relevance as well as compliance with related criteria to the excipients used in the formulation manufacture [2]. Some biowaiver monographs have been published for class I and III drugs (high solubility drugs) [3] but for its physicochemical and clinical characteristics, no biowaiver monograph has been published for carbamazepine.

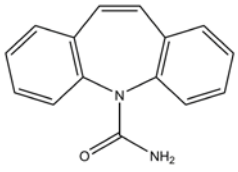

Fig. 1: Molecular structure of carbamazepine

Carbamazepine is a poorly soluble drug with a narrow therapeutic window used to treat epilepsy and other neurological disorders as trigeminal neuralgia [4]. Molecular structure of carbamazepine is shown in fig. 1. The drug is available as generic drug products and Mexican health authorities request bioequivalence studies to approve the marketing of these formulations. Considering BCS criteria carbamazepine has been classified as a class II drug (low solubility/high permeability) and for its low solubility, dissolution problems of two different doses in the same volume of dissolution medium could be observed. Class II drugs are expected to have a dissolution-limited absorption and a significant *in vitro*/*in vivo* correlation (IVIVC) should be expected using a well-designed *in vitro* dissolution test.

For multiple strengths of immediate-release products with linear kinetics, the bioequivalence study may be performed at the highest strength and waivers of *in vivo* studies may be granted on lower strengths, based on an adequate dissolution test, provided the lower strengths are proportionately similar in composition [5]. It is possible that this assertion does not apply to carbamazepine however, it is important to investigate the *in vitro* dissolution performance of two doses of carbamazepine reference tablets under hydrodynamic environments generated by commonly used dissolution apparatuses with the aim of gather information to suggest a biowaiver mechanism for carbamazepine drug products, starting at least, with the available doses of reference and pharmacopeial conditions.

Official dissolution test for carbamazepine tablets is described in United States Pharmacopoeia (USP) [6]. The method indicates the use of USP Apparatus 2 (paddle) at 75 rpm and 900 ml of 1% sodium lauryl sulfate aqueous solution at 37.0±0.5 °C as dissolution medium. Under these conditions and for carbamazepine immediate-release tablets labeled as 200-mg there are two tests with the following times and tolerances: *TEST 2* between 45 and 75% of the labeled amount of carbamazepine is dissolved in 15 min; not less than 75% (*Q*) of the labeled amount of carbamazepine is dissolved in 60 min and *TEST 3* between 60 and 85% of the labeled amount of carbamazepine is dissolved in 15 min; not less than 75% (*Q*) of the

labeled amount of carbamazepine is dissolved in 60 min. However, some authors reported lack of correlation between *in vitro* data using these conditions and *in vivo* results [7, 8].

A dissolution equipment different to USP Apparatus 1 (basket) and 2 (paddle) is USP Apparatus 4 (flow-through cell method) [9, 10]. Its advantages, over USP basket and paddle apparatuses, have been widely demonstrated especially in the study of dissolution performance of poorly soluble drugs [11, 12]. The flow-through cell method has a continuous extraction of the drug, simulating the absorption into the systemic circulation, generating an intermittent flow of dissolution medium into the cells where the tablets are placed [13]. USP Apparatus 4 can be used as an open system that operates under *sink* conditions which facilitates the dissolution of poorly soluble drugs as well as changing the dissolution medium throughout the test [14]. Flow-through cell method better simulates the hydrodynamic environment found in the gastrointestinal tract and some authors have demonstrated that *in vitro* data obtained with flow-through cell method better reflect *in vivo* performance of drugs with solubility problems [15, 16]. Despite the advantages of USP Apparatus 4, information about dissolution performance of commercially available doses of carbamazepine reference tablets under hydrodynamic environment generated by the flow-through cell method is scarce.

The main objective of this *in vitro* equivalence study was to evaluate the release performance of two doses of carbamazepine reference tablets under the hydrodynamic environment generated by USP Apparatus 4. Data obtained were compared with the pharmacopeial test that uses USP Apparatus 2. The results could be of interest for pharmaceutical laboratories or health authorities that classify some drug products as a reference to be used in dissolution and bioequivalence studies.

MATERIALS AND METHODS

Materials

In this pharmaceutical equivalence study carbamazepine tablets (Tegretol® 200-mg, lot TL005, round tablets of 9×3.7 mm and Tegretol® 400-mg, lot TL534, cuboid tablets of 17×5.5×5.1 mm; Novartis Farmacéutica SA de CV) from the Mexican market were used. National health authorities (COFEPRIS) has established this brand as a reference for bioequivalence studies [17]. Sodium lauryl sulfate was purchased from Distribuidora Química Lufra-México. Carbamazepine standard was purchased from Sigma-Aldrich Co. (St. Louis MO, USA).

Content uniformity and assay

Content uniformity and assay tests were performed on both drug products, according to the procedures described in USP [6].

Dissolution profiles

USP Apparatus 2

Dissolution profiles of carbamazepine were determined according to USP test [6] in an automated USP paddle apparatus (Sotax AT-7 Smart, Switzerland) with a piston pump (Sotax CY7-50, Switzerland). An UV/Vis spectrophotometer with 1 mm flow cells (Perkin Elmer Lambda 35, USA) was used. All equipment and data generated were controlled by specific software designed by Sotax. Both doses of carbamazepine reference tablets were sprinkled on 900 ml of 1% sodium lauryl sulfate aqueous solution at 37.0±0.5 °C as dissolution medium. The rotational speed of 75 rpm was tested. Sequential sampling using 0.45 µm nitrocellulose filters (Millipore®) occurred over 60 min at regular 5 min intervals with 12 replicates. The amount of carbamazepine dissolved was determined with a standard calibration curve at 285 nm.

USP Apparatus 4

Dissolution profiles of both doses of carbamazepine tablets were obtained in an automated flow-through cell apparatus 4 (Sotax CE6, Sotax AG, Switzerland) with 22.6 mm cells (i.d.) and a piston pump (Sotax CY7-50, Sotax AG, Switzerland). Laminar flow (with a bed of 6 g of glass beads) was used. The degassed dissolution medium, 1% sodium lauryl sulfate aqueous solution at 37.0±0.5 °C was pumped at a flow rate of 16 ml/min. An open system was used, without recycling the dissolution medium. Sequential sampling using nitrocellulose filters was set at regular 5 min intervals over 60 min, with 12 replicates. The amount of carbamazepine dissolved was determined in an UV/Vis spectrophotometer with 1 mm cells (Perkin Elmer Lambda 10, USA) at 285 nm. For every trial, a standard calibration curve was prepared.

Data analysis

Dissolution profiles of carbamazepine (low *vs*. high dose) were compared using model-independent and-dependent methods. For model-independent methods f_2 similarity factor, mean dissolution time (MDT) and dissolution efficiency (DE) were calculated. Mean values were compared by a Student's t-test and significant differences were considered if *P<0.05. For model-dependent comparisons, dissolution data were adjusted to First-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Makoid-Banakar, Weibull and Logistic model. The model with the highest determination coefficient ($R^2_{adjusted}$) and lowest Akaike information criterion (AIC) was chosen as the best-fit model [18]. Data analysis was carried out using the Excel add-in DDSolver program [19]. Mathematical equations used to fit carbamazepine dissolution data are shown in table 1.

Table 1: Mathematical equations used to fit dissolution data

Model	Equation
First-order	$F = 100 \cdot (1 - e^{-k_1 \cdot t})$
Higuchi	$F = k_H \cdot t^{0.5}$
Korsmeyer-Peppas	$F = k_{KP} \cdot t^n$
Hixson-Crowell	$F = 100[1 - (1 - k_{HC} \cdot t)^3]$
Makoid-Banakar	$F = k_{MB} \cdot t^n \cdot e^{-k \cdot t}$
Weibull	$F = F_{max} \cdot \left(1 - e^{-\frac{t^\beta}{\alpha}}\right)$
Logistic	$F = 100 \cdot \frac{e^{\alpha+\beta \cdot log\,(t)}}{1 + e^{\alpha+\beta \cdot log\,(t)}}$

RESULTS AND DISCUSSION

Content uniformity and assay

All carbamazepine drug products were within USP limits. The percentages of carbamazepine on content uniformity test ranged from 85-115% and assay test between 90-110%. Results are shown in table 2.

In vitro dissolution performance

Dissolution profiles of two doses of carbamazepine reference tablets, in both USP Apparatuses, are shown in fig. 2. To compare the dissolution process between doses, *Y*-axis is expressed as the percentage of drug dissolved.

Table 2: Content uniformity and assay results, mean, *n* = 10*, *n* = 3†

Dose	Content uniformity (min-max)*	Assay (%)†
Low	95.26–96.49	96.10
High	91.96–94.83	93.85

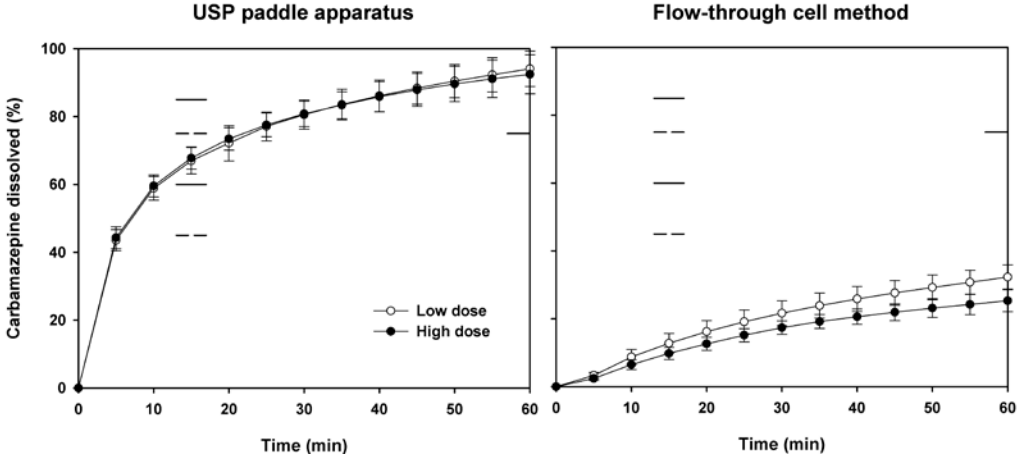

Fig. 2: Dissolution profiles of carbamazepine from two doses of reference tablets. Slashed line shows tolerances of *TEST 2* and continuous line shows tolerances of *TEST 3*. mean±SD, *n* = 12

Carbamazepine 200-mg reference tablets *et al.* l dissolution tolerances only when tests were carried out with USP Apparatus 2. Tolerance of USP *TEST 2* at 15 min is 45-75% of drug dissolved and at 60 min not less than 75% of drug dissolved should be found while tolerance of *TEST 3* at 15 min is 60-85% of drug dissolved and at 60 min not less than 75% of drug dissolved should be found. These criteria were also fulfilled by carbamazepine 400-mg tablets. With flow-through cell method, any dissolution criteria were fulfilled.

In each USP dissolution apparatus, similar dissolution profiles of low *vs*. high dose were found, f_2 = 94.46 when USP Apparatus 2 was used and f_2 = 66.51 when USP Apparatus 4 was used. On the other hand, and despite the obvious differences in dissolution profiles of both carbamazepine doses, between USP Apparatuses 2 and 4, f_2 similarity factors were also calculated and results were 12.99 when the dose of 200-mg was compared and 11.36 when dose of 400-mg was compared. A limited dissolution of 200-mg reference tablets was also reported by Medina *et al.*, [20] when simulated gastric fluid without pepsin and flow-through cell method were used. Values of 17.99% as drug dissolved at 60 min and 9.81% as DE were found.

With USP Apparatus 4 both formulations showed a slower dissolution rate than that found with USP paddle apparatus. Some authors have published that this performance can be explained by the hydrodynamic conditions found in USP Apparatus 4, where there are no agitation mechanisms and the dosage form and drug particles are continuously exposed to a uniform laminar flow, similar to the natural environment of the gastrointestinal tract, causing a different dissolution pattern [21]. In the flow-through cell method, cell size, glass beads and flow rate are critical factors to form this dissolution pattern. Considering USP Apparatus 4 as a dissolution apparatus that better simulates *in vivo* conditions and for the low dissolution rate and extent observed with this apparatus clinical problems of carbamazepine could be explained. 30% of patients with focal epilepsy do not respond to maximum dosages of carbamazepine resulting in the need to administer polytherapy with additional antiepileptic drugs to control seizures [22].

Model-independent comparisons

Percentage of carbamazepine dissolved at 15 and 60 min and model-independent parameters MDT and DE mean values±standard error medium (SEM) are shown in table 3. Data of low *vs*. high dose were compared and significant differences were found only in the percentage of drug dissolved at 15 and 60 min with USP Apparatus 4 (*P<0.05).

Table 3: Model-independent parameters of carbamazepine, mean±SEM, *n* = 12

USP Apparatus	Dose	Diss. at 15 min (%)	Diss. at 60 min (%)	MDT (min)	DE (%)
2	Low	66.97±1.13	94.05±1.50	12.85±0.16	73.90±1.18
	High	67.75±0.95	92.77±1.66	11.95±0.43	73.93±1.00
4	Low	12.77±0.83	32.26±1.03	23.68±0.67	19.58±0.85
	High	9.76±0.51*	25.30±0.95*	23.31±0.44	15.45±0.56

*P<0.05, Low *vs*. High dose.

Dissolution performance of carbamazepine from reference tablets shows a dependence on the hydrodynamic conditions to which tablets were subjected. Statistical comparison of model-independent parameters MDT and DE confirm this result. No significant differences were found between doses in each USP apparatus (*P>0.05) but between USP apparatuses each dose was totally different.

Dissolution profiles comparison were carried out with model-independent parameters MDT and DE. MDT is the time interval necessary to dissolve 63.2% of the drug contained in the pharmaceutical dosage form and it was calculated according to statistical moment's theory [23]. On the other hand, DE is the area under the dissolution curve up to a certain time *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [24]; so, while MDT is related to dissolution rate, DE is related to drug dissolution extent. Cardot *et al.*, [25] remark that these model-independent parameters have been proposed as adequate parameters for some IVIVC levels. IVIVC Level B is based on the comparison of parameters calculated by statistical moment's theory as MDT is while Level C requires the calculation of an *in vitro* parameter that expresses a global drug dissolution performance as is the case of DE.

Table 4: Criteria used for selection of the best-fit model, mean, *n* = 12

USP Apparatus	Dose	First-order	Higuchi	Korsmeyer-Peppas	Hixson-Crowell	Makoid-Banakar	Weibull	Logistic
$R^2_{adjusted}$								
2	Low	0.7321	0.5455	0.9814	0.4621	0.9954	0.9971	0.9733
	High	0.6002	0.3488	0.9707	0.2511	0.9956	0.9985	0.9813
4	Low	0.9396	0.9228	0.9815	0.9222	0.9968	0.9975	0.9905
	High	0.9341	0.9173	0.9731	0.9208	0.9972	0.9978	0.9814
AIC								
2	Low	78.67	86.10	48.43	87.48	30.40	20.86	50.97
	High	80.02	87.77	51.77	88.66	28.18	11.80	38.84
4	Low	44.11	52.46	34.18	48.16	13.34	10.77	24.50
	High	44.61	48.39	33.40	47.04	8.59	4.69	27.65

As Weibull function was the best-fit model *Td* values were calculated and dissolution profiles were compared with these values. No significant differences were found between low and high dose (*P>0.05). Results are shown in table 5.

Table 5: Weibull parameters and *Td* values derived from data adjusted to this mathematical model, mean, *n* = 12

USP Apparatus	Dose	α	β	F_{max}	*Td* (±SEM)
2	Low	4.56	0.53	109.55	17.72±1.31
	High	4.40	0.57	103.50	14.66±2.15
4	Low	58.02	1.11	40.25	39.42±4.21
	High	77.27	1.22	30.34	35.94±3.99

*P<0.05, Low *vs*. High dose.

Model-dependent comparisons

Considering established criteria to choose the best-fit model (highest $R^2_{adjusted}$ and lowest AIC values) Weibull function was the best mathematical model to explain *in vitro* dissolution performance of carbamazepine from reference tablets. Results are shown in table 4.

In this *in vitro* equivalence study of low and high dose, data fitting to mathematical equations previously described were carried out without any physiological significance in order to find a mathematical model that explains the *in vitro* dissolution behavior of carbamazepine from Mexican reference products. The purpose of using mathematical models to adjust *in vitro* dissolution data is that they facilitate the analysis and interpretation of observed results and because they describe the dissolution profiles as a function of only a few parameters that can be easily statistically compared [26].

Dissolution study of two doses of carbamazepine reference tablets carried out with USP paddle apparatus and flow-through cell method reveals similar dissolution profiles in each USP apparatus. The manufacturing process of reference tablets and dissolution conditions used allowed the complete release of the drug under official conditions. It is important to highlight that these reference tablets show congruence between doses in two different systems what represents a product of good quality and ensures the proper biowaiver of low dose. This is not always the case. Medina *et al.,* [27] studied two doses of metronidazole reference tablets (250-mg and 500-mg) using USP basket apparatus and flow-through cell method with pharmacopeial dissolution medium (0.1 N hydrochloric acid) and dissolution process was different in each dose and in each USP apparatus.

Despite low solubility of carbamazepine, it is significant the compliance of pharmacopeial criteria of 400-mg tablets (dissolution criteria at 15 and 60 min are only for 200-mg tablets) however, the main problem identified in this comparative study was the low dissolution rate and extent of carbamazepine with USP Apparatus 4. The flow-through cell apparatus is an equipment that better reflects *in vivo* environment of the gastrointestinal tract and it is an appropriate option to find a significant IVIVC for drugs with solubility problems. On this apparatus, several authors have reported a better estimate of absorption rate (which is a better predictor of *in vivo* dissolution) of cilostazol and diclofenac sodium [15, 16] both poorly soluble drugs.

In order to develop suitable *in vitro* dissolution tests, it is important to document dissolution performance of all carbamazepine doses of reference tablets in dissolution media with pH of physiological relevance (pH 1.2, 4.5, and 6.8) as well as studies with flow-through cell method. Satisfactory dissolution conditions should predict *in vivo* absorption to avoid clinical problems. Several authors have found significant differences in plasma patients undergoing therapy with this drug [28] and loss of seizure control when a drug product is exchanged for another formulation [29]. In the present *in vitro* equivalence study, similar dissolution performance of two doses of carbamazepine reference tablets, independently of USP apparatus used, was found. The study was carried out with 1% sodium lauryl sulfate aqueous solution as dissolution medium. If this performance is observed with dissolution media of physiological relevance it is possible to suggest waiver of *in vivo* studies for lower carbamazepine dose since bioavailability will be proportional to the highest dose. More research on this field is necessary for all available doses of reference drug products since the quality of generic formulations depends on the quality of references.

CONCLUSION

Similar dissolution performance of two doses of carbamazepine reference tablets was found in each USP dissolution apparatus used. Dissolution performance of carbamazepine shows a dependence on the hydrodynamic conditions to which tablets were subjected. The main problem identified in this comparative study is the low dissolution rate and extent found with USP Apparatus 4. More research on this field is necessary for all available doses of reference drug products since the quality of generic formulations depends on the quality of references.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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