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Original Article

DISSOLUTION PERFORMANCE OF MELOXICAM FORMULATIONS UNDER HYDRODYNAMICS OF USP PADDLE APPARATUS AND FLOW-THROUGH CELL METHOD

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ABSTRACT

Objective: To study the *in vitro* dissolution performance of four generic formulations of the poorly soluble drug meloxicam and the reference under hydrodynamic environments generated by flow-through cell method and USP paddle apparatus (pharmacopeial test).

Methods: Dissolution method was validated according to ICH guidelines. Dissolution profiles were carried out with an automated flow-through cell apparatus (laminar flow at 16 ml/min with 22.6 mm cells) and USP paddle apparatus at 75 rpm. Phosphate buffer pH 7.5 at 37.0±0.5 °C was used as dissolution medium. Spectrophotometric determination of drug at 362 nm was carried out during 30 min. Dissolution profiles were compared with model-dependent and-independent methods.

Results: Practically, all generic formulations showed significant differences with the percentage of drug dissolved at 30 min, mean dissolution time and dissolution efficiency, when USP paddle apparatus was used (*P<0.05), while only two generic formulations were different to reference using flow-through cell method. After adjustment to different mathematical equations, Weibull function was the best model to describe meloxicam dissolution performance and significant differences were found with all drug products when USP paddle apparatus was used, while only one formulation was different with flow-through cell method.

Conclusion: The study reveals the need to look for better dissolution schemes for meloxicam tablets since USP paddle apparatus may not reflect properly the *in vitro* dissolution performance of meloxicam generic formulations and reference.

Keywords: Meloxicam, Flow-through cell method, Generic formulations, USP paddle apparatus

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INTRODUCTION

Meloxicam is a member of enolic acid group of non-steroidal anti-inflammatory drugs (NSAIDs) used to treat rheumatoid arthritis, osteoarthritis and other joint pains. The drug is practically insoluble in water (8 µg/ml) which directly influences the C_{max}, T_{max} and its bioavailability [1]. Meloxicam has pKa values of 1.1 and 4.2 and is considered a class II drug [2]. Class II drugs are expected to have a dissolution-limited absorption and significant *in vitro*/*in vivo* correlation should be projected using a well-designed *in vitro* dissolution test. Molecular structure of meloxicam is shown in fig. 1.

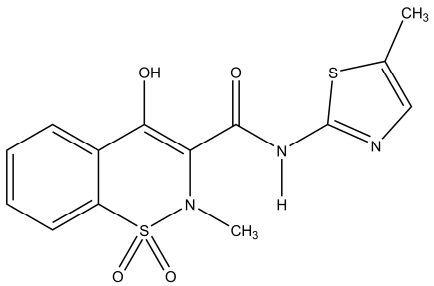

Fig. 1: Molecular structure of meloxicam

In vitro dissolution studies are not only used to assess batch-to-batch consistency of drug release from solid dosage forms, but they are also essential in several stages of formulation development, for screening and proper assessment of different formulations [3]. Some methods have been proposed to compare dissolution profiles of reference and test formulations. FDA use f_2 similarity factor [4] while model-dependent,-independent and ANOVA-base comparisons are the most commonly approaches used for a complete evaluation [5, 6].

Several authors have studied dissolution test optimization for meloxicam tablets [2] and the use of 900 ml phosphate buffer (pH 7.5, 37.0±0.5 °C) with USP paddle apparatus (USP Apparatus 2) at 100 rpm was considered satisfactory. Official dissolution test maintains similar conditions and only changes the agitation rate (75 rpm) [7]. Pharmacopeial criteria establishes that not less than 70% of drug should be dissolved in 30 min ($Q \geq 70\%$). To date, there is no information confirming significant *in vitro*/*in vivo* correlation under these conditions.

An alternative dissolution apparatus to determinate the release performance of drugs is the flow-through cell method (USP Apparatus 4) [8, 9]. Their advantages over conventional USP basket and paddle apparatus (USP Apparatus 1 and 2, respectively) have been widely demonstrated especially with poorly soluble drugs [10, 11]. The flow-through cell method better simulates the hydrodynamic environment of the gastrointestinal tract. *In vitro* data obtained with USP Apparatus 4 better reflects the *in vivo* performance of some drugs with solubility problems [12, 13]. USP Apparatus 4 works as an open system that can operate under sink conditions and it is easy to change the dissolution medium (within a range of physiological pH) throughout the test [14]. Emara *et al.,* [15] reported dissolution profiles of five meloxicam generic formulations and reference product (7.5-mg) obtained with flow-through cell method (phosphate buffer pH 7.5 at 8 ml/min, laminar flow, and 22.6 mm cells). After several studies, three generic formulations showed less than 70% of drug dissolved at 30 min.

Generic formulations are off-patent drug products that contain the same active ingredient in the same dose as the reference product [16]. These drug products represent saving for patients and hospitals and for its safe interchangeability, they must show the same quality as reference. However, some authors confirmed that during dissolution tests many generic formulations showed differences from their branded counterparts [17]. Some formulations showed incomplete dissolution and others showed that they dissolve slower or faster than their branded counterparts. Other generics, from the same manufacturer with different batches

of the same drug, showed significant differences suggesting that substitution among generics themselves can be risky. This is the case of meloxicam generic formulations (7.5 and 15-mg) when USP paddle apparatus at 50 rpm and 1000 ml of phosphate buffer pH 7.5 was used [17].

The main objective in this *in vitro* dissolution behavior study is to evaluate the release performance of meloxicam from immediate-release generic formulations sold in the local market. Due to its poor solubility, investigation of dissolution performance of this NSAID under the hydrodynamic environment generated by the flow-through cell method is important. Data obtained were compared with the official USP paddle apparatus. Result could support the design of better drug products available for the population that uses them.

MATERIALS AND METHODS

Chemical and reagents

Meloxicam tablets (15-mg) of the reference product Mobicox® (Boehringer Ingelheim) (coded as R product) and four generic formulations (A, B, C, and D products) with the same dose were used. Mexican health regulatory agency COFEPRIS has established Mobicox® as the reference product to be used in bioequivalence studies [18]. Hydrochloric acid and methanol analytical grade were purchased from J. T. Baker-Mexico (Xalostoc, Mexico). Meloxicam standard was purchased from Sigma-Aldrich Co. (St. Louis MO, USA).

Content uniformity and assay

Content uniformity and assay tests were carried out with all formulations according to the procedures described in the USP [7].

Analytical method validation

Before the determination of dissolution profiles, dissolution method was validated according to ICH guidelines [19].

Linearity

Three standard calibration curves in phosphate buffer pH 7.5 (2.5-20 µg/ml, 362 nm) were prepared and data were fitted to the straight-line equation ($y = bx+a$). The coefficients of regression and regression analysis of variance (ANOVA) were calculated. The absorbance *vs.* meloxicam concentration proportionality was demonstrated by calculating the percentage relative standard deviation (RSD): [((standard deviation)/mean) × 100] of the response factor across the entire range of concentration.

Accuracy and precision

The accuracy and precision of the method were evaluated with the added standard method. With this method matrix, effects can easily be removed. Twenty tablets were accurately weighed and crushed in a mortar; then, quantities of powder of meloxicam tablets plus a quantity of meloxicam standard (10 mg) to finally give the equivalent of 80, 100, and 120% of the dose, were dissolved in 900 ml of phosphate buffer pH 7.5 at 37.0±0.5 °C. USP paddle apparatus at 75 rpm was used. At 30 min the amount of meloxicam dissolved was calculated with reference to a standard calibration curve prepared on the same day of the experiment. Each determination was performed in triplicate. The percentage relative error (RE): [((found–added)/added) × 100] was taken as a measure of the accuracy and RSD as a measure of precision. Experiments were carried out in three different days.

USP paddle apparatus

Dissolution profiles of meloxicam were obtained using the dissolution test described in USP (USP 2018). USP Apparatus 2 (Model AT-7 Smart, Sotax, Basel, Switzerland) at 75 rpm was used (Q = 70% at 30 min). The UV/Vis spectrophotometer (Model Lambda 35, Perkin Elmer, USA) with 1 mm flow cells was used. Equipment was controlled by specific software designed by Sotax. Meloxicam tablets were sprinkled on 900 ml of phosphate buffer pH 7.5 at 37.0±0.5 °C. Automatic samples were taken every 5 min to 30 min (n = 12). Meloxicam dissolved was determined with a standard calibration curve.

Flow-through cell method

Dissolution profiles of meloxicam were obtained with an USP Apparatus 4 (Model CE6, Sotax AG, Basel, Switzerland) and 22.6 mm cells (i.d.). Laminar flow (originated with 6 g of glass beads) at 16 ml/min was tested. Phosphate buffer pH 7.5 at 37.0±0.5 °C was used as dissolution medium. Automatic samples were taken every 5 min up to 30 min (n = 12). Meloxicam dissolved was determined in an UV/Vis spectrophotometer (Model Lambda 10, Perkin Elmer, USA) with 1 mm cells at 362 nm. For every trial, a standard calibration curve was prepared.

Dissolution data analysis

Meloxicam dissolved at all sampling times, and not only data at 30 min, from generic *vs.* reference formulations were compared. One-way analysis of variance (ANOVA) followed by a Dunnett or Dunnett's T3 multiple comparisons test was used. Significant differences were considered if *P<0.05. Dissolution data obtained with the flow-through cell method were compared by the same way. Dissolution profiles of reference and generic formulations were compared by model-independent and-dependent methods. For model-independent comparisons mean dissolution time (MDT) and dissolution efficiency (DE) were calculated. MDT is time to dissolve 63.2% of drug and it was calculated according to statistical moment's theory [20]. 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 [21]. Both parameters were calculated with the Excel add-in DDSolver program [22]. For model-dependent comparisons dissolution data were adjusted to hyperbola equation ($y = ax/b+x$) and with a and b constants, $t_{50\%}$, $t_{63.2\%}$, and $t_{85\%}$ values were calculated. This fit was carried out with SigmaPlot software (version 11.0).

Additionally, and for a complete comparison of dissolution profiles by model-dependent approach, dissolution data were fitted to First-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Makoid-Banakar, Weibull, and Logistic equation. The model with the highest determination coefficient ($R^2_{adjusted}$) and minimum Akaike Information Criterion (AIC) was chosen as the best fit model [6]. Data analysis was carried out using Excel add-in DDSolver program [22]. Table 1 shows the mathematical equations of each model.

Table 1: Mathematical models used to fit dissolution data of meloxicam formulations

Model	Equation
Hyperbole	$y = \frac{ax}{b+x}$
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	$F = 100 \cdot [1 - (1 - k_{HC} \cdot t)^3]$
Makoid-Banakar	$F = k_{MB} \cdot t^n \cdot e^{-k \cdot t}$
Weibull	$F = F_{max} \cdot \left[1 - e^{-\frac{(t-Ti)^\beta}{\alpha}}\right]$
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

Results of content uniformity and assay test made to meloxicam formulations are shown in table 2. All meloxicam formulations met the content uniformity and assay standard criteria. The percentages of meloxicam content ranged from 85 to 115% and the assay test was between 90 to 110%.

Linearity

Mean regression equation from three standard calibration curves was $y = 0.0423x+0.0264$. linear regression was significant ($R^2 = 0.995$, *P<0.05). The RSD value of response factor was 5.6%.

Accuracy and precision

To evaluate the accuracy and precision of the dissolution method, analysis of several percentages of dose (80, 100, and 120%) was carried out for three different days (n = 3/d). The within-run and between-run precision and accuracy were calculated. Results are shown in table 3. RSD obtained was in the range of 0.02-1.58% and RE was lower than 5.0% what indicates good accuracy and precision of the dissolution method.

Dissolution performance

Dissolution profiles of all meloxicam formulations, obtained with USP paddle apparatus and flow-through cell method, are shown in fig. 2.

Table 2: Content uniformity and assay results of meloxicam formulations

Code	Content uniformity (min-max %)	Assay (%)
R	99.87-103.93	102.57
A	100.58-109.04	106.54
B	100.44-109.48	100.80
C	103.36-108.61	101.58
D	102.19-109.92	100.54

Table 3: Accuracy and precision data of meloxicam, mean±SD

	Within-day (n = 3)			Between-day (n = 9)		
Added (mg)	Found (mg)	RSD (%)	RE (%)	Found (mg)	RSD (%)	RE (%)
12	12.35±0.02	0.17	2.92	12.59±0.20	1.58	4.92
15	15.35±0.00	0.02	2.35	15.47±0.14	0.91	3.13
18	18.18±0.27	1.48	1.01	18.13±0.19	1.02	0.74

RSD: Relative standard deviation; RE: Relative error

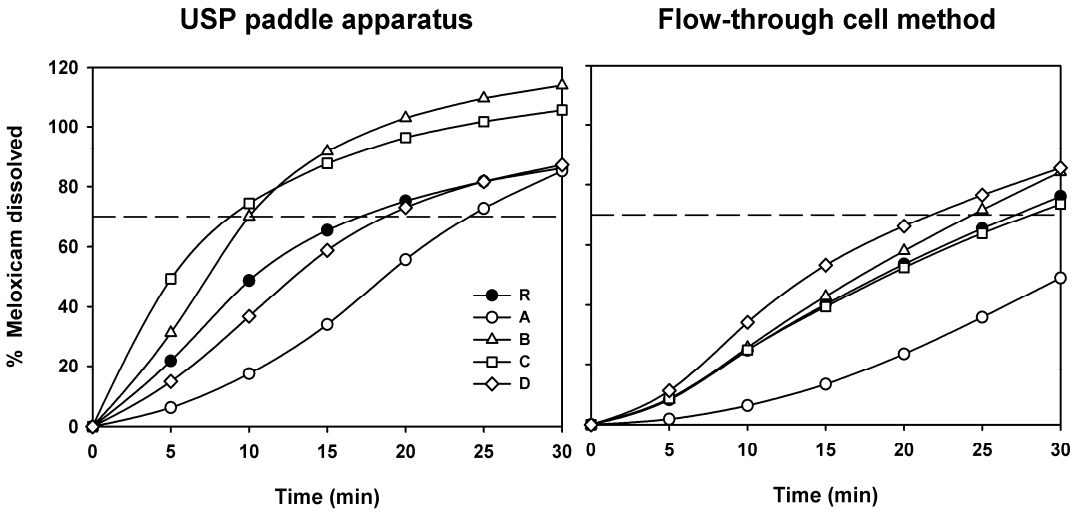

Fig. 2: Dissolution profiles of meloxicam reference (R) and generic formulations (A-D). The dashed line shows Q = 70%. For clarity the error bars were omitted, mean, n = 12

Under official conditions, all drug products met the pharmacopeial Q criterion (70% dissolved at 30 min). Results with USP Apparatus 4 were similar excepting product A which less than 50% of meloxicam dissolved was found from this generic formulation.

The rate and extent of meloxicam dissolved, from all formulations used and with USP Apparatus 4, was less than data obtained with USP paddle apparatus. Usually, with a flow-through cell method, it is possible to observe slower dissolution rates than those reported with USP basket or paddle apparatus [23, 24]. This performance can be explained by the hydrodynamic environment of USP Apparatus 4 which better reflects the natural setting of the gastrointestinal tract than other USP dissolution apparatuses [25]. Cell size, glass beads and flow rate are critical factors to form a special dissolution pattern useful to compare the manufacture quality of generic formulations. Flow rate of 16 ml/min was used since it is one suggested by European and US Pharmacopeias (others are 4 and 8 ml/min) [26].

In order to compare the percentage of the drug found at each sampling time, of each generic formulation *vs*. reference, a one-way ANOVA followed by a Dunnett's multiple comparison test was performed. Results are shown in table 4.

Table 4: Difference of meloxicam dissolved, at each sampling time, between generic formulations (A-D) and reference product (R)

Comparison	Time (min)	USP paddle apparatus		Flow-through cell method	
		Difference	*P	Difference	*P
A *vs*. R	5	15.62	<0.05	6.43	<0.05
	10	31.34	<0.05	18.45	<0.05
	15	31.41	<0.05	26.82	<0.05
	20	19.52	<0.05	30.11	<0.05
	25	8.91	<0.05	29.53	<0.05
	30	0.99	>0.05	27.07	<0.05
B *vs*. R	5	9.41	<0.05	0.03	>0.05
	10	21.29	<0.05	0.92	>0.05
	15	26.24	<0.05	2.72	>0.05
	20	27.70	<0.05	4.38	>0.05
	25	27.84	<0.05	6.26	>0.05
	30	27.69	<0.05	8.14	>0.05
C *vs*. R	5	26.88	<0.05	0.37	>0.05
	10	24.67	<0.05	0.11	>0.05
	15	21.60	<0.05	0.78	>0.05
	20	20.48	<0.05	1.14	>0.05
	25	19.81	<0.05	1.57	>0.05
	30	19.44	<0.05	2.56	>0.05
D *vs*. R	5	7.44	<0.05	2.95	<0.05
	10	11.63	<0.05	9.37	<0.05
	15	5.26	<0.05	13.09	<0.05
	20	0.37	>0.05	12.67	<0.05
	25	1.28	>0.05	11.14	<0.05
	30	1.99	>0.05	9.46	<0.05

Almost all data obtained with USP paddle apparatus showed significant differences (*P<0.05). With flow-through cell method significant differences with data of generic formulations A and D were found (*P<0.05).

Because variability of results was higher than that established for calculation of f_2 similarity factor (CV ≤ 20% at first sampling time and ≤ 10% at other sampling time) [4], dissolution profiles were compared by model-independent and model-dependent methods.

Model-independent comparisons

Percentage of meloxicam dissolved at 30 min, as well as MDT and DE [mean±standard error medium (SEM)], of each formulation, are shown in table 5.

Table 5: Dissolution parameters of meloxicam from reference (R) and generic formulations (A-D), mean±SEM, *n* = 12. *P<0.05

Code	Diss. at 30 min (%)	MDT (min)	DE (%)	$t_{50\%}$ (min)	$t_{63.2\%}$ (min)	$t_{85\%}$ (min)
USP paddle apparatus						
R	86.15±0.54	10.50±0.12	56.00±0.47	10.75±0.20	15.49±0.24	27.18±0.35
A	85.15±1.40	16.58±0.10*	38.12±0.84*	18.42±0.37*	23.28±0.46*	31.31±0.62*
B	113.84±2.90*	9.70±0.18*	77.06±2.18*	6.61±0.36*	9.23±0.50*	15.02±0.83*
C	105.56±0.34*	8.10±0.19*	77.05±0.51*	5.07±0.17*	7.54±0.22*	14.31±0.29*
D	87.18±0.62	12.30±0.13*	51.45±0.65	13.05±0.32	17.55±0.37*	26.43±0.42
Flow-through cell method						
R	76.11±1.86	14.84±0.22	38.36±0.66	19.24±0.37	24.63±0.50	33.89±0.85
A	49.03±2.58*	23.51±1.17*	23.91±1.40*	36.07±2.22*	44.33±3.18*	57.64±5.01*
B	84.25±3.57	15.33±0.28	41.42±2.29	18.07±0.96	22.95±1.19	31.11±1.55
C	73.55±2.37	14.60±0.18	37.65±1.00	19.86±0.55	25.50±0.78	35.24±1.28
D	85.56±1.04*	13.39±0.05	47.35±0.48*	15.05±0.17*	19.87±0.26	28.87±0.47

With official dissolution test, model-independent parameters were ranked with respect to significant differences found as percentage of meloxicam dissolved at 30 min<DE<MDT. In the same way, for flow-through cell method, parameters were ranked as MDT<DE = percentage of meloxicam dissolved at 30 min.

Significant differences with percentage dissolved at 30 min were found with generic products B and C (using USP paddle apparatus) and with products A and D (using flow-through cell method). Comparing dissolution performance of generic drug products with MDT data, significant differences were found with all generic formulations using USP Apparatus 2 (*P<0.05) whereas with flow-through cell method, significant differences were found only with generic formulation A (*P<0.05). With DE data as comparison parameter, significant differences were found with three generic drug products (A, B, and C) when USP paddle apparatus was used (p<0.05), while with USP Apparatus 4 only generic product A was different.

Comparisons using percentage dissolved at 30 min (*Q* values) are important for quality control purposes since these values give a measure of dissolution extent reached by each formulation under the same experimental conditions. MDT and DE were calculated because they have been proposed as acceptable parameters for *in vitro*/*in vivo* correlations levels B and C [27]. *In vitro*/*in vivo* correlation level B is established by the relationship between MDT and mean residence time (both parameters calculated by statistical moments theory), whereas *in vitro*/*in vivo* correlation level C uses the association of DE or another parameter as a dissolution time point ($t_{50\%}$, $t_{80\%}$, etc.) with one pharmacokinetic parameter, such as AUC, C_{max} or T_{max}. Previous reports suggest DE as a suitable parameter that reflects global drug dissolution behavior to compare dissolution profiles [21].

Model-dependent comparisons

After adjustment of dissolution data to hyperbole equation $t_{50\%}$, $t_{63.2\%}$, and $t_{85\%}$ values were calculated. Results are shown in table 5. These time data reflect meloxicam dissolution rate differences showed by all drug products used under the same experimental conditions. With USP paddle apparatus, model-dependent

parameters were ranked respect significant differences as $t_{50\%}$ = $t_{85\%}$<$t_{63.2\%}$. In the same way, for flow-through cell method, parameters were ranked as $t_{63.2\%}$ = $t_{85\%}$<$t_{50\%}$. Comparing dissolution profiles of meloxicam drug products by these time data, when USP paddle apparatus was used, almost all generic formulations were different to the reference product; but when flow-through cell method was used, only one or two generic formulations were different to the reference product. In dissolution studies, it is common to calculate this time data since $t_{x\%}$ corresponds to time required to release a certain percentage of drug (e. g., $t_{20\%}$, $t_{50\%}$, $t_{90\%}$) and sampling time corresponds to the amount of drug dissolved in that time (e. g., $t_{20\ min}$, $t_{50\ min}$, $t_{90\ min}$). Pharmacopeias often use this time parameter as an acceptance limit of dissolution test (e. g., $t_{45\ min} \geq 80\%$) [5]. In order to find a relationship between model-independent and-dependent data, MDT and $t_{63.2\%}$ values of each USP apparatus were plotted, then a lineal regression was calculated. Results are shown in fig. 3.

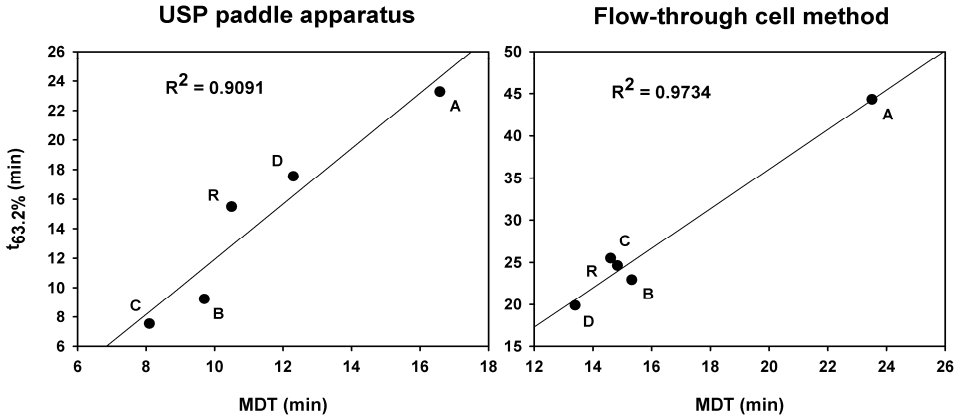

Fig. 3: Relationship between MDT and $t_{63.2\%}$ of meloxicam from reference (R) and generic formulations (A-D), mean, *n* = 12

In this dissolution performance study, time to dissolve 63.2% of meloxicam dose was calculated by different methodology. USP paddle apparatus gives more dispersed results meanwhile better results were found with flow-through cell method. Linear regression equation with USP paddle apparatus data was $y = 1.87x–6.84$ and with USP Apparatus 4 data was $y = 2.34x–10.80$. Although significant linear regression was found with both dissolution equipment (*P<0.05) a high R^2 value was found only with the flow-through cell method.

The trend presented by data of flow-through cell method, when using dissolution results of all meloxicam formulations, can be explained by the mathematical equation $y = bx+a$. USP Apparatus 4 generates more stable hydrodynamic conditions than USP paddle apparatus and this advantage can help to better design dissolution tests to accurately reveal the quality of commercial formulations. Results agree with those found with naproxen generic tablets [28] and ibuprofen generic suspensions [29] where model-independent and-dependent parameters obtained with data generated by USP Apparatuses 2 and 4 were associated and flow-through cell method showed better adjustments.

For a complete comparison of dissolution profiles by model-dependent approach data of all meloxicam, formulations were fitted to different mathematical equations. Results are shown in table 6.

Table 6: Criteria used to select the best-fit model, mean, *n* = 12

Code	First-order	Higuchi	Korsmeyer-peppas	Hixson-crowell	Makoid-banakar	Weibull	Logistic
$R^2_{adjusted}$							
USP paddle apparatus							
R	0.9805	0.9205	0.9334	0.9750	0.9938	0.9997	0.9989
A	0.8284	0.6836	0.9853	0.8723	0.9963	0.9984	0.9870
B	0.7977	0.9070	0.9016	0.8827	0.9897	0.9997	0.8506
C	0.9626	0.9006	0.9605	0.9708	0.9977	0.9997	0.9235
D	0.9325	0.8483	0.9411	0.9661	0.9980	0.9988	0.9965
Flow-through cell method							
R	0.9288	0.7869	0.9871	0.9573	0.9986	0.9999	0.9938
A	0.8094	0.5761	0.9991	0.8296	0.9996	0.9991	0.9958
B	0.8910	0.7637	0.9879	0.9309	0.9987	0.9993	0.9827
C	0.9399	0.7973	0.9872	0.9656	0.9990	0.9999	0.9945
D	0.9376	0.8347	0.9664	0.9693	0.9956	0.9993	0.9961
AIC							
USP paddle apparatus							
R	25.55	34.55	34.25	27.41	19.77	-1.51	6.80
A	42.34	46.03	27.92	40.56	18.51	13.33	27.04
B	42.34	38.57	39.62	38.42	26.10	1.76	38.22
C	28.38	33.44	29.45	26.83	12.22	-4.25	33.50
D	35.58	40.57	35.43	31.20	13.92	10.40	17.82
Flow-through cell method							
R	33.99	41.12	24.47	30.62	11.01	-9.63	17.49
A	36.28	41.12	1.96	35.61	-3.36	-2.37	11.96
B	38.25	43.06	24.19	35.39	11.02	-0.11	25.47
C	32.43	40.30	23.95	28.89	8.68	-16.12	15.28
D	34.83	40.77	31.83	30.55	19.86	8.30	18.06

R: reference. A-D: generic formulations. AIC: Akaike Information Criterion.

Considering established criteria to choose the best-fit model (highest $R^2_{adjusted}$ and lowest AIC value) all data generated by both USP dissolution apparatuses adjusted to Weibull equation, excepting generic formulation A with flow-through cell method, that adjusted to Makoid-Banakar equation. As almost all meloxicam dissolution data adjusted to the Weibull model, parameters derived to this adjustment (α, β, Ti, and F_{max}) were used to calculate $t_{50\%}$. Results are shown in table 7.

Table 7: Weibull parameters and $t_{50\%}$ values (min) derived from data adjustment to this mathematical model, mean, *n* = 12

Code	α	β	Ti	F_{max}	$t_{50\%}$ (±SEM)
USP paddle apparatus					
R	9.11	0.93	2.50	94.29	10.26±0.16
A	45608.45	2.89	-5.24	96.26	18.81±0.29*
B	7.69	0.95	2.68	119.13	7.08±0.30*
C	4.70	0.69	1.45	118.90	5.21±0.16*
D	180.00	1.80	-0.68	90.39	12.70±0.26*
Flow-through cell method					
R	57.81	1.06	2.54	181.00	18.72±0.35
B	535.21	1.19	2.09	882.36	17.77±0.98
C	48.81	1.08	2.30	142.80	19.25±0.54
D	19.20	1.00	3.04	113.89	14.23±0.15*

With USP paddle apparatus significant differences were found for $t_{50\%}$ values of all generic formulations (*P<0.05) meaning that dissolution profiles of meloxicam from these drug products were not similar to dissolution profile of reference formulation. With flow-through cell method, significant differences were found only with generic product D (*P<0.05).

Data fitting to mathematical equations described above was carried out without any physiological significance to find a model that explains the *in vitro* dissolution performance of meloxicam formulations. The purpose of using mathematical models to adjust dissolution profiles is that they facilitate the analysis and interpretation of results because they describe the dissolution profiles as a function of only a few parameters that can be statistically compared [30]. Silva Oliveira *et al.*, [2] found the first-order kinetic model more appropriate to explain dissolution data of three meloxicam commercial formulations (they used only zero-order and first-order models). Significant differences were found between generic and reference formulations when comparing $t_{50\%}$ data derived from the adjustment to this kinetic model.

Similar results to those found in this work were reported by Medina *et al.*, [28] where dissolution profiles of five generic formulations of naproxen sodium, obtained with USP Apparatuses 2 and 4, were compared with the reference formulation by model-dependent and-independent approaches. With USP paddle apparatus, all generic formulations were different to reference product while with USP Apparatus 4 only two drug products were different to reference.

In general, the comparisons made above indicate that when using USP paddle apparatus all dissolution profiles of generic formulations are different from dissolution profile of reference product while when using the flow-through cell method only one generic product shows a dissolution profile totally different to the profile of reference. This is relevant when considering that generic formulations must have a biopharmaceutical quality such as the reference product has in order to maintain the same safety and efficacy and authorize their commercialization. Laboratories that manufacture generic formulations, in extreme cases, must reformulate their product to equalize the dissolution process to that presented by reference, so before making this decision it is necessary to consider different dissolution schemes and choose the most adequate to not change the formulation due to a dissolution method that does not adequately reflect the dissolution performance of the products under study.

Several authors reported that development of a dissolution procedure involves selecting the dissolution tester, media, apparatus type and hydrodynamic (agitation rate) appropriate for the product [17]. An alternative to evaluate drug dissolution is the flow-through cell method. Their advantages over conventional basket and paddle apparatus are widely demonstrated especially in dissolution of poorly soluble drugs in immediate-release dosage forms [24, 25, 31] and in modified-release dosage forms [32]. As USP Apparatus 4 best simulates hydrodynamic conditions of gastrointestinal tract it is important to investigate the applicability of flow-through cell method on the study of *in vitro* release of meloxicam generic formulations to develop dissolution methods with high discriminative capacity.

A previous study with diclofenac sodium generic formulations shows that release characteristics vary considerably among different manufacturers and that even identical formulations showed rather dissimilar release profiles, therefore the interchangeability of the drugs used in that study is questioned [33]. Other authors reported that many potential factors can explain the differences between the branded and their generic counterparts [17]. Those included the manufacturer, apparatus type, surface area of a drug, surfactants, storage, dosage form and the level and type of excipients.

Always *in vitro*/*in vivo* correlations are required to confirm differences in dissolution performance of generic formulations. The choice of the hydrodynamic environment under which the drug release is evaluated is a key factor in finding significant *in vitro*/*in vivo* correlation. Results suggest that manufacturers seeking significant *in vitro*/*in vivo* correlation with meloxicam formulations it is more advisable to look for it with flow-through cell method instead of USP paddle apparatus. Better results can be obtained with flow-through cell method since formulations may not be the problem.

Owing to the lack of similarity between the release performance of some meloxicam generic products used in this study, it is necessary to conduct correlation studies to verify whether the *in vitro* differences are reflected *in vivo* before considering being safely interchangeable with the reference drug product.

CONCLUSION

This dissolution performance study reveals the need to look for better *in vitro* dissolution schemes for meloxicam tablets since USP paddle apparatus may not reflect properly the dissolution performance of meloxicam generic formulations and reference. It is suggested to evaluate *in vivo* performance of meloxicam formulations to confirm the predictability of this *in vitro* proposed methodology.

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CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Awasthi SS, Kumar TG, Manisha P, Preeti V, Kumar SS. Development of meloxicam formulations utilizing ternary

complexation for solubility enhancement. Pak J Pharm Sci 2011;24:533–9.
2. Silva Oliveira EF, Pimentel Azevedo RC, Bonfilio R, Borges de Oliveira D, Pereira Ribero G, Benjamim de Araujo M. Dissolution test optimization for meloxicam in the tablet pharmaceutical form. Braz J Pharm Sci 2009;45:67–73.
3. Induri M, Mantripragada BR, Yejella RP, Kunda PR, Nannapaneni DT, Boddu R. Dissolution studies and quantification of meloxicam in tablet dosage form by spectrophotometry. Pak J Pharm Sci 2010;25:283–7.
4. Food and Drug Administration. Guidance for Industry: Dissolution testing of immediate release solid dosage forms; 1997. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm070237.pdf. [Last accessed on 26 Mar 2019].
5. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13:123–33.
6. Yuksel N, Kanik AE, Baykara T. Comparison of *in vitro* dissolution profiles by ANOVA-based, model-dependent and independent-methods. Int J Pharm 2000;209:57–67.
7. United States Pharmacopeia and National Formulary USP 41-NF 36; The United States Pharmacopeial Convention, Inc: Rockville MD; 2018.
8. Qui S, Wang K, Li M. *In vitro* dissolution studies of immediate-release and extended-release formulations using flow-through cell apparatus 4. Dissol Technol 2014;21:6–15.
9. Singh I, Aboul Enein HY. Advantages of USP Apparatus IV (flow-through cell apparatus) in dissolution studies. J Iran Chem Soc 2006;3:220–2.
10. Sunesen VH, Pedersen BL, Kristensen HG, Müllertz A. *In vivo in vitro* correlations for a poorly soluble drug, danazol, using the flow-through dissolution method with biorelevant dissolution media. Eur J Pharm Sci 2005;24:305–13.
11. Szymanska E, Winnicka K. Comparison of flow-through cell and paddle methods for testing vaginal tablets containing a poorly water-soluble drug. Trop J Pharm Res 2013;12:39–44.
12. Jantratid E, De Maio V, Ronda E, Mattavelli V, Vertzoni M, Dressman JB. Application of biorelevant dissolution tests to the prediction of *in vivo* performance of diclofenac sodium from an oral modified-release pellet dosage form. Eur J Pharm Sci 2009;37:434–41.
13. Jinno J, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, *et al. In vitro-in vivo* correlation for wet-milled tablet of poorly water-soluble cilostazol. J Controlled Release 2008;130:29–37.
14. Fotaki N, Reppas C. The flow through cell methodology in the evaluation of intralumenal drug release characteristics. Dissol Technol 2005;12:17–21.
15. Emara LH, Emam MF, Taha NF, El-Ashmawy AA, Mursi NM. *In vitro* dissolution study of meloxicam immediate release products using flow through cell (USP Apparatus 4) under different operational conditions. Int J Pharm Pharm Sci 2014;6:254–60.
16. Ruiz ME, Gregorini A, Talevi A, Volonte MG. Dissolution studies of generic medications: new evidence of deviations from the transitivity principle. Dissol Technol 2012;19:13–24.
17. Al Ameri MN, Nayuni N, Anil Kumar KG, Perrett D, Tucker A, Johnston A. The differences between the branded and generic medicines using solid dosage forms: *in vitro* dissolution testing. Results Pharm Sci 2012;2:1–8.
18. COFEPRIS. Listado actualizado de medicamentos de referencia 2017/08, mexico. Available from: https://www.gob.mx/cms/uploads/attachment/file/197452/lMR_2017-08_V006.pdf. [Last accessed on 26 Mar 2019].
19. ICH Harmonised Tripartite Guidelines. Q2B Validation of Analytical Procedures: Metodology. International Conference on Harmonization; 1996. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm073384.pdf [Last accessed on 26 Mar 2019]
20. Podczeck F. Comparison of *in vitro* dissolution profiles by calculating mean dissolution time (MDT) or mean residence time (MRT). Int J Pharm 1993;97:93–100.
21. Anderson NH, Bauer M, Boussac N, Khan Malek R, Munden P, Sardaro M. An evaluation of fit factors and dissolution efficiency for the comparison of *in vitro* dissolution profiles. J Pharm Biomed Anal 1998;17:811–22.
22. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, *et al.* DD solver: an add-in program for modeling and comparison of drug dissolution profiles. AAPS J 2010;12:263–71.
23. Medina JR, Ortiz HD, Hurtado M, Dominguez Ramirez AM. Influence of dose and the USP basket and flow-through cell dissolution apparatuses in the release kinetics of metronidazole immediate-release products. Int J Res Pharm Sci 2014;5:137–46.
24. Medina JR, Salazar DK, Hurtado M, Cortes AR, Dominguez Ramirez AM. Comparative *in vitro* dissolution study of carbamazepine immediate-release products using the USP paddles method and the flow-through cell system. Saudi Pharm J 2014;22:141–7.
25. Langenbucher F, Benz D, Kurth W, Moller H, Otz M. Standardized flow-cell method as an alternative to existing pharmacopoeial dissolution testing. Pharm Ind 1989;51:1276–81.
26. Steffansen B, Brodin B, Und Nielsen C. editors. Molecular Biopharmaceutics. ULLA Pharmacy Series. Pharmaceutical Press; 2010.
27. Dermirtürk E, Oner L. *In vitro-in vivo* correlations. FABAD J Pharm Sci 2003;28:215–24.
28. Medina JR, Uribe A, Hurtado M, Dominguez Ramirez AM. *In vitro* equivalence study of generic naproxen sodium tablets using the USP paddle apparatus and the flow-through cell method. Int J Pharm Pharm Sci 2015;7:348–54.
29. Medina JR, Cortes M, Romo E. Comparison of the USP Apparatus 2 and 4 for testing the *in vitro* release performance of ibuprofen generic suspensions. Int J Appl Pharm 2017;9:90–5.
30. Adams E, Coomans D, Smeyers Verbeke J, Massart DL. Non-linear mixed effects models for the evaluation of dissolution profiles. Int J Pharm 2002;240:37–53.
31. Bhattachar SN, Wesley JA, Fioritto A, Martin PJ, Babu SR. Dissolution testing of a poorly soluble compound using the flow-through cell dissolution apparatus. Int J Pharm 2002;236:135–43.
32. Chevalier E, Viana M, Artud A, Chomette L, Haddouchi S, Devidts G, *et al*. Comparison of three dissolution apparatuses for testing calcium phosphate pellets used as ibuprofen delivery systems. AAPS PharmSciTech 2009;10:597–605.
33. Bertocchi P, Antoniella E, Valvo L, Alimonti S, Memoli A. Diclofenac sodium multisource prolonged release tablets-a comparative study on the dissolution profiles. J Pharm Biomed Anal 2005;37:679–85.