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Original Article

INFLUENCE OF DOSE AND USP DISSOLUTION APPARATUS IN THE RELEASE PERFORMANCE OF REFERENCE TABLETS: PROPRANOLOL-HCl AND RANITIDINE-HCl CASES

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ABSTRACT

Objective: Due to quality of generic formulations depends on available information of reference drug products the aim of this work was to perform an *in vitro* dissolution study of two doses of propranolol-HCl and ranitidine-HCl reference tablets using USP basket or paddle apparatus and flow-through cell method.

Methods: Two doses of propranolol-HCl (10-mg and 80-mg) and ranitidine-HCl (150-mg and 300-mg) of Mexican reference products were used. Dissolution profiles of propranolol-HCl were obtained with USP basket apparatus at 100 rpm and 1000 ml of 1% hydrochloric acid. Profiles of ranitidine-HCl were determined with USP paddle apparatus at 50 rpm and 900 ml of distilled water. All formulations were also studied with the flow-through cell method using laminar flow at 16 ml/min. Dissolution profiles were compared by model-independent (f_2 similarity factor, mean dissolution time and dissolution efficiency) and model-dependent methods (dissolution data adjusted to some mathematical equations). Time data, derived from these adjustments, as $t_{50\%}$, $t_{63.25\%}$, and $t_{85\%}$ were used to compare dissolution profiles.

Results: With all approaches used and being high solubility drugs significant differences were found between low and high doses and between USP dissolution apparatuses (*P<0.05).

Conclusion: *In vitro* dissolution performance of two doses of propranolol-HCl and ranitidine-HCl was not expected. Considering the same USP dissolution apparatus, the reference tablets did not allow the simultaneous release of the used doses. 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.

Keywords: Flow-through cell method, Propranolol-HCl tablets, Ranitidine-HCl tablets, Reference drug products, USP basket apparatus, USP paddle apparatus

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INTRODUCTION

Propranolol is a non-selective β-adrenergic receptor-blocking agent. It is used to treat high blood pressure (hypertension) and severe infantile hemangioma [1]. Due to propranolol short biological half-life (3-5 h), it needs to be administered in two or three doses of 40 to 80 mg per day [2]. Ranitidine-HCl is a H_2 receptor antagonist used in the treatment of gastric and duodenal ulceration and gastro-oesophageal reflux disease. It is absorbed from the gastrointestinal tract with the bioavailability of about 50% and an elimination half-life of 3 h [3]. Chemical structures of used drugs are shown in fig. 1.

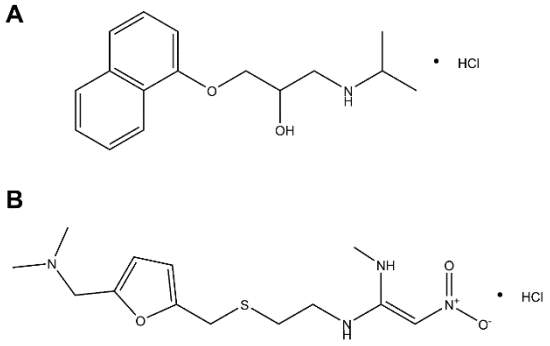

Fig. 1: Chemical structures of propranolol-HCl (A) and ranitidine-HCl (B)

Propranolol-HCl and ranitidine-HCl are included in the WHO Model List of Essential Medicines [4], and because of its wide use, these drugs are manufactured as generic formulations. This kind of formulations offer savings for patients, hospitals and pharmaceutical laboratories. Generic formulations should be evaluated periodically to ensure a similar therapeutic effect to that of the reference, so quality of generic formulations depends on the quality of reference drug products. *In vitro* dissolution studies are important to know the dissolution performance of reference products considering factors as dose and hydrodynamics.

According to the Biopharmaceutics Classification System (BCS), propranolol is a class I drug (high solubility/high permeability) [5]. Solubility of propranolol-HCl in water is reported as 1 g in 10-30 ml [6]. Ranitidine-HCl is a class III drug (high solubility/low permeability). Solubility of ranitidine-HCl in water is 660 mg/ml [7]. For propranolol-HCl, solubility within the physiological pH is not critical, so the dissolution rate of the formulation will be the decisive factor for its bioavailability [6]. For class I drugs, the dissolution of more than 85% at 30 min makes the comparison of dissolution profiles between reference and test (generic) formulation unnecessary [8].

Official dissolution tests for propranolol-HCl and ranitidine-HCl tablets are described in United States Pharmacopoeia (USP) [9] and Mexican Pharmacopoeia [10]. Dissolution conditions for propranolol-HCl include USP basket apparatus (USP Apparatus 1) at 100 rpm and 1000 ml of 1% hydrochloric acid at 37.0±0.5 °C as dissolution medium. Under these conditions, not less than 75% of drug should be dissolved in 30 min (Q ≥ 75%). Dissolution conditions for ranitidine-HCl include USP paddle apparatus (USP Apparatus 2) at 50 and 900 ml of distilled water at 37.0±0.5 °C. Not less than 80% should be dissolved at 45 min (Q ≥ 80%). Biowaiver monographs for propranolol-HCl [6] and ranitidine-HCl [7] have been published suggesting the replacing of *in vivo* studies for *in vitro* dissolution studies.

Additional dissolution tests to those established with USP vessels apparatus (USP Apparatus 1 or 2) have been developed with flow-through cell method (USP Apparatus 4). Its advantages over conventional USP basket and paddle apparatuses have been widely demonstrated, especially with dissolution 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, by generating intermittent flow of dissolution medium inside the compartment where the dosage form is placed [13]. The USP Apparatus 4 better simulates the hydrodynamic environment found in the gastrointestinal tract. Previous reports show that *in vitro* data obtained with flow-through cell method better reflect *in vivo* performance of some drugs [14, 15]. Despite the advantages of USP Apparatus 4, information about dissolution performance of propranolol-HCl and ranitidine-HCl reference tablets is scarce.

A comparative dissolution study of metronidazole with reference and generic formulations has been published [16]. In the study, two doses of metronidazole tablets and two USP dissolution apparatuses were used and significant differences in dissolution profiles of metronidazole from reference formulation were found. For this antimicrobial drug a biowaiver monograph has also been published [17]. For its high solubility and dissolution conditions used no problem should present the *in vitro* dissolution of both metronidazole doses however, its dissolution performance was not as expected. Daousani and Macheras [18], based on a previous analysis of theoretical and experimental data, established the drug dose as an important parameter for drug dissolution and biopharmaceutic drug classification.

The main objective of this *in vitro* release study was to evaluate the dissolution performance of propranolol-HCl and ranitidine-HCl reference tablets using two doses of each drug and two dissolution apparatuses. 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

Propranolol-HCl (Inderalici®, 10-mg and 80-mg, AstraZeneca SA de CV) and ranitidine-HCl (Azantac®, 150-mg and 300-mg, Grimann SA de CV) tablets were used. Mexican health regulatory agency COFEPRIS has established both drug products as a reference to be used in bioequivalence studies [19]. Hydrochloric acid and methanol analytical grade were purchased from J. T. Baker-Mexico. Propranolol-HCl and ranitidine-HCl standard were purchased from Sigma-Aldrich Co. (St. Louis MO, USA).

Content uniformity and assay

Content uniformity and assay tests with all reference formulations were performed according to the procedures described in US Pharmacopeia [9].

Dissolution profiles

USP vessels apparatus

Dissolution profiles of propranolol-HCl and ranitidine-HCl were determined according to USP tests [9] using an automated USP vessels 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. Dissolution profiles of propranolol-HCl tablets were determined with USP Apparatus 1 at 100 rpm. Tablets were sprinkled on 1000 ml of 1% hydrochloric acid. Dissolution profiles of ranitidine-HCl were obtained with USP Apparatus 2 at 50 rpm. Tablets were sprinkled on 900 ml of distilled water. Temperature of dissolution media was 37.0±0.5 °C. Sequential sampling using 0.45 µm nitrocellulose filters (Millipore®) occurred over 30 min (propranolol-HCl) or 45 min (ranitidine-HCl) at regular 5-min intervals with 12 replicates. The amount of propranolol-HCl and ranitidine-HCl dissolved was determined with standard calibration curves at 289 and 314 nm, respectively.

Flow-through cell method

Dissolution profiles of propranolol-HCl and ranitidine-HCl were obtained in an automated USP 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 media at 37.0±0.5 °C, 1% hydrochloric acid and distilled water, were pumped at 16 ml/min. An open system was used without recycling the dissolution media. Sequential sampling using nitrocellulose filters was set at regular 5-min intervals over 30 or 45 min, with 12 replicates. The amount of propranolol-HCl and ranitidine-HCl dissolved was determined in a UV/Vis spectrophotometer with 1-mm cells (Perkin Elmer Lambda 10, USA) at 289 and 314 nm, respectively. For every trial, a standard calibration curve was prepared.

Dissolution data analysis

Dissolution profiles of propranolol-HCl and ranitidine-HCl were compared by model-independent and model-dependent approaches. For the first kind of comparison, f_2 similarity factor was calculated according to equation 1 [20]:

$$f_2 = 50 \times \log\{[1 + (\frac{1}{n})\sum_{j=1}^{n}|R_j - T_j|^2]^{-0.5}\} \times 100 \quad \text{Eq. [1]}$$

Where n is the number of time points used to evaluate the amount of drug dissolved, Rj and Tj are the average percentages of drug dissolved at a j specific time from reference and test products, respectively.

Similar dissolution profiles were found when f_2 = 50-100 [20]. Then, dissolution profiles were compared with the following model-independent parameters: percentage of drug dissolved at last sampling time (Q criterion), mean dissolution time (MDT) and dissolution efficiency (DE). Q value is a quality pharmacopeial criterion used to compare the extent of drug dissolved (batch-to-batch or after some modifications of the manufacturing process) [9]. MDT is the time necessary to dissolve 63.2% of drug and it is calculated with statistical moment's theory [21]. 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 over the same time [22]. MDT and DE are commonly used parameters to IVIVC level B and C, respectively [23].

For model-dependent comparisons, dissolution data of propranolol-HCl and ranitidine-HCl formulations were fitted to Hyperbole, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Makoid-Banakar, Weibull, Logistic, and Gompertz model. Mathematical equations of all models (excepting Hyperbole model) were described by Zhang *et al.* [24] and are shown in table 1.

Table 1: Mathematical equations used to fit dissolution data

Model	Equation	Model	Equation
Hyperbole	$y = \frac{ax}{b+x}$	Makoid-Banakar	$F = k_{MB} \cdot t^n \cdot e^{-kt}$
Higuchi	$F = k_H \cdot t^{0.5}$	Weibull	$F = F_{max} \cdot \left[1 - e^{-\frac{(t-t_i)^\beta}{\alpha}}\right]$
Korsmeyer-Peppas	$F = k_{KP} \cdot t^n$	Logistic	$F = 100 \cdot \frac{e^{\alpha-\beta \cdot log\,(t)}}{1 - e^{\alpha+\beta \cdot log\,(t)}}$
Hixson-Crowell	$F = 100[1 - (1 - k_{HC} \cdot t)^3]$	Gompertz	$F = 100 \cdot e^{-\alpha \cdot e^{-\beta \cdot log\,(t)}}$

Dissolution data were adjusted to hyperbole equation with SigmaPlot software (version 11.0) and $t_{50\%}$, $t_{63.2\%}$, and $t_{85\%}$ values were calculated after adjustment to this mathematical equation. For the rest of the adjustments, the model with the highest determination coefficient ($R^2_{adjusted}$) and the minimum Akaike Information Criterion (AIC) was chosen as the best fit model [25]. f_2, MDT, DE, and adjustment to all

models (excepting hyperbole) was calculated with Excel add-in DDSolver program [24]. Mean values were compared by a Student's *t*-test and significant differences were considered if *P<0.05.

RESULTS AND DISCUSSION

Content uniformity and assay

All formulations were within USP limits. The percentages of propranolol-HCl and ranitidine-HCl on the content uniformity tests ranged from 85-115% and the assay tests between 90-110%. Results are shown in table 2.

Dissolution profiles

Model-independent comparisons

Dissolution profiles of propranolol-HCl and ranitidine-HCl from reference formulations, obtained with USP basket or paddle apparatus and flow-through cell method, are shown in fig. 2.

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

Drug	Dose	Content uniformity (min-max%)*	Assay (%)†
P	Low	95.27-110.68	106.34±1.72
	High	101.15-108.45	97.78±1.86
R	Low	101.96-107.95	101.84±4.65
	High	101.72-109.07	108.00±7.50

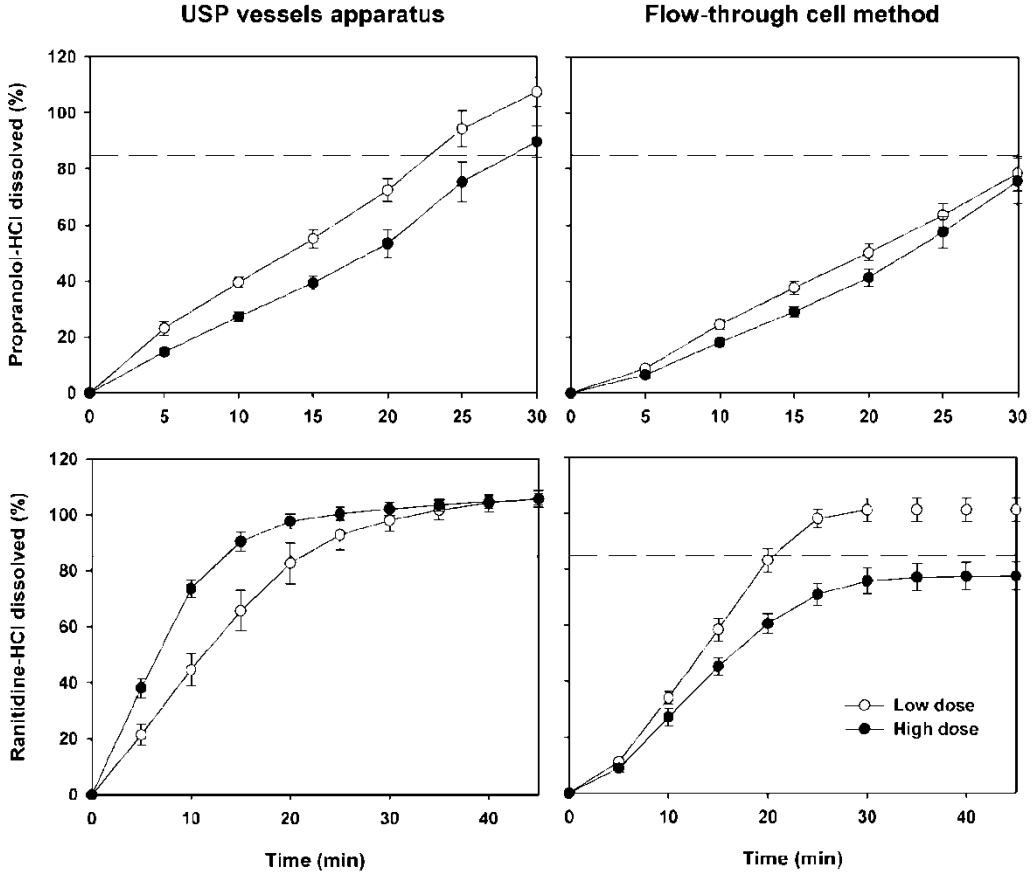

Fig. 2: Dissolution profiles of propranolol-HCl and ranitidine-HCl from reference formulations, the dotted line shows 85% of drug dissolved. mean±SD, *n* = 12

Table 3: Model-independent and-dependent parameters of propranolol-HCl (P) and ranitidine-HCl (R). mean±SEM, *n* = 12. *P<0.05, Low *vs.* High dose

Drug/Dose	Diss. at last sampling time (%)	MDT(min)	DE (%)	$t_{50\%}$ (min)	$t_{63.2\%}$ (min)	$t_{85\%}$ (min)
USP vessels apparatus						
P/low	107.49±1.49	14.27±0.15	56.33±0.86	13.08±0.23	16.76±0.28	23.08±0.35
P/High	89.68±1.64*	15.80±0.18*	42.42±0.76*	17.33±0.32*	21.94±0.41*	29.60±0.57*
R/low	105.72±0.87	13.60±0.37	73.76±1.12	10.17±0.45	14.37±0.57	24.04±0.77
R/High	105.57±0.64	8.87±0.09*	84.77±0.57*	5.18±0.11*	7.84±0.17*	15.67±0.34*
Flow-through cell method						
P/low	78.41±1.77	15.72±0.16	37.27±0.64	19.73±0.35	24.91±0.45	33.44±0.62
P/High	75.69±2.36	17.39±0.23*	31.65±0.66*	22.12±0.58*	27.96±0.74*	37.61±0.99*
R/low	101.20±1.20	13.40±0.26	71.00±0.53	11.37±0.18	15.84±0.21	25.69±0.35
R/High	77.51±1.45*	13.93±0.16	53.50±0.99*	17.30±0.58*	25.30±0.89*	46.09±1.94*

All formulations met the pharmacopeial Q criterion ($Q \geq 75\%$ for propranolol-HCl and $Q \geq 80\%$ for ranitidine-HCl), excepting high dose of ranitidine-HCl with flow-through cell apparatus (Q = 77.51%). Specific data and comparison of drug dissolved at the last sampling time are shown in table 3.

It is important to highlight the lack of compliance of Q criterion of a high dose of ranitidine-HCl with flow-through cell method. Dose, the total volume of dissolution medium and high solubility should be factors that favor ranitidine-HCl dissolution however, this does not happen. Something similar is observed with the dissolution of both drugs at 15 and 30 min. A very rapid drug dissolution can be achieved if ≥ 85% drug is dissolved in 15 min [26] and rapid drug dissolution can be achieved if the same percentage of drug is reached in 30 min [27]. More than 85% of drug dissolved at 15 min is reached only by a high dose of ranitidine-HCl in USP paddle apparatus. More than 85% of drug dissolved at 30 min is reached by both doses of propranolol-HCl in USP basket apparatus, both doses of ranitidine-HCl in USP paddle apparatus and a low dose of ranitidine-HCl with flow-through cell method. Under dissolution conditions used, reference formulations should allow the complete release of both drugs, however, as previously mentioned, the high solubility of each drug and the volume of dissolution media are not enough factors to obtain the extent of dissolution that characterizes a drug product with very rapid or rapid dissolution.

As observed, with flow-through cell method the used formulations showed slower dissolution rates than that found with USP basket or paddle apparatus. Langenbucher *et al.* [28] stated that this kind of behavior can be explained by the hydrodynamic conditions generated by 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. With flow-through cell method, cell size, glass beads and flow rate are critical factors to form this special pattern. In this *in vitro* release study of propranolol-HCl and ranitidine-HCl flow rate of 16 ml/min was used because it is one of the three suggested by European and United States Pharmacopeias [29].

To compare dissolution profiles of low *vs*. high dose of propranolol-HCl and ranitidine-HCl f_2 similarity factors were calculated. Additionally, USP vessels apparatus *vs*. flow-through cell method was also compared. Results are shown in table 4.

Table 4: f_2 similarity factor calculated to compare dissolution profiles of propranolol-HCl (P) and ranitidine-HCl (R) formulations

Comparison	Drug	Apparatus/Dose	f_2
Low *vs*. High	P	USP 1	41.58
		USP 4	61.12
	R	USP 2	42.24
		USP 4	35.39
USP 1 *vs*. USP 4	P	Low	34.08
		High	46.97
USP 2 *vs*. USP 4	R	Low	61.57
		High	24.75

Table 5: Criteria used for the selection of the best fit model, mean, n = 12

Drug/dose	Higuchi	Korsmeyer-Peppas	Hixson-Crowell	Makoid-Banakar	Weibull	Logistic	Gompertz
USP vessels apparatus							
$R^2_{adjusted}$							
P/low	0.8344	0.9905	0.9065	0.9915	0.9877	0.8475	0.7802
P/High	0.7556	0.9862	0.9063	0.9896	0.9784	0.9123	0.8534
R/low	0.9078	0.9093	0.9659	0.9938	0.9974	0.9473	0.9074
R/High	0.6297	0.7972	0.9688	0.9584	0.9975	0.9542	0.9423
AIC							
P/low	42.57	25.16	38.99	22.57	25.93	42.57	44.85
P/High	43.39	25.13	37.14	22.12	27.18	37.67	40.91
R/low	60.11	60.51	49.64	34.26	26.87	55.44	60.91
R/high	67.35	62.79	44.11	48.54	20.14	47.79	50.43
Flow-through cell method							
$R^2_{adjusted}$							
P/low	0.7692	0.9963	0.9459	0.9966	0.9968	0.9756	0.9436
P/High	0.6859	0.9954	0.8889	0.9968	0.9886	0.9608	0.9218
R/low	0.8255	0.8314	0.9153	0.9899	0.9981	0.9681	0.9485
R/High	0.8565	0.8695	0.9286	0.9969	0.9994	0.9725	0.9808
AIC							
P/low	41.70	16.95	32.58	16.66	14.93	28.26	33.68
P/High	43.53	17.46	36.89	16.23	21.24	30.98	35.58
R/low	68.56	68.95	61.93	43.16	28.21	53.05	57.91
R/High	62.39	61.31	54.77	27.06	12.13	46.07	43.74

Only dissolution profiles of two doses of propranolol-HCl with flow-through cell method and dissolution profiles of low dose of ranitidine-HCl, obtained with USP paddle apparatus and flow-through cell method, were similar (f_2 = 50-100). Although USP Apparatuses 2 and 4 have different characteristics (especially hydrodynamic condition) it should be noted that dissolution profiles of low dose of ranitidine-HCl are similar. Results suggest that dissolution performance of low dose of ranitidine-HCl is independent of the hydrodynamic environment to which tablets were subjected.

Values of model-independent parameters: percentage of drug dissolved at last sampling time, MDT and DE of all formulations, are shown in table 3. Significant differences in all comparisons (Low *vs*. High dose) were found (*P<0.05) excepting percentage of ranitidine-HCl dissolved at 45 min with USP paddle apparatus as well as the percentage of propranolol-HCl dissolved at 30 min and MDT of ranitidine-HCl with flow-through cell method.

Model-dependent comparisons

The $t_{50\%}$, $t_{63.2\%}$, and $t_{85\%}$ values derived from the adjustment to hyperbole model are shown in table 3. Significant differences in all dissolution profiles of low *vs*. high dose, of both drugs, were found (*P<0.05). Dissolution data of USP basket or paddle apparatus *vs*.

flow-through cell were also compared and only dissolution profiles of low dose of ranitidine-HCl were similar (*P>0.05) which corroborates the independence of low dose of this drug of the hydrodynamic environment surrounding the tablets.

Values of $R^2_{adjusted}$ and AIC obtained after the adjustment of dissolution data to all mathematical equations described above are shown in table 5. Considering the established criteria to choose the best fit model (highest $R^2_{adjusted}$ and lowest AIC) with USP vessels apparatus dissolution profiles of both doses of propranolol-HCl adjusted to Makoid-Banakar model and both doses of ranitidine-HCl adjusted to Weibull function. With the flow-through cell method both doses of ranitidine-HCl adjusted to Weibull model. Apparently, dissolution performance of both doses of ranitidine-HCl from the reference product can be explained with the same mathematical equation regardless of the dissolution system used.

To compare dissolution profiles of propranolol-HCl and ranitidine-HCl with the previous settings $t_{50\%}$, $t_{75\%}$, and $t_{80\%}$ of propranolol-HCl (with USP basket apparatus data) were calculated and compared. Results are shown in table 6. Moreover, Weibull parameters of ranitidine-HCl (with both USP apparatuses data) were used to calculate the model-dependent parameter *Td*. Results are shown in table 7.

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Table 6: Time parameters after adjustment of propranolol-HCl data to Makoid-Banakar model, mean±SEM, *n* = 12. *P<0.05, low *vs.* high dose

Dose	$t_{50\%}$ (min)	$t_{75\%}$ (min)	$t_{80\%}$ (min)
USP basket apparatus			
Low	13.15±0.26	20.48±0.35	21.91±0.36
High	18.39±0.37*	25.88±0.45*	27.26±0.47*

Table 7: Parameters after adjustment of ranitidine-HCl data to Weibull function. Mean, *n* = 12. *P<0.05, low *vs.* high dose

Dose	α	β	Ti	F_{max}	*Td* (±SEM)
USP paddle apparatus					
Low	1980.87	1.78	-3.03	105.72	15.34±0.56
High	7.81	0.94	2.14	105.24	8.53±0.16*
Flow-through cell method					
Low	155557.80	3.54	-8.57	101.65	15.86±0.32
High	598.82	2.14	-1.69	77.83	16.04±0.19

Significant differences were found with $t_{50\%}$, $t_{75\%}$, and $t_{80\%}$ data of propranolol-HCl (*P<0.05) meaning that dissolution profiles of low and high dose of propranolol-HCl, obtained with USP basket apparatus, were not similar while significant differences in *Td* values of ranitidine-HCl were found only with data obtained with USP paddle apparatus (*P<0.05). Dissolution profiles of ranitidine-HCl, obtained with USP paddle apparatus and flow-through cell method, were also compared and similar profiles were found only with the low dose.

In this *in vitro* release study of low and high dose, data fitting to models previously described were carried out without any physiological significance in order to find a mathematical equation that explains the *in vitro* dissolution performance of propranolol-HCl and ranitidine-HCl from Mexican reference products. The purpose of using mathematical models to adjust dissolution data is that they facilitate the analysis and interpretation of observed results because they describe the dissolution profiles as a function of only a few parameters that can be statistically compared [30].

Form a scientific point of view propranolol-HCl is a candidate for granting a biowaiver when the immediate-release tablets are formulated with well-known excipients, show rapid *in vitro* dissolution, and meet the dissolution profile comparison criteria as defined in the Guidances (f_2 = 50-100 in dissolution media with pH of physiological relevance). The USP criteria and method are suitable to assure batch to batch consistency [6]. On the other hand, it would be reasonably safe to grant biowaivers for ranitidine-HCl immediate-release solid oral dosage forms, provided that the test product is formulated with some excipients, in amounts typically used in this kind of formulations, and the test product is also rapidly dissolving [7]. In this sense, the drug products used are commercial products of which the type of excipients and the manufacturing process are unknow, but for their safety and efficacy previously proven, they have been chosen by the Mexican Health Authorities as reference drug products to be used in bioequivalence studies. These products are also used for *in vitro* dissolution studies of generic formulations.

The BCS suggests that for class I drugs and in some instances for class III drugs, 85% dissolution in 0.1 N HCl in 15 min can ensure that the bioavailability of the drug is not limited by dissolution. In these cases, the rate limiting step for drug absorption is gastric emptying [31]. Of all dissolution profiles obtained in this *in vitro* dissolution study, only high dose of ranitidine-HCl with USP paddle apparatus met this dissolution criterion. The mean $t_{50\%}$ gastric residence (emptying) time is 15-20 min under fasting conditions. Based on this information, a conservative conclusion is that a drug product undergoing 85% dissolution in 15 min under mild dissolution test conditions in 0.1 N HCl behaves like a solution and generally should not have any bioavailability problems. If the dissolution is slower than gastric emptying, a dissolution profile with multiple points in multimedia is recommended [31]. On the other hand, for submission of a biowaiver request, an immediate-release product (test and reference) should be rapidly dissolving (BSC class I) or very rapidly dissolving (BCS class III) [8]. Under pharmacopeial dissolution conditions used low dose of ranitidine-HCl and all formulations with flow-through cell method do not comply with the requirement requested in the Guidance.

This is the first *in vitro* dissolution study with reference tablets of propranolol-HCl and ranitidine-HCl using USP vessels apparatus and flow-through cell method since comparative dissolution profiles with two doses of reference products are scarce. This work reveals significant differences in dissolution rate and extent of two doses of each drug used. On the other hand, comparative dissolution studies between USP paddle apparatus and flow-through cell method have been reported with ibuprofen and carbamazepine generic suspensions [32, 33] with the aim of improving these dosage forms. Hydrodynamics of USP Apparatus 4 best simulates human gastrointestinal tract. Shah *et al.* [34] stated that in order to increase the ability to detect any changes in the manufacturing process, a dissolution test at a lower agitation rate is preferred. Attentions should be given to the conditions to which the ingested solid dosage forms may be exposed in the stomach.

As dissolution data obtained with the flow-through cell method have been proved to better correlate with *in vivo* data [28, 35] and some pharmacopeial dissolution tests (that generally use USP vessels apparatus) do not allow to differentiate the rate and extent of *in vitro* release from generic drug products [36, 37] it is necessary to investigate new dissolution conditions that reflect the quality of generic formulations and estimate the *in vivo* performance of drugs. The quality of generic formulations depends on the available information of the dissolution performance of reference drug

products under different conditions (e. g. hydrodynamics or pH medium). From a quality assurance point of view, a more discriminative dissolution method is preferred, because the test will indicate possible changes in the quality of the product before *in vivo* performance is affected [31].

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 [31]. This assertion may not be an absolute rule especially if significant differences in dissolution performance of two doses of drugs with high solubility (class I or III) are documented. The search of "adequate dissolution test" must be essential for to ensure quality, safety and efficacy of drug products of any country. Some authors have reported that the effect of propranolol on portal pressure in patients with portal hypertension is highly variable and does not correlate with propranolol racemate or stereoisomer plasma concentrations [38]. Differences on *in vitro* behavior found in this work could explain *in vivo* performance of propranolol.

It is important to consider bioequivalence data of the drugs used in this work. Polli [39] reported the association of dissolution rate of three ranitidine-HCl tablets and their bioequivalences relative to the reference product. He found all formulations bioequivalent despite differences in dissolution rates. The author asserts that differences in dissolution rates observed earlier than 30 min had negligible consequences *in vivo*. It is necessary to carry on IVIVC studies with both doses of propranolol-HCl and ranitidine-HCl to evaluate the predictability of the proposed methodology since if problems are reported with reference drug products the quality of generic formulations will be affected.

CONCLUSION

In vitro dissolution performance of two doses of propranolol-HCl and ranitidine-HCl under the hydrodynamic environment of USP basket or paddle apparatus and the flow-through cell was not expected. It is essential to carry out bioequivalence studies with the lowest and highest doses of reference products used. This action seems not to be necessary for class I and III drugs, however, due to the results obtained in the present work it must be confirmed that significant differences in dissolution profiles do not affect the bioequivalence of both doses. More research on *in vitro* dissolution performance of all available doses of reference products is necessary.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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