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Shuma, Madhabi Lata

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Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Research Article

In vitro Comparative Dissolution Studies of Different Propranolol Generic Tablets Available in Bangladesh

Madhabi Lata Shuma[1], Bishyajit Kumar Biswas[2], Sheikh Zahir Raihan[3] and Shimul Halder[4]*

[1] *Department of Pharmacy, Stamford University Bangladesh, Siddeswari Dhaka-1217, Bangladesh*
[2] *Department of Pharmacy, Jagannath University, Dhaka-1100, Bangladesh*
[3] *Department of Clinical Pharmacy and Pharmacology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh*
[4] *Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh*

Article Info:

Article History:

Received 11 October 2021
Reviewed 30 November 2021
Accepted 07 December 2021
Published 15 December 2021

Cite this article as:

Shuma ML, Biswas BK, Raihan SZ, Halder S, *In vitro* Comparative Dissolution Studies of Different Propranolol Generic Tablets Available in Bangladesh, Journal of Drug Delivery and Therapeutics. 2021; 11(6-S):86-91

DOI: http://dx.doi.org/10.22270/jddt.v11i6-S.5225

Abstract

The present study focused to assess *in vitro* dissolution profiles of four different products of propranolol 10 mg Tablets (Randomly coded as PRP1-PRP4) available in Bangladesh comparing with the reference brand (coded as REF). Propranolol is a competitive non selective beta-adrenergic receptor antagonist used to amend or restore normal heart rhythm in cardiovascular diseases. An *in vitro* dissolution study was carried out using the United States Pharmacopoeia (USP) paddle method at 75 rpm with 500 mL of 0.1N HCl dissolution media at 37.0± 0.5 ^{0}C. All the tested locally manufactured propranolol products; PRP1, PRP2, PRP3, PRP4 showed compatible dissolution (87%, 86%, 87%, and 80%, respectively) pattern (dissolution criterion Q=80% in 30 minutes) compared with the reference brand (88% dissolution in 30 minutes). The dissolution behavior was estimated with the reference brand using a model dependent and model-independent approach (f_2>50, f_1 < 15). A mechanistic mathematical release kinetics was also evaluated. The best-fit kinetic model was Hixon-Crowell release kinetics for reference brand and PRP1; and first order release kinetics was predominant for PRP2, PRP3 and PRP4.

Keywords: propranolol, dissolution, similarity factor, difference factor, dissolution kinetics

*Address for Correspondence:

Dr. Shimul Halder, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh.

INTRODUCTION

Dissolution testing is an empirical *in vitro* laboratory performance test that characterizes how a drug is released from its dosage form efficiently. It can be used in the calculation of active ingredients and in understanding of potential risks in case of modified release dosage forms, interaction with other medication, food impact on bioavailability, etc. [1–5]. Dissolution testing has expanded its contributions in drug product development stage, quality control and approval of regulatory process since its outset in early 1960s [6]. *In vitro* dissolution test is one of the most vital tests to assess release profiles of drugs in pharmaceutical formulations [7–10]. It allows the process to be cost-effective and less time-consuming. It has several significant applications as a quality control tool for ensuring batch to batch uniformity, any relationship between i*n vitro* dissolution and *in vivo* performance (IVIVR), registration and in research and development to examine the performance and stability of new formulations [11–14].

Propranolol is a beta-adrenergic receptor antagonist widely used in numerous conditions such as hypertension, cardiac arrhythmias, myocardial infarction, migraine, portal hypertension, anxiety, essential tremors, hyperthyroidism, and pheochromocytoma [15,16]. Its chemical Formula is: $C_{16}H_{22}C_lNO_2$ and Molecular Weight: 295.80 as HCl form (Fig. 1). In Bangladesh, propranolol is marketed as 10 mg and 40 mg tablet forms. Drug release profiles of different brands may vary due to differences in formulations and other critical manufacturing processes. But the differences must not compromise the bioequivalence as well as quality [17] Due to availability of different brands in the market, there is a possibility of getting substandard or counterfeit products. Sometimes it becomes difficult for drug regulatory affairs to access the quality of products [18]. According to the Biopharmaceutical Classification System (BCS) [19], propranolol is classified as a class I drug and it is soluble in water. These properties can be helpful to assess propranolol by *in vitro* dissolution for bioequivalence study easily [9]. Pharmaceutical equivalence test can be used to compare the release profiles of generic drugs to that of reference drug.

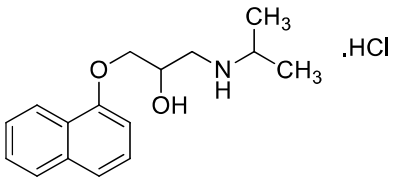

Figure 1: Chemical structure of Propranolol hydrocholoride

The purpose of this study was to compare the quality of commercially available propranolol tablets to that of a reference brand in terms of *in vitro* dissolution behavior. To clarify the interchangeability of commercially available propranolol tablets, the dissolution behavior was also statistically treated using both model-dependent and model-independent approaches.

MATERIALS AND METHODS

Materials

Propranolol HCl reference standard was obtained from ACI Pharmaceuticals Ltd. as a gift. All others commercially available analytical grade chemicals and reagents were used without further purification.

Collection of samples

Reference brand of Propranolol tablet and locally manufactured four products of Propranolol tablets were purchased commercially from different drug shops of Dhaka city. The samples were properly checked for their Manufacturing license numbers, batch numbers, and production and expiry dates before purchasing. The WHO guidelines were followed during sampling strategies [20,21]. They were randomly coded from PRP1 to PRP4 and stored under appropriate condition until further study. The labels of all the products claimed to contain 10 mg of the active ingredient per tablet.

Determination of propranolol

The amount of propranolol in the commercial products and in reference brand were determined using the UV visible spectrophotometer (DR/ 4000U (HACH, USA)) at an absorbance of 289 nm according to a previous report [22]. Potency was calculated against the standard solution.

$$\text{Potency (\%)} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times \frac{\text{concentration of standard solution}}{\text{concentration of sample solution}} \times \text{potency of standard (\%)} \quad (1)$$

Construction of standard curve

Propranolol reference standard 20 mg was taken in 20 mL and made up to the mark with the dissolution media. Concentration was 1 mg/mL. Then 10 mL of this solution was diluted to 100 mL with dissolution media. Concentration was 100 µg/mL. From this solution further dilution was carried to prepare (10–24 µg/mL) as working solutions for calibration curve. Then absorbance was taken from UV-VIS spectrophotometer according to the method mentioned earlier. The mean regression equation of the curve was y = 0.0329x + 0.0129 (Fig.2). The Linear regression was significant (R^2 = 0.9989; p = 0.0001).

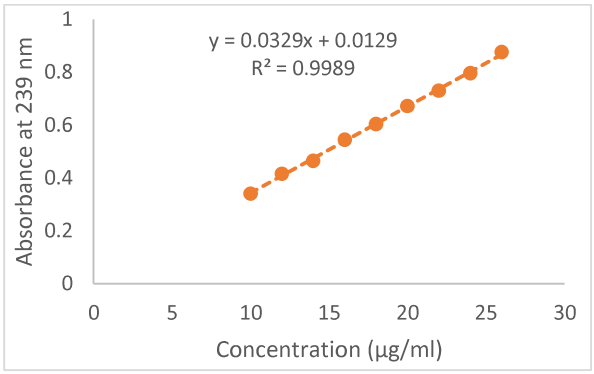

Figure 2: Calibration curve of Propranolol reference standard

Preparation of dissolution media

The dissolution media containing simulated fasted sate gastric fluid was prepared (0.1N HCl) by adding 9.865 mL hydrochloric acid (37% v/v) with sufficient water to produce 1000 mL.

Dissolution test of propranolol samples

Dissolution studies were conducted on an USP standard Dissolution apparatus (Pharmatest, Germany) having six paddle assembly. The dissolution medium was 500 mL of 0.1 N HCl maintained at a temperature of 37±0.5^0 C and the stirring rate was maintained at 75 rpm as mentioned at USP [23]. Six tablets were tested in each case. Samples were withdrawn at 10, 20, 30, and 45 minutes time intervals and their absorbance were recorded.

At first, all parts of the dissolution test apparatus were cleaned properly and its tank was filled with tap water up to the specified level. All the six vessels were filled with 500 mL 0.1 N HCl prepared before and the stirrers were set properly with 75 rpm to the machine. Six tablets of each brand were tested in each case. After that, for each brand, four different test tubes were labeled and arranged serially. Then, the machine was started and set for 75 rpm (rotation per minute) for each beaker and the time was set to run for 45 minutes. At 10, 20, 30 and 45 minutes, 5 mL of the sample from each beaker was taken and filtered into its respective test Tube. At each time point, equal fresh medium was added to maintain the constant total volume in each vessel. After 45 minutes, the machine was stopped and cleaned properly and the sample solutions were arranged accordingly for spectrometric analysis.

Model independent fit factors

Fit factors compare a test's percent of drug dissolve per unit time to a reference's percent of drug dissolve per unit time. The difference factor (f_1) calculates the percentage difference between the two curves (reference and test drug) at each time point; whereas, the similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution from the following equations.

$$f_1 = \left\{\frac{\sum(R_t - T_t)}{\sum R_t}\right\} \times 100 \text{ Where, } t = 1 \text{ to } n \quad (2)$$

$$f_2 = 50\, log\left\{[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - t_t)^2]^{-0.5} \times 100\right\} \quad (3)$$

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

The parameter f_1, whose values range from 0 to 15, and for f_2, whose values range from 50 to 100, are used to define in vitro equivalence between test and reference samples [24,25].

Another model independent factor, mean dissolution time (MDT) is determined from the accumulative curves of dissolved DES as function of time [26].

$$MDT = \frac{\sum[t_i.\Delta Q_i]}{Q_\infty} \quad (4)$$

Where t_i is an intermediate time of the intervals of sampling time, ΔQ_i is the amount of PRP dissolved in every interval of t and Q_∞ is the maximum of PRP dissolved.

In addition, Dissolution efficiency (DE) is the area under the dissolution curve within a time range, and it was calculated by using the following equation:

$$DE\ (\%) = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\% \quad (5)$$

Where, y is the drug percent dissolved at time t.

Model dependent dissolution kinetics

To investigate the *in vitro* release kinetics, various model-dependent mathematical models [27,28] such as zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, and Weibull were used. Following are the equations to describe the model dependent mathematical kinetics:

Zero Order kinetics:

$$Q_t = Q_0 + K_0 t \quad (7)$$

First Order kinetics:

$$lnQ_t = lnQ_0 + K_1 t \quad (8)$$

Higuchi kinetics:

$$Q_t = K_h\, t^{1/2} \quad (9)$$

Hixson–Crowell kinetics:

$$Q_0^{1/3} + Q_t^{1/3} = K_d\, t \quad (10)$$

Korsmeyer Peppas kinetics:

$$\frac{Q_t}{Q_\infty} = K_{kp} t^n \quad (11)$$

Weibull kinetics:

$$\log[-\ln(1-m)] = \beta \log(t - T_i) - \log \alpha \quad (12)$$

Where, Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution, k_0 is the zero-order release constant, k_1 is the first-order release constant, K_h is the Higuchi rate constant, K_d is the dissolution constant of Hixson–Crowell kinetics, Q_t/Q_∞ is a fraction of drug released at time t, K_{kp} is the Korsmeyer release rate constant, m is accumulated fraction of the drug, β is shape parameter, T_i is the location parameter, α is the scale parameter.

Statistical analysis

All data are represented as mean ± standard deviation (SD). The mathematical parameters were calculated using DDSolver program [29]. Graphs were charted using Graphpad, Prism 6.0, (GraphPad Software, LaJolla, CA).

RESULTS AND DISCUSSION

***In vitro* dissolution studies**

From the Fig. 3 of the release profile graph, we observed that the reference brand REF and the marketed product PRP1 gave the best response in the shortest possible time. After 10 minutes, more than 50% propranolol was dissolved from REF and PRP1 (53.35% and 50.01%, respectively). However, the remaining brands showed moderate dissolution pattern by this first 10 minutes. After 20 minutes, REF and PRP3 crossed the level of 65% i.e. more than 65% propranolol was dissolved. But, PRP4 showed a little slow dissolution (58.32%) compared with REF, PRP1, PRP2, and PRP3 (68.62%, 64.16%, 64.18%, 67.32%, respectively). After 30 minutes, REF and PRP1, PRP2 and PRP3 crossed the level of 85% i.e. more than 85% of propranolol was dissolved after 30 minutes. On the other hand, PRP4 showed 79.95 % dissolution that might be a poor dissolution pattern compared to other brands. After 45 minutes of dissolution studies, three local products PRP1, PRP2, PRP3 crossed the level of 90% which indicates the desired dissolution pattern attained by these three local brands with the reference brand REF that is of 98.18%. Here PRP4 showed a little poor dissolution pattern 88.70 % compared to other products however PRP4 also met the official requirement [23].

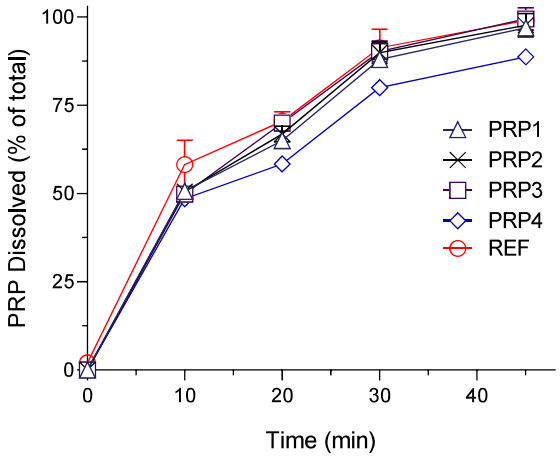

Figure 3: Comparative *in vitro* dissolution profiles of different PRP samples at simulated gastric fluid (0.01N HCl). Each bar represents mean ± S.D. of 3 experiments.

Dissolution profile comparison

Non-linear one-way ANOVA was used to analyze the dissolution profiles of the propranolol samples, including the reference brand, by fitting both model dependent and model-independent fit factors. Fit factors are key quantitative metrics explaining and comparing dissolution profiles among different samples with reference brand, according to the United States Food and Drug Administration (USFDA). The similarity factor, f_2, is more accurate in determining dissimilarities among samples, according to USFDA recommendations, and an f_2 value greater than 50 suggests same dissolution behavior. The difference factor, f_1, on the other hand, clarifies the difference in dissolution profile based on sample times. The value of f_1 must be in the range of 0 to 15. From the result at 95% confidence interval (CI) for the model independent fit factors as per USP specified time, it found that there were no significant differences in the release pattern of various PRP samples (Table 1) (P<0.05). This implies all the available PRP products in market might statistically comparable with respect to their *in vitro* release profile paralleled to reference brand.

Table 1: Various dissolution related model independent fit factors of different of PRP samples

Sample	Similarity factor (f_2)	Difference factor (f_1)	MDT (min)	T_{75} (min)	Dissolution efficiency (%)
REF			13.83	28.63	68.00
PRP1	76.33	3.80	14.23	29.54	65.45
PRP2	71.22	5.05	13.98	29.93	64.67
PRP3	76.32	3.45	14.12	29.40	65.69
PRP4	55.77	10.68	14.19	31.94	60.74

f_2, Similarity factor; f_1, difference factor (f_1); MDT, mean dissolution time; T_{50}, time to dissolve 50% of PRP; T_{75}, time to dissolve 75% of PRP; and DE, dissolution efficiency

DE and MDT values, on the other hand, are model independent characteristics that can determine interchangeability between different formulations. The results (Table 1) show that all test samples are equivalent to the reference brand, with a DE difference of less than 10% [30]. From the results of model independent fit factors, all PRP samples can be considered as interchangeable with reference brand.

Furthermore, multiple model dependent kinetic models such as zero order, first order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas, and Weibull models were examined by fitting experimental data in this study. The model with the highest correlation coefficient (R^2) value is regarded the best fitted model of the release data after fitting models to the individual kinetic model of the dissolution data [31]. In Table 2, correlation coefficient, adjusted correlation coefficient, and dissolution constant values are presented to identify and clarify the best fitted model. From table 2, the Hixon-Crowell model provides the highest correlation coefficient both actual and adjusted for reference brand and PRP1 and first order release kinetics provides for PRP2, PRP3, and PRP4.

Table 2: Determination of dissolution kinetics of different model dependent release kinetic models

Model	Parameters	Samples				
		REF	PRP1	PRP2	PRP3	PRP4
Zero Order	R^2	0.9518	0.9392	0.9261	0.9320	0.9421
	Adjusted R^2	0.9277	0.9088	0.8892	0.8980	0.9132
	K_0	2.620	2.539	2.506	2.551	2.348
First-order	R^2	0.9607	0.9764	0.9772	0.9893	0.9686
	Adjusted R^2	0.9410	0.9646	0.9658	0.9840	0.9529
	K_1	0.00027	0.00032	0.00035	0.00032	0.00040
Higuchi	R^2	0.9772	0.9631	0.9589	0.9715	0.9536
	Adjusted R^2	0.9658	0.9447	0.9383	0.9572	0.9303
	K_h	35.368	34.096	33.659	34.247	31.611
Hixon-Crowell	R^2	0.9893	0.9782	0.9688	0.9891	0.9640
	Adjusted R^2	0.9839	0.9673	0.9532	0.9836	0.9460
	K_d	0.00026	0.00024	0.00023	0.00024	0.00019
Korsmeyer-Peppas	R^2	0.9831	0.9705	0.9718	0.9826	0.9516
	Adjusted R^2	0.9747	0.9558	0.9578	0.9739	0.9275
	K_{kp}	1.720	1.689	1.680	1.681	1.670
	n	0.294	0.320	0.327	0.338	0.303
Weibull	R^2	0.8622	0.8190	0.8216	0.8660	0.8041
	Adjusted R^2	0.7932	0.7285	0.7325	0.7990	0.7061
	β	1.018	9.201	5.061	0.748	0.686

R^2, correlation coefficient; adjusted R^2, adjusted correlation coefficient using nonlinear regression; k_0, zero-order release constant; k_1, first-order release constant; K_h, Higuchi rate constant; K_d, Hixson–Crowell kinetics constant; K_{kp}, Korsmeyer release rate constant; n, diffusion coeeficent; β, shape parameter.

CONCLUSION

The goal of the *in vitro* dissolution study was to look at the release profiles of four local products and compare them to a reference brand. For the reference brand and PRP1, the Hixon-Crowell model was dominating, while first order release kinetics was prevalent for PRP2, PRP3, and PRP4. According to the USP criteria, all four local products had a suitable dissolution pattern with the reference brand (at least 80% of the propranolol was dissolved in the medium after 30 minutes). The dissolution efficiency (DE) difference was less than 10%. The four products of propranolol 10 mg generic tablets available in Bangladesh are found to be equivalent to the reference brand. They may have similar biopharmaceutical equivalence and can be used to treat hypertension interchangeably.

Acknowledgement

The authors wish to thank ACI Pharmaceuticals Ltd., Dhaka, Bangladesh for their generous help in providing the propranolol reference drug.

Conflict of interest

The authors declare no conflict of interest related to this article.

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