© 2024 Journal of Pharmacy & Pharmacognosy Research, 12 (5), 814-821, 2024
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres23.1853_12.5.814

Original Article

Dissolution kinetics of propranolol hydrochloride 40 mg tablets under biowaiver conditions

[Cinética de disolución de tabletas de propanolol clorhidrato 40 mg en condiciones de bioexención]

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Abstract

Context: Ensuring the quality of a generic drug is essential for its commercialization. Propranolol hydrochloride is a drug in great demand on the market as it is widely used as an antihypertensive, antianginal, antiarrhythmic, and for the treatment of migraine, requiring a complete evaluation to determine equivalence.

Aims: To evaluate the dissolution biopharmaceutical characteristic in multisource products marketed in the Peruvian market, taking Inderal® as a reference product.

Methods: *In vitro* conditions are simulated using the USP apparatus II at 50 rpm and 900 mL of the dissolution media pH 1.2, 4.5, and 6.8 at 37°C. The dependent mathematical models were characterized by the Akaike information criterion, and the similarity was evaluated using the independent parameters (MDT, DE, and the similarity factor f2).

Results: The average dissolution percentages demonstrate a difference between the multisource and the innovator in the three-dissolution media. The model that best characterizes the dissolution kinetics in all products is that of Hixson–Crowell. A significant difference was obtained in the MDT and DE between the innovative and multisource products and in the three-dissolution media. The similarity factor was not within the acceptable range for multisource products in the three-dissolution media.

Conclusions: The 40 mg propranolol hydrochloride tablets included in the study are not equivalent *in vitro* to the innovative product and, therefore, are not interchangeable.

Keywords: beta-blockers; bioequivalence; interchangeability; similarity factor.

Resumen

Contexto: Garantizar la calidad de un medicamento genérico es esencial para su comercialización. El clorhidrato de propranolol es un fármaco de gran demanda en el mercado por ser ampliamente utilizado como antihipertensivo, antianginoso, antiarrítmico y para el tratamiento de la migraña, requiriendo una evaluación completa para determinar su equivalencia.

Objetivos: Evaluar la característica biofarmacéutica de disolución en productos multifuentes comercializados en el mercado peruano, tomando como producto de referencia el Inderal®.

Métodos: Se simulan condiciones *in vitro* utilizando el aparato USP II a 50 rpm y 900 mL del medio de disolución pH 1,2, 4,5 y 6,8 a 37°C. Los modelos matemáticos dependientes se caracterizaron con el criterio de información de Akaike, y la similitud se evaluó con los parámetros independientes (MDT, DE y el factor de similitud f2).

Resultados: Los porcentajes medios de disolución demuestran una diferencia entre la multifuente y el innovador en los tres medios de disolución. El modelo que mejor caracteriza la cinética de disolución en todos los productos es el de Hixson-Crowell. Se obtuvo una diferencia significativa en la MDT, DE entre el producto innovador y los productos multifuente y en los tres medios de disolución. El factor de similitud no estuvo dentro del rango aceptable para los productos multifuente en los medios de tres disoluciones.

Conclusiones: Los comprimidos de clorhidrato de propranolol 40 mg incluidos en el estudio no son equivalentes *in vitro* al producto innovador y, por tanto, no son intercambiables.

Palabras Clave: betabloqueantes; bioequivalencia; intercambiabilidad; factor de similitud.

ARTICLE INFO
Received: October 17, 2023.
Accepted: March 17, 2024.
Available Online: March 31, 2024.

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INTRODUCTION

The development of a new drug and its launch on the market implies a series of direct and indirect costs that influence the final cost. Pharmaceutical companies seek to recover their investment through sales during the period of exclusivity. Drug prices in each country depend on market conditions, regulatory mechanisms and how they are applied in practice (Moreno and Epstein, 2019).

One option to reduce the financial burden of drug costs and ensure greater access to treatment has been the production of generic drugs. The approval of its health registration, and therefore its commercialization, requires quality. The quality of generic drugs ensure that patients receive an effective product (FDA, 2017).

Generic drugs demonstrate guarantee and quality when their drug dissolution parameters, stability in biological fluids and permeability are like the reference product (Kaplan, 1972).

Dissolution tests can evaluate and compare the kinetics and dissolution efficiency of single point, two point or dissolution profiles. Dissolution profiles are obtained from the dissolved percentage of the drug in a series of sampling times under conditions similar to those of the gastrointestinal tract (Abend et al., 2019; FDA, 2017).

Dissolution profiles are useful to demonstrate the equivalence of pharmaceutical products in an optimal, economical and fast way. They are performed on drugs that belong to class I and III of the biopharmaceutical classification system (BCS) based on their characteristics of aqueous solubility and intestinal permeability (Amidon et al., 1995; Cook et al., 2008; Yu et al., 2002). The equivalence is determined from the comparison of the dissolution profiles obtained from the experimental data. Several have been proposed for comparison, highlighting model-independent and model-dependent methods (Yuksel et al., 2000).

Propranolol hydrochloride is found in tablets of 10 and 40 mg. All comparison methods (dependent and independent) of the dissolution profiles of propranolol hydrochloride in 10 mg tablets have been used (Shuma et al., 2021). In 40 mg tablets, the comparison has been evaluated by different authors only based on the similarity factor (f2) (Conceição et al., 2018; Volonté et al., 2005). In Peru, propranolol hydrochloride 40 mg tablets are marketed by different manufacturers, but their quality in relation to the reference product (Inderal) is unknown, so it is necessary to perform an *in vitro* biopharmaceutical evaluation by comparing their dissolution profiles, which will allow predicting their therapeutic equivalence.

Thus, the objective of the research is to compare the biopharmaceutical characteristic of dissolution in 40 mg propranolol hydrochloride tablets marketed in Peru, to establish its possible interchangeability.

MATERIAL AND METHODS

Material

The 40 mg propranolol hydrochloride tablets (multisource and innovative) were acquired in an authorized establishment after a random choice. The propranolol hydrochloride standard had a potency of 92.22% (Sigma-Aldrich, USA). Hydrochloric acid 37% (EMSURE®, Germany), glacial acetic acid 99.7% (J.T. Baker, USA), sodium hydroxide (EMPLURA®, Germany), an anhydrous sodium acetate 99.65% (J.T. Baker, USA) and monobasic potassium phosphate 99.63% (J.T. Baker, USA) were used. All reagents were ACS (American Chemical Society) grade.

Two multisource products of 40 mg propranolol hydrochloride tablets (A and B) were evaluated. The reference product was Inderal® from Laboratorios AstraZeneca Peru S.A.

The inactive ingredients contained in the tablets: Inderal® (lactose, magnesium stearate, microcrystalline cellulose, and stearic acid, FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10), multisource A (stearic acid, microcrystalline cellulose, red lacquer coloring No. 40, lactose monohydrate, magnesium stearate, sodium starch glycolate) and multisource B (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, FD&C alumina lacquer blue No. 2 CI 73015, stearic acid, magnesium stearate).

Quantification of propranolol hydrochloride by spectrophotometry

For the preparation of the reference solution, 15 mg of propranolol hydrochloride secondary standard were weighed, dissolved in a 25 mL volumetric flask with 15 mL of hydrochloric acid (1:100), placed in an ultrasound bath for 10 minutes and brought to volume level with hydrochloric acid (1:100), the working temperature was 25°C. A dilution of 1 mL in 25 mL was made with the same solvent, measuring the absorbance of the solution at 290 nm in a UV-Vis spectrophotometer (Perkin Elmer Lambda 365, USA). In the case of the preparation of the sample solution, 20 tablets were weighed and pulverized; a quantity of powder equivalent to 15 mg of propranolol hydrochloride was weighed, following the same procedure

as the reference solution until the solution was obtained at a volume of 25 mL, then it was centrifuged for 10 minutes at 2500 rpm. Finally, the same dilution as the reference solution was carried out, being measured at the same spectrophotometric conditions. The procedure for both solutions was performed in triplicate (Conceição et al., 2018; Volonté, 2005).

Preparation of dissolution media

The dissolution media at pH 1.2, 4.5, and 6.8, and the working temperature of 25°C, were prepared following the procedure established in USP 42 (United States Pharmacopoeia) (USP, 2019).

Preparation of the calibration curves

From a stock solution with a concentration of 0.04 mg/mL of propranolol hydrochloride secondary standard, volumetric with hydrochloric acid (1:100), dilutions were made to obtain the concentrations 0.004, 0.009, 0.018, 0.027, 0.036 and 0.053 mg/mL using each dissolution medium to volume (pH 1.2, 4.5 and 6.8). Each prepared solution was read in triplicate on a UV-visible spectrophotometer (Perkin Elmer Lambda 365, USA) at the wavelength of 290 nm. The experiment was made in triplicate.

Dissolution profiles

A dissolution equipment (Sotax AT7 Smart, USA) was used, 12 tablets of each multisource formulation (A and B) and innovative were used in the three different dissolution media, according to the following conditions: Apparatus II at 50 rpm, 900 mL of the dissolution medium, 37 ± 0.5°C. A 5 mL sample was taken from each vessel at times of 3, 6, 9, 12, 15, 20, 30, 45, 60, 90, and 120 minutes, without replacement. The 5 mL of samples taken at each time were quickly filtered, and samples were read in triplicate in the UV-visible spectrophotometer at a wavelength of 290 nm (USP, 2019).

Characterization of model-dependent dissolution kinetics

They were evaluated according to the models of order zero, order one, Higuchi, Hixson-Crowell, and Weibull. The Akaike information criterion was used to identify the best-fit model (Akaike, 1974; Costa and Sousa Lobo, 2001). Twelve units were considered for each model.

Determination of the independent model parameters

Mean dissolution time (MDT)

It is evaluated starting from the sum of the intermediate time of the time intervals sampled by the increase in the amounts of the dissolved drug between the maximum amount dissolved (Brockmeier et al., 1985; Podczeck, 1993). Twelve units were considered for each model.

Dissolution Efficiency (DE)

It is equal to the areas under the dissolution profile curve obtained at each time, calculated with the trapezoid method, between the area formed by the maximum amount dissolved and the last time sampled multiplied by 100, since it is expressed in percentage (Khan, 1975). Twelve units were considered for each model.

Similarity factor (f2)

The *in vitro* equivalence of two formulations is considered when the values obtained are between 50 and 100 (USP, 2019; WHO, 2022). It is calculated with equation [1], where R and T are the average percentages dissolved at each time for the reference product and multisource, respectively, and n is the number of sampling times.

$$f_2 = 50.log\left(\frac{1}{\sqrt{1+\frac{\sum_{t=1}^{n}(R-T)^2}{n}}}.100\right) \quad [1]$$

Validation development

The method for propranolol quantification was validated at a wavelength of 290 nm, considering that there were no changes in the maximum absorbance wavelength due to pH changes (1.2, 4.5, and 6.8). The method was specific, with no changes in the spectrophotometric run profiles of the standard solutions and tablet powder samples. The linear regression equation was Y = 19.9113x + 0.0115, with a value of r^2 = 0.9998. Seven levels of concentrations were worked with 3 replicates for each level. The response factor had a percentage coefficient of variation (CV%) of 3.5220%, less than 5%. The working range was 0.00444 mg/mL and 0.05328 mg/mL. The CV% for repeatability was 1.1231%, and for intermediate precision (two spectrophotometers and two analysts) was 1.77%, less than 2%. The recovery interval for assessing accuracy

was 98.1071% -102.8227%, with a CV% of 1.9465%, less than 2%. The limit of detection (LOD) was 0.000538045 mg/mL, and the limit of quantification (LOQ) was 0.001350775 mg/mL. The percentage retention of propranolol on the Whatman 41 filter used was evaluated, and an absolute difference of 0.7%, less than 2%, was found. The method was stable for up to 12 h.

Statistical analysis

The percentages and temporal amounts dissolved were evaluated by their arithmetic mean and their variation by standard deviation (S.D.) together with the number of observations (n). To infer differences between dissolution rate constants (Kd), mean dissolution time (TMD) and dissolution efficiency (ED%), the t-student statistical test was used, with a confidence level of 95% ($\alpha = 0.05$) (Bolton and Bon, 2010).

RESULTS AND DISCUSSION

The quantification of an active principle is a specific test and indicator of stability to determine the potency of the drug. The quantification made to the propranolol hydrochloride tablets complies with what is specified in all the products, being 103.02, 98.23, and 100.95% for the innovative product and the multisource A and B, respectively. These variations can occur due to different manufacturing processes and stability during the useful life. The coefficients of variation (CV%) are less than 2% (0.18-0.27) acceptable value for validation parameters (USP, 2019).

The World Health Organization (WHO) declares that a product dissolves very quickly when it has a dissolution percentage of not less than 85% in 15 minutes in each of the dissolution media. Multisource A and B meet this criterion, while the innovative drug released 85.86% in 15 minutes only at pH 4.5 (Fig. 1). Likewise, it should be noted that it is necessary for the CV% to be less than 20% and less than 10% in the first and last sampling times, respectively, fulfilling this by always obtaining CV% less than 10% and in the three-dissolution media (WHO, 2017).

There are several factors that influence the solubility of a drug and are responsible for the visible differences between multisource and innovative products. Physicochemical factors include polymorphism, wetting, and particle size. On the other hand, there are technological factors, among which the manufacturing procedure, granule size, and compression force stand out. Likewise, the amount and type of excipients can directly affect the rate of dissolution (Ghayas et al., 2013; Vogelpoel et al., 2004). The FDA considers that to biowaiver request support, the manufacturer must document that the excipients do not affect the amount and speed of absorption of the drug. In addition, it recommends avoiding the use of excessive amounts of certain excipients, such as surfactants (polysorbate 80) and sweeteners (mannitol or sorbitol), proposing percentages of excipients to be used, such as filler (±10%), disintegrant, starch (±6%), disintegrant other (±2%), binder (±1%), lubricant, calcium or magnesium stearate (±0.5%), lubricant other (±2%), glidant, talc (±2%), glidant other (±0.2%) o film coat (±2%) (FDA, 2017; Sweetman, 2009).

Another physicochemical factor that influences solubility is the pH of the dissolution medium. Propranolol hydrochloride has a basic pKa of 9.45. Considering the Henderson-Hasselbach equation, a high percentage of ionized (soluble) drugs will be found in the media pH 1.2, 4.5 and 6.8, and it will not be a relevant factor in solubility. This explains why a similar behavior is present in the three-dissolution media in the innovative product and multisource A and B (Fig. 1) (Ruiz-Caballero et al., 1998).

The model-dependent and model-independent methods for comparing dissolution profiles are determined based on the values that are used to perform the calculation. The independent method uses the dissolution data in its original form. In contrast, the dependent method is based on different mathematical functions that describe the dissolution profile (Yuksel et al., 2000).

All dissolution data were fitted to the dependent method models. The selection was made based on the Akaike Information Criterion (AIC). The AIC is widely used to choose the model that best explains the dissolution process, since the lower average of each kinetic obtained is indicative of the model that best fits the experimental data or that is less complex. It was determined as a model of a better fit to that of Hixson-Crowell for multisource and innovative products in the three means of dissolution (Table 1). When this model is used, it is assumed that the release rate is limited by the dissolution rate of the drug particles and not by the diffusion that could occur through the polymeric matrix (Akaike, 1974; Costa and Sousa Lobo, 2001).

Being propranolol hydrochloride a highly soluble drug, the dissolution rate is expected to be conditioned by the structure of the tablet, the product of the formulation, and the technological process of each laboratory. To determine this behavior, the dissolution rate constants of the Hixson-Crowell model are evaluated, showing higher values for the reference product (R) compared to tests A and B, with statistically significant differences ($p<0.05$) (Table 2). This behavior would seem contradictory; however, it is explained because multisources A and B at the first

sampling point (3 minutes) had already released more than 85% and the innovative product less than 25%. The very rapid dissolution of multisources A and B can be explained by the type and concentration of binders and disintegrants used in the formulation (García-Arieta, 2014; Ghayas et al., 2013).

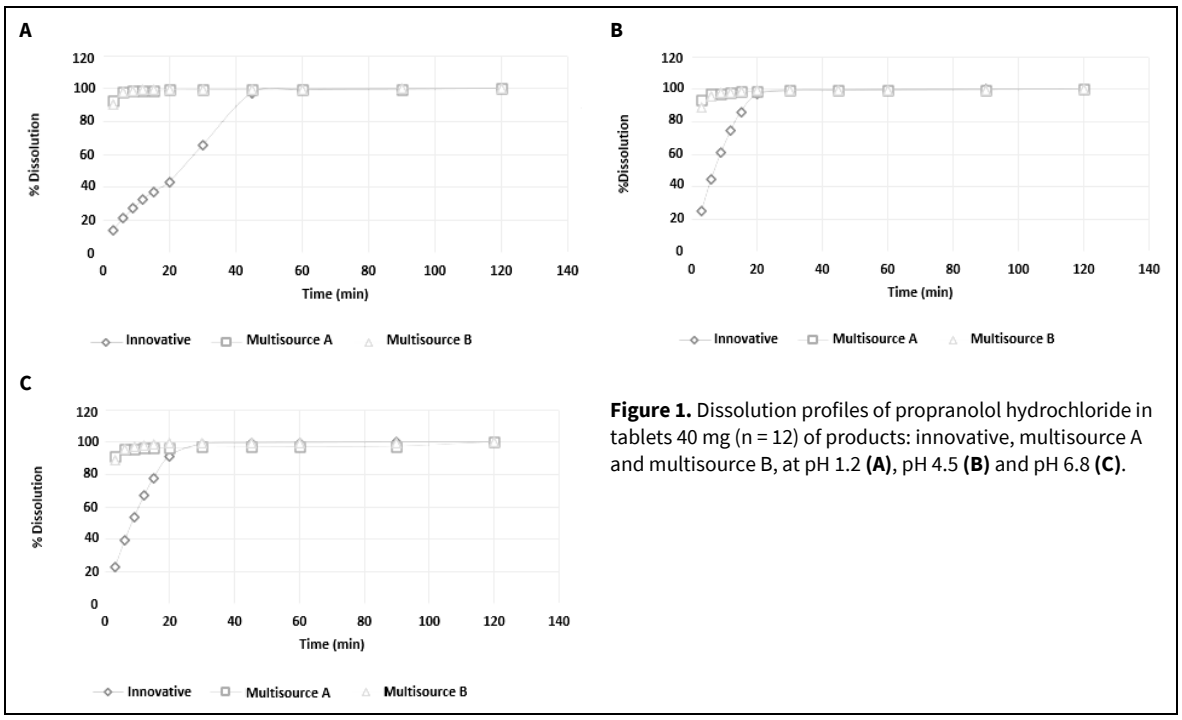

Figure 1. Dissolution profiles of propranolol hydrochloride in tablets 40 mg (n = 12) of products: innovative, multisource A and multisource B, at pH 1.2 **(A)**, pH 4.5 **(B)** and pH 6.8 **(C)**.

Table 1. Akaike Information Criterion (AIC) for different model functions of the dissolution of propranolol hydrochloride in 40 mg tablets.

Model function	pH 1.2			pH 4.5			pH 6.8		
	R	A	B	R	A	B	R	A	B
Order zero	75.80	35.23	42.61	83.53	31.83	44.37	83.16	30.45	43.13
Order one	13.85	7.64	13.52	24.18	5.23	14.01	20.41	-2.96	11.99
Higuchi	49.89	14.75	22.75	61.24	10.16	24.09	60.49	9.87	22.59
Hixson – Crowell[a]	2.42	-12.12	-5.71	12.98	-15.21	-5.57	11.02	-21.29	-7.09
Weibull	37.31	2.50	7.97	32.11	-0.04	5.76	33.24	-14.44	6.20

[a]Model that better explains the dissolution phenomenon for R and multisource products. R: innovative product; A: multisource A and B: multisource B in the three-dissolution media.

Table 2. Dissolution constants (Kd) of propranolol hydrochloride in 40 mg tablets of products (n = 12).

Parameter	pH 1.2			pH 4.5			pH 6.8		
	Kd ($mg^{1/3/min}$)			Kd ($mg^{1/3/min}$)			Kd ($mg^{1/3/min}$)		
	R	A	B	R	A	B	R	A	B
Mean	0.0375	0.0091	0.0115	0.0351	0.0077	0.0100	0.0374	0.0037	0.0119
S.D.	0.0006	0.0036	0.0031	0.0077	0.0010	0.0025	0.0079	0.0019	0.0053
t-Student g.l. = 22 (α = 0.05)	$p < 0.05^a$		$p < 0.05^a$	$p < 0.05^a$		$p < 0.05^a$	$p < 0.05^a$		$p < 0.05^a$

[a]Model that better explains the dissolution phenomenon for R and multisource products. R: innovative product; A: multisource A and B: multisource B in the three-dissolution media.

Table 3. Mean dissolution times (MDT) and dissolution efficiencies (DE-120 min) of propranolol hydrochloride tablets 40 mg of products (n = 12).

Parameter	pH 1.2				pH 4.5				pH 6.8			
	MDT (min)		DE %		MDT (min)		DE %		MDT (min)		DE %	
	R	A	R	A	R	A	R	A	R	A	R	A
Mean	22.44	2.36	81.30	98.03	8.43	2.57	92.97	97.86	9.91	4.74	91.74	96.05
S.D.	1.0456	0.2203	0.8735	0.1835	0.7126	0.3246	0.5939	0.2705	1.1822	1.2318	0.9852	1.0265
t-Student g.l. = 22 (α = 0.05)	$p< 0.05^a$		$p< 0.05^a$		$p< 0.05^a$		$p< 0.05^a$		$p< 0.05^a$		$p< 0.05^a$	

[a]Significant difference. R: innovative and A: multisource A in the three-dissolution media.

The MDT comprises the average residence time in minutes of propranolol hydrochloride in the tablet and indicates a very precise rate of drug release (Rinaki et al., 2003). On the other hand, DE is a parameter that is related to the actual amount of drug dissolved in the solution and, therefore, can give a better prognosis of *in vivo* results.

The MDT values of the innovator were higher than multisource A in the three-dissolution media. An MDT of 22.44 and 2.36 min was obtained for the innovative and multisource product A, respectively. There were even differences in the innovative product between the dissolution media, thus obtaining a difference of 14.01 min between the pH 1.2 and 4.5 media. This great difference does not appear between the values obtained for multisource A. In the case of DE, despite obtaining minor differences between the innovative and multisource product A, there was still a significant difference between the values ($p<0.05$) (Table 3) (Chatzizaharia and Hatziavramidis, 2015; Costa and Sousa Lobo, 2001; Podczeck, 1993).

For multisource B, lower MDT values were reported for the innovative product in the three-dissolution media. The difference was much greater in the pH 1.2 medium, being 20.23 min. If the variation of these values in the three-dissolution media is compared, a great difference is observed between the pH 1.2 medium and the other pH only for the innovative product. In the case of DE, the values obtained for the innovative product were lower than those of multisource B, differing between 5 and 6% in the media pH 4.5 and 6.8, the opposite of pH 1.2, where the difference is 16.85%. When analyzing the differences between the media, there is a value of 81.30, 92.97 and 91.74% for the media pH 1.2, 4.5, and 6.8 of the innovative products, showing a lower value for pH 1.2 (Table 4) (Costa and Sousa Lobo, 2001; Chatzizaharia and Hatziavramidis, 2015; Podczeck, 1993).

The differences between multisource A and B with respect to the innovator product are consistent with the visible differences in the dissolution profiles. However, when analyzing the values obtained from both multisource, similar values are evident. Equal values of MDT and DE were even presented among the multisource in the pH 4.5 medium, differing only in the S.D. (Tables 4 and 5).

The similarity factor (f2) is a measure of the similarity in percent dissolution between two curves. The f2 of the multisources compared to the innovative product in the three-dissolution media vary between 11 and 21, values that are not within the specified (50-100). In the pH 4.5 medium, the three products had a dissolution percentage greater than 85%, but not for the other two media (WHO, 2017; 2022) (Table 5). These values agree with the evaluation carried out by Oyetunde et al. (2012), in multisource 40 mg propranolol hydrochloride tablets marketed in Nigeria, where f2 less than 50 were found for dissolution profile studies.

Table 4. Similarity factor (f2) of the dissolution profiles of propranolol hydrochloride in 40 mg tablets of multisources A and B compared to the innovative product in three dissolution media (n = 12).

Drugs	Similarity factor f_2		
	pH 1.2	pH 4.5	pH 6.8
Multisource A	11	20	18
Multisource B	11	21	18

Table 5. Mean dissolution times (MDT) and dissolution efficiencies (DE-120 min) of propranolol hydrochloride tablets 40 mg (n = 12).

Parameter	pH 1.2				pH 4.5				pH 6.8			
	MDT (min)		DE %		MDT (min)		DE %		MDT (min)		DE %	
	R	B	R	B	R	B	R	B	R	B	R	B
Mean	22.44	2.21	81.30	98.15	8.43	2.57	92.97	97.86	9.91	2.62	91.74	97.82
S.D.	1.0456	0.1216	0.8713	0.0963	0.7126	0.2463	0.5939	0.2053	1.1822	0.3387	0.9852	0.2822
t-Student g.l. =22 (α=0.05)	p< 0.05[a]		p< 0.05[a]		p< 0.05[a]		p< 0.05[a]		p< 0.05[a]		p< 0.05[a]	

[a]Significant difference. R: innovative and B: multisource B in the three-dissolution media.

Study limitations

The research was conducted using as **a** reference the innovative product marketed in Peru by Astra-Zeneca Perú S.A. and produced by AstraZeneca-Mexico**.** However, the WHO recommends using the one produced in Switzerland. In Peru, the reference product is Atnahs Pharma Netherlands B.V., which was purchased in France. Therefore, the authors recommend that biowaiver studies of propranolol 40 mg tablets be performed using the reference product established by each country.

CONCLUSION

The dissolution profiles of propranolol hydrochloride 40 mg multisource tablets A and B marketed in Peru are not equivalent to the innovative product in dissolution media pH 1.2, 4.5 and 6.8, so it is not possible to ensure their interchangeability, it is important to continue research to ensure the quality of the multisource drugs marketed.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors express their gratitude to the project Tuberculosis, Parasitosis, Diabetes and Hypertension: Physicochemical Quality of Drugs acquired by the Peruvian State (PIC code 06-2014) for financing this research work.

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Concepts or ideas	x	x			x		x	x
Design	x	x	x	x				
Definition of intellectual content	x	x		x	x	x		x
Literature search	x	x	x	x	x	x	x	x
Experimental studies	x	x	x	x	x	x	x	x
Data acquisition	x	x			x	x	x	x
Data analysis	x	x	x	x	x			
Statistical analysis	x	x		x		x	x	x
Manuscript preparation	x	x	x		x	x	x	
Manuscript editing	x	x	x	x				x
Manuscript review	x	x	x	x	x	x	x	x

Citation Format: Rodriguez-Saavedra LR, Alva-Plasencia PM, Curo-Vallejos YF, Saavedra-Suárez SF, Chávez-Abanto LA, Caballero-Aquiño OE, Gutiérrez-Ramos ME, Sánchez-Bautista JF (2024) Dissolution kinetics of propranolol hydrochloride 40 mg tablets under biowaiver conditions. J Pharm Pharmacogn Res 12(5): 814–821. https://doi.org/10.56499/jppres23.1853_12.5.814