ORIGINAL ARTICLE

In Vitro Dissolution Kinetics of Bisoprolol Tablets Under Biowaiver Conditions

Liliya Logoyda[1], Nataliy Horlachuk[1], Nadiya Zarivna[1], Olgya Polyauk[1], Yuriy Soroka[2], Maksym Herasymiuk[3]

[1]Department of Pharmaceutical Chemistry, I. Ya. Horbachevsky Ternopil State Medical University, Ukraine, Europe, [2]Department of Anaesthesiology and Intensive-Care Medicine, I. Ya. Horbachevsky Ternopil State Medical University, Ukraine, Europe, [3]Department of Otolaryngology and Ophthalmology, I. Ya. Horbachevsky Ternopil State Medical University, Ukraine, Europe

Abstract

Introduction: Biowaiver procedure, nowadays, is a trend of Modern Biopharmaceuticals. The biowaiver approach based on Biopharmaceutical Classification System BCS is intended to replace bioequivalence *in vivo* studies. Bisoprolol is a medicine most commonly used for heart diseases, the beta blocker family of medications, and is of the β_1-selective type. **The Aim of the Study:** The aim was to study the dissolution kinetics of bisoprolol tablets to assess their equivalence under conditions *in vitro* according to the biowaiver. **Methods:** The study of dissolution kinetics of drugs in the form of bisoprolol tablets has been carried out in accordance with the requirements of the "biowaiver" procedure, the recommendations of the SPhU, and the WHO requirements to assess the possibility of replacing the pharmacokinetic studies *in vivo* by tests *in vitro*. **Results and Discussion:** The possibility to use the recommendations of the "biowaiver" procedure for the registration of generics bisoprolol tablets has been found. The studies conducted have shown that bisoprolol can be referred to Class I of the BCS, i.e., substances with a high biopharmaceutical solubility and a high penetration rate. It will allow conducting comparative studies *in vitro* to confirm the equivalence of drugs. **Conclusions:** The evaluated bisoprolol drugs fulfill biowaiver criteria for drugs containing BCS Class I active pharmaceutical ingredients. Both drugs are "rapidly dissolving," both meet the criteria of dissolution profile similarity, f_2 (i.e., the dissolution profile of the test product is similar to that of the reference product in pH 1.2, 4.5, and 6.8 buffers using the paddle method at 75 rpm), and both are considered to be *in vitro* equivalent without *in vivo* evaluation.

Key words: Bisoprolol, dissolution, standardization, tablets

INTRODUCTION

Understanding the process of delivery of drugs to the organ or target cell is one of the tasks of modern pharmacy. In order for the drug to reach the systemic blood flow, it passes through many stages, namely, release from the dosage form, dissolution in the physiological environments of the digestive tract, and absorption through the gastrointestinal membrane. Biowaiver procedure, nowadays, is a trend of Modern Biopharmaceuticals. The biowaiver approach based on Biopharmaceutical Classification System (BCS) is intended to replace bioequivalence *in vivo* studies.[1-3]

Bisoprolol is a medicine most commonly used for heart diseases, the beta blocker family of medications, and is of the β_1-selective type. Bisoprolol is beneficial in treatment for high blood pressure (hypertension), reduced blood flow to the heart (cardiac ischemia), congestive heart failure, and preventive treatment before and primary treatment after heart attacks, decreasing the chances of recurrence. Its structure is shown in Figure 1. The chemical name is 1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol.

Bisoprolol fumarate used in the product complies with its European Pharmacopoeia monographs. Bisoprolol fumarate is described as very soluble in water and methanol and freely

Address for correspondence:
Liliya Logoyda, Department of Pharmaceutical Chemistry, I. Horbachevsky Ternopil State Medical University,Ruska, 36, Ternopil, Ukraine, Europe.
E-mail: logojda@tdmu.edu.ua

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soluble in alcohol. Ukraine has marketing authorizations for bisoprolol as an immediate-release dosage form in strengths of 2.5, 5, and 10 mg. According to the Caco-2 test results (permeability), bisoprolol appeared to have moderate-to-high permeability. Caco-2 permeability values for bisoprolol are in agreement with BCS Class I and high bioavailability in humans.[4-20]

In Ukraine, bisoprolol tablets are produced by different manufacturers. The aim of our research was to study dissolution kinetics of bisoprolol tablets to assess their equivalence under conditions *in vitro* according to the biowaiver.

METHODS

Innovator bisoprolol immediate release tablets, used as reference product, and a generic version (test product) marketed in Ukraine were evaluated. The study of dissolution kinetics was conducted in accordance with the monograph of the SPhU, Supplement 2 "5.N.2. Studies on bioavailability and bioequivalence of generic medicines," guidance on bioavailability and bioequivalence research,[11] methodological recommendations, as well as the WHO Guide in three media with different pH values: Hydrochloric acid solution with pH 1.2, acetate buffer solution with pH 4.5, and phosphate buffer solution with pH 6.8. All buffer solutions were prepared according to the SPhU.

All dissolution studies were performed using USP Apparatus 2 (Erweka DT 600, Frankfurt, Germany); the device with basket was used; the volume of the dissolution medium - 1000 ml; the temperature of the dissolution medium - 37.0+0.5°C; and the rotation speed of the basket - 100 rpm. Sampling was carried out in 15, 30, and 45 min manually with a 10.0 ml pipette from the plot midway between the surface of the dissolution medium and the basket at the distance of 2 cm from the wall of the dissolution vessel. The samples obtained were filtered through a filter paper with the pore size of from 2 to 3 μm. 5.0 ml of the filtrate obtained was diluted to the volume of 100.0 ml with the corresponding dissolution medium. The volume selected was compensated by the corresponding dissolution medium. To obtain statistically reliable results, the test was carried out on 12 samples of each of the study objects. Drug release was assayed using high-performance liquid chromatography (Agilent 1260). Twelve tablets of each preparation were studied to obtain statistically significant results. Dissolution profile comparisons were made according to the WHO guidances (1). Statistical treatment was carried out using Microsoft Excel software. The equivalence of dissolution kinetics of drugs in the form of bisoprolol tablets was assessed by the value of the similarity factor (f_2), which should be from 50 to 100, to make a conclusion about conformity of the kinetic curves. For each time interval, the standard deviation of the mean value (SD) was calculated. It must keep the following requirements: Should be <10% starting from the second to the last point of control and <20% for the 1st time point.

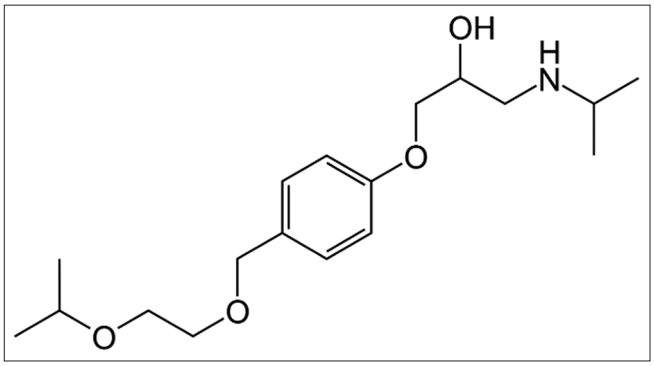

Figure 1: Structure of bisoprolol

RESULTS AND DISCUSSION

Biowaiver criteria for drugs containing BCS Class I active pharmaceutical ingredients (1) are as follows:

1. The dosage form is rapidly dissolving (dissolution amount is >85% at 30 min in all media with pH 1.2, 4.5, and 6.8) and the dissolution profile of the test product is similar to that of the reference product in pH 1.2, 4.5, and 6.8 buffers using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, f_2 ≥50 (or equivalent statistical criterion).
2. If both the test and the reference dosage forms are very rapidly dissolving (dissolution amount is >85% at 15 min in all media with pH 1.2, 4.5, and 6.8), the two products are deemed equivalent, and a profile comparison is not necessary. Both evaluated drugs were "rapidly dissolving" [Table 1] because the active pharmaceutical ingredient release at time point 30 min was >85%.[21-25]

Table 1: Dissolution amount ("rapidly dissolving," "very rapidly dissolving," or "not rapidly dissolving") for evaluated drugs

Medium	Test product		Reference product	
	% Dissolved 15 min	% Dissolved 30 min	% Dissolved 15 min	% Dissolved 30 min
pH 1.2	92.18	95.81	90.18	94.51
pH 4.5	93.24	96.75	92.84	93.12
pH 6.8	87.21	92.63	88.99	90.83

Table 2: Dissolution test results

Medium	Time, min	Test product		Reference product	
		% Dissolved	RSD, %	% Dissolved	RSD, %
pH 1.2	10	87.38	3.13	89.47	3.41
	15	92.18	2.56	93.18	3.21
	20	93.87	2.79	94.49	2.30
	30	95.81	3.01	94.51	2.86
	45	94.97	2.71	95.16	2.67
pH 4.5	10	90.18	3.07	90.01	3.37
	15	93.24	2.87	90.84	2.56
	20	93.78	2.61	90.81	2.87
	30	96.75	3.08	93.12	2.89
	45	94.91	3.23	93.28	3.24
pH 6.8	10	85.10	3.47	87.62	3.28
	15	87.21	2.89	88.99	3.13
	20	87.89	2.96	89.16	2.82
	30	92.63	3.14	90.83	2.99
	45	91.42	3.03	92.42	2.53

RSD: Relative standard deviation

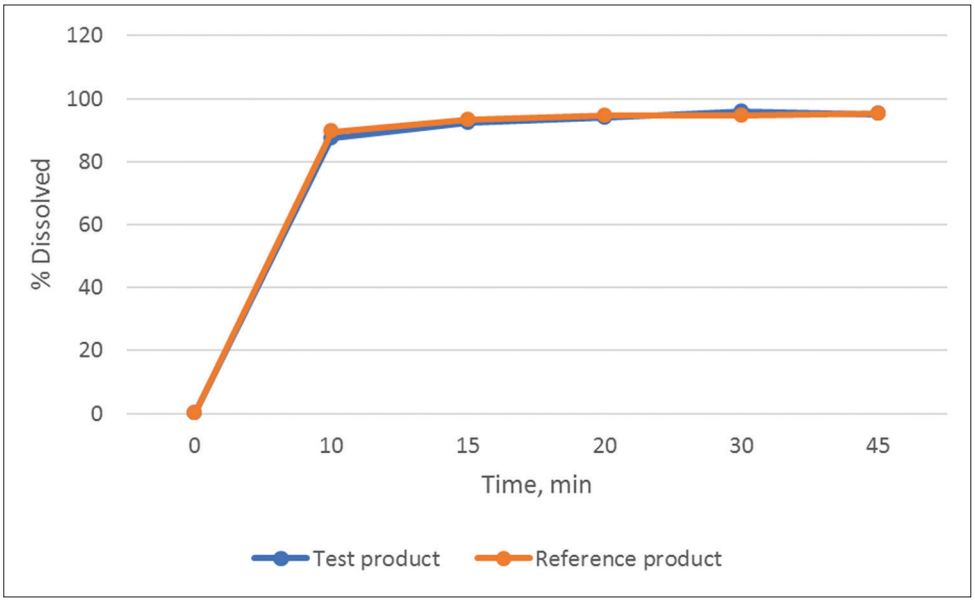

Figure 2: Dissolution profiles of test and reference drugs at pH 1.2

Dissolution profiles and corresponding data are shown in Figures 2-4 and Table 1.

On the basis of the data obtained, it has been found that the equivalence of dissolution profiles for all recommended dissolution media is observed (pH 1.2, 4.5, and 6.8) for the drugs studied. In all three dissolution media, the release of bisoprolol is >85% in 15 min [Tables 1 and 2], i.e., the drugs under research can be classified as "highly soluble," and their equivalence can be determined by the method *in vitro*. The percent relative standard deviation for all time points fulfills all requirements (≤10% for 15 min and other time points), so results are valid [Table 2]. The studies conducted have shown that bisoprolol can be referred to Class I of the BCS, i.e., substances with a high biopharmaceutical solubility and a high penetration rate. It will allow conducting comparative studies *in vitro* to confirm the equivalence of drugs.

CONCLUSIONS

The evaluated bisoprolol drugs fulfill biowaiver criteria for drugs containing BCS Class I active pharmaceutical ingredients. Both drugs are "rapidly dissolving," both meet

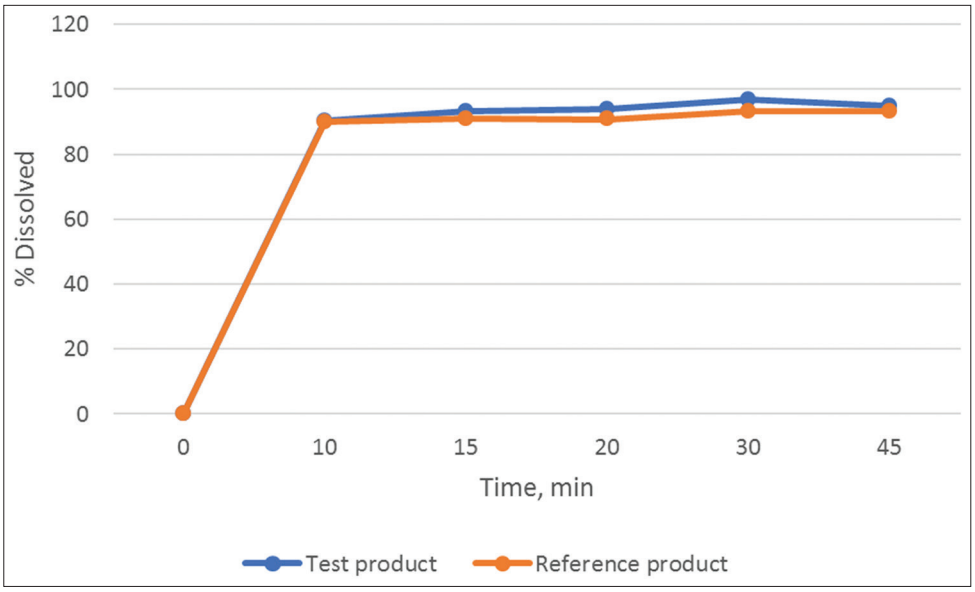

Figure 3: Dissolution profiles of test and reference drugs at pH 4.5

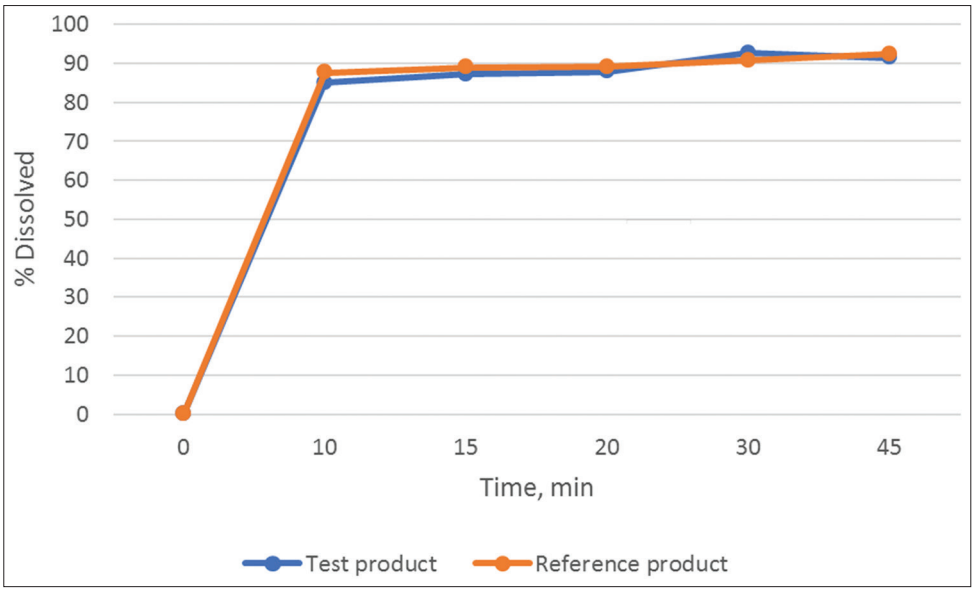

Figure 4: Dissolution profiles of test and reference drugs at pH 6.8

the criteria of dissolution profile similarity, f_2 (i.e., the dissolution profile of the test product is similar to that of the reference product in pH 1.2, 4.5, and 6.8 buffers using the paddle method at 75 rpm), and both are considered to be *in vitro* equivalent without *in vivo* evaluation.

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