ESKİŞEHİR TEKNİK ÜNİVERSİTESİ BİLİM VE TEKNOLOJİ DERGİSİ C- YAŞAM BİLİMLERİ VE BİYOTEKNOLOJİ

Eskişehir Technical University Journal of Science and Technology C- Life Sciences and Biotechnology

2020, 9(2), pp. 179 - 189, DOI: 10.18036/estubtdc.661691

ASSESSMENT OF PHARMACEUTICAL QUALITY AND RELEASE KINETICS OF METOPROLOL TARTRATE EXTENDED RELEASE TABLETS AVAILABLE IN TURKISH DRUG MARKET

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ABSTRACT

Cardioselective β-adrenergic blocker metoprolol tartrate, is used in the treatment of different diseases such as cardiac arrhythmias, hypertension, heart failure, angina pectoris, migraine, and hyperthyroidism. Beside dosage forms of the parenteral ampoule and conventional tablets of different manufacturers, there are extended release tablets of metoprolol tartrate in the Turkish Drug Market. In this research work, comparative quality control studies of metoprolol tartrate extended release tablets (original and generic) produced by two different pharmaceutical companies in the Turkey were carried out and evaluated according to the related guidelines. Thickness and diameter, hardness, weight variation, friability, content uniformity and dissolution rate were examined as quality control parameters. A new validated HPLC method for the quantification of metoprolol tartrate has been developed. An ACE column (C18, 5 µm, 250x4.6 mm) and acetonitrile:phosphate buffer (30:70, v/v) mobile phase were used for the determination of metoprolol tartrate. The tablets showed extended release for 8 hours (70.74% release from drug A, 76.87% from the drug B). Both products have acceptable hardness, friability and weight variation values. Content of the active ingredient of the tablets was consistent with label claim (99.45% for drug A and 96.45% for drug B). The dissolution data were evaluated by model dependent and model independent methods using DDSolver program. The obtained results showed that release kinetics of both drugs were well fitted with the Korsmeyer-Peppas model.

Keywords: Metoprolol tartrate, Modified release, Pharmaceutical quality control, Release kinetics, DDSolver

1. INTRODUCTION

Quality control (QC) is an activity including all the processes and procedures that determine the efficiency, safety and suitability with all required properties of a pharmaceutics. From raw material to finished product, QC is a mandatory requirement for all processes of pharmaceutical product manufacturing and improvement [1-3]. The quality of medicines is one of the major issues of health care providers and patients, and a major public health problem in developing countries. Various mechanisms and several guidelines have been developed for ensuring quality of pharmaceuticals [4-6]. Additionally, QC studies are also carried out to demonstrate quality differences between pharmaceutically equivalent formulations [7-11].

Metoprolol tartrate (MT) (Figure 1) is a cardioselective β-adrenergic blocker used in the treatment of different diseases such as cardiac arrhythmias, hypertension, heart failure, angina pectoris, migraine, and hyperthyroidism [12, 13]. MT is also a class I active ingredient according to the Biopharmaceutics Classification System (BCS). Because of its rapid absorption and short half-life (3-4 hours), repeated doses are required to maintain effective blood concentration during long-term treatment. Therefore, it is necessary to prepare its controlled release dosage forms to improve patient compliance [14, 15].

*Corresponding Author: msinankaynak@gmail.com
Received: 23.12.2020 Published: 30.07.2020

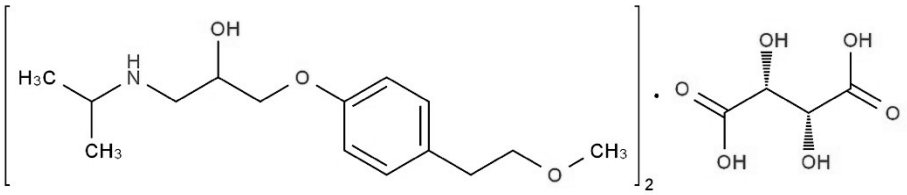

Figure 1. Chemical structure of MT

Investigation of pharmaceutical QC of MT extended release tablets manufactured by two different pharmaceutical companies in the Turkish Drug Market was the purpose of this study. A simple, cost efficient and validated HPLC method was developed for the determination of MT in tablet matrix. Content uniformity, dissolution rates, weight variation, hardness, diameter-thickness-width and friability of extended release tablets were evaluated as QC parameters according to guidelines [6, 16]. The results obtained from these studies for both tablets (one original and one generic) were compared.

2. MATERIALS AND METHODS

2.1. Chemicals and Reagents

MT was supplied by Sigma-Aldrich (USA). Acetonitrile and methanol and were HPLC grade solvents and supplied by Carlo Erba (France) and J.T. Baker (USA) respectively. All other used chemicals were of analytical grade.

2.2. Tablet Samples

One reference and one generic extended release tablets manufactured and distributed by two different pharmaceutical companies available in the Turkish Drug Market (labelled randomly as A and B) were obtained from local pharmacies. General information about the tablets were given in **Table 1**.

Table 1. General information about the extended release tablets

Parameters	Drug A	Drug B
Active ingredient	metoprolol tartrate	metoprolol tartrate
Dosage form	tablet	tablet
Route of administration	oral	oral
Strength (mg)	200	200
Product description	oblong tablets	oblong tablets
Batch number	002024	K0036

2.3. Apparatus and Equipments

Thermo Finnigan Surveyor HPLC System (USA) equipped with isocratic/gradient pump and UV/DAD detector was used for the HPLC analysis. Dissolution test were performed by using Pharma Test PTW 2 Apparatus (Germany). Pharma Test PTB 311E tablet hardness tester and Pharma Test PTF 10ER friabilitor (Germany) were used for determination of hardness and friability of dosage forms, respectively.

2.4. Quality Control Studies

The QC studies on all tablets were carried out according to the guidelines and literature [6, 16].

2.4.1. Weight variation

Weight uniformity is an important QC parameter for better tablet hardness and friability [11]. For determination of weight variation, twenty randomly selected tablets of both brands were individually weighted and the mean weight with standard deviation (SD) were calculated.

2.4.2. Hardness

Tablet hardness is an important parameter for tablet disintegration, and resistance of tablets to such processes as coating, packaging, transportation and handling. The hardness of randomly selected ten tablets from each brand was determined according to USP guidelines using a hardness tester. The forces applied to break tablets across the diameters were measured and the hardness of tablets were expressed in Newton [17].

2.4.3. Friability

Tablet friability is another essential QC parameter that shows durability of tablets during coating, packaging and handling. Once, tablets corresponding to 6.5 g of each brand were weighed separately, then friability test was performed by a friabilator (25 rpm, 4 minutes) according to USP guidelines. The tablets were taken from the friabilator, removed from small particles and weighed again. The friability percentage was calculated by comparing the weights of tablets before and after the testing. Results with a weight loss of less than 1% were considered as appropriate. [18].

2.4.4. Measurement of thickness, width and diameter

Thickness, width and diameter of ten tablets from each brand were measured using a caliper. Results were expressed as the mean and SD.

2.4.5. Content uniformity

Content uniformity is the degree of consistency in active ingredient amount among all dosage units. Ten tablets from both brands were finely powdered for the determination of MT. The amount of powder equivalent to one tablet mean weight was examined. The powder was dissolved in 50 mL methanol and then diluted with pH 3.0 acetonitrile-phosphate buffer (30:70, v/v) mobile phase mixture up to 20 times in a 100 mL volumetric flask and then sonicated for 30 minutes. After the dilution, the solutions were filtered through membrane filter (0.22 μm) and diluted up to 10 times with mobile phase before the injection to HPLC.

2.4.6. Dissolution test

To determine MT release profile from tablets, *in vitro* dissolution tests were performed according to USP guideline on six tablets using the paddle apparatus (Apparatus 2) with stirring rate of 100 rpm and 900 mL of Simulated Intestinal Fluid (SIFsp) pH 6.8 medium at 37 ± 0.5°C [12, 19]. Two mL aliquots were periodically withdrawn and replaced with fresh medium at time intervals of 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours. The samples were analyzed by HPLC after diluting 10 times with mobile phase after filtering through membrane filter (0.22 μm). Cumulative percentages of the released MT from the tablets were calculated. All studies were performed in duplicate.

2.5. Analytical Method Validation for HPLC

Analyses were performed on a Thermo Finnigan Surveyor HPLC system (USA) with a UV/DAD detector. An ACE C18 column (250 x 4.6 mm, 5 μm) was used for separation of MT from tablet matrix

components by performing isocratic elution. pH 3.0 acetonitrile-phosphate buffer (30:70, v/v) mixture was used as the mobile phase. Mobile phase was filtered through a membrane filter (0.45 µm) and degassed before using. Analyses were conducted at a flow rate of 1 mL/min at an ambient temperature (25°C). Injection volume was 20 µL, and the detection was performed at 221 nm wavelength. Peak identity was confirmed by comparison of retention times.

Calibration standards for MT (2.5, 5.0, 10.0, 20.0, 30.0, 40.0 and 50.0 µg/mL) were prepared from a 250 µg/mL standard stock solution by diluting with mobile phase within the linearity range. The proposed method was validated as to linearity, precision, accuracy, specificity, sensitivity, repeatability, and range according to the ICH guidelines [16]. The validated method was used to determine MT content and its dissolution rate from tablets.

2.6. Dissolution Profile Comparison

The dissolution data were evaluated by model independent and model dependent methods using DDSolver add-in program.The most common and simple model-independent approach to compare dissolution profiles is to use the difference factor (f_1) and the similarity factor (f_2). In these methods, f_1 value less than 15 and f_2 value between 50 and 100 are required for curves to be considered similar [20]. In the model-dependent approach, zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell and Hopfenberg models were used for evaluation of the release kinetics.

2.7. Model Selection Criteria

DDSolver evaluates the goodness of model fit with statistical parameters such as correlation coefficient (R), coefficient of determination (R^2), adjusted coefficient of determination (R^2_{adj}), mean square error (MSE), SD of the residuals (Sy.x), sum of squares (SS), within sum of squares (WSS), Akaike Information Criterion (AIC), and Model Selection Criterion (MSC). Among these comparison parameters, the most preferred ones for the selection of dissolution model are R^2_{adj}, AIC, and MSC [21]. R^2 can be used to determine the most appropriate model for the release profiles with the same number of parameters. However, R^2_{adj} should be used when the models have different numbers of parameters. The best model is the one with the highest R^2_{adj}. Furthermore, AIC is based on maximum likelihood. The model associated with the smallest value of AIC is regarded as the best fit [22]. The MSC is another statistical data for model selection and nowadays it attracts increasing attention in the field of dissolution data modeling. The MSC is a modified form of AIC and has been normalized so that it is independent of the scaling of the data points. The most appropriate model will be the one with the highest MSC [21].

3. RESULTS

Under the optimum conditions, MT was successfully determined at 4.5 min in the presence of tablet components, in a total run time of 7 min (Figure 2). Calibration curve was linear over the concentration range of 2.5 - 50.0 µg/mL (Table 2).

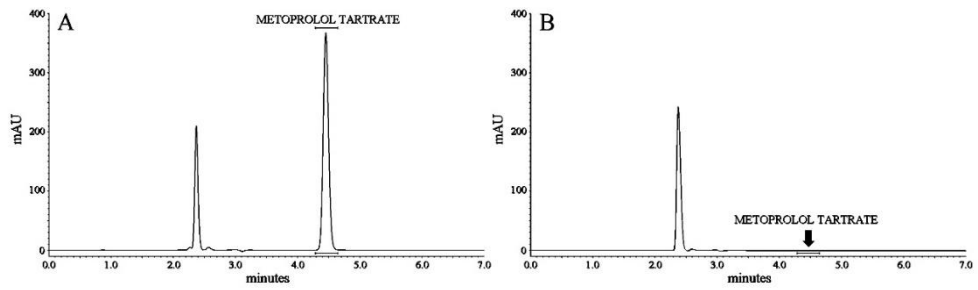

Figure 2. HPLC chromatograms of MT (A) and placebo tablets (B)

Table 2. Linearity and sensitivity results (n=6)

Parameters	Results
Regression equation*	y=105371x + 81900
Standard error of intercept	5189
Standard error of slope	121
Determination coefficient (R^2)	0.9997
Range (µg/mL)	0.5 - 250.0
Limit of detection (µg/mL)	0.40
limit of quantification (µg/mL)	1.21

* y is peak area and x is µg/mL concentration of MT

Different concentrations of MT (5, 20 and 40 µg/mL) within the range were analyzed (n=6) on the same day to determine the intra-day precision, and the same analyses were performed to determine the inter-day precision in three different days. The intra-day and inter-day precision were determined by calculating recovery percentage, and accuracy of the method was evaluated by calculating relative standard deviation (RSD). The results are summarized in Table 3. The RSD % of the intra- and inter-day precision were 2.12% or less.

Table 3. Precision and accuracy results (mean ± SD, n=6)

Concentration (µg/mL)	Recovery %		RSD %	
	Intra-day	Inter-day	Intra-day	Inter-day
5	100.32 ± 2.13	100.60 ± 0.44	2.12	0.44
20	100.91 ± 0.50	100.30 ± 0.15	0.50	0.15
40	99.21 ± 0.25	98.67 ± 0.27	0.25	0.27

The results of the QC tests are summarized in Table 4 and Table 5. It was obtained that weights of tablets were in the range of 0.3365-0.3568 g for drug A and 0.4325-0.4497 g for drug B. Content uniformity of the drug products were consistent with the label claim of MT (90.0-110.0%).

Table 4. Weight variation results (n=10)

Parameters	Drug A	Drug B
Minimum tablet weight (g)	0.337	0.433
Maximum tablet weight (g)	0.357	0.450
Average tablet weight (g)	0.346	0.439
Standard deviation	0.005	0.004

Table 5. QC test results (mean ± SD, n=10)

Parameters	Drug A	Drug B
Width (cm)	0.715 ± 0.005	0.622 ± 0.003
Length (cm)	1.312 ± 0.007	1.662 ± 0.006
Thickness (cm)	0.518 ± 0.006	0.543 ± 0.004
Hardness (N)	144.01 ± 10.627	193.89 ± 1.050
Friability (%)	0.016	0.018
Content uniformity (%)	99.45 ± 1.48	96.45 ± 1.64

The dissolution profiles of the drugs containing 200 mg MT are given in Figure 3. At the end of 8 hours, 70.74% of the MT from the drug A, 76.87% of the MT from the drug B were released to the dissolution medium.

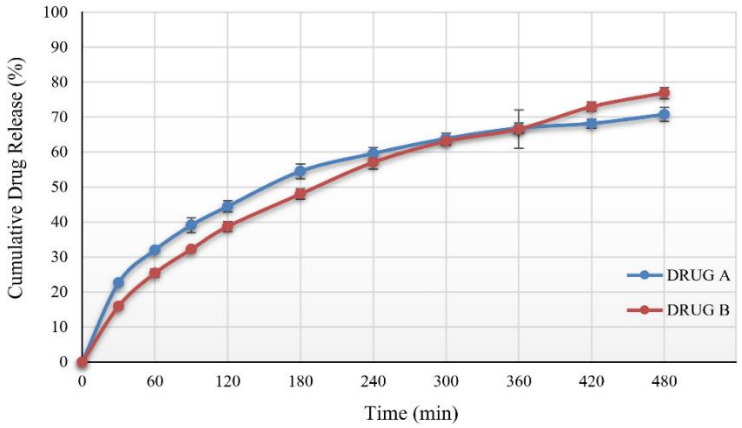

Figure 3. Dissolution profiles of the MT tablets (mean ± SD, n=6)

Comparison of the drug A and drug B release profiles, f_1 (8.99) and f_2 (63.50) tests clearly indicates that the drug release profiles are similar. The evaluation parameters, R^2, AIC and MSC were statistically analyzed and presented in Table 6. Korsmeyer-Peppas model was selected for both drugs, based on the highest R^2 and MSC; the lowest AIC.

Table 6. Evaluation parameters for best fit model selection

Kinetic Models	Parameters	Drug A	Drug B
Zero-order	R^2_{adj}	-0.1428	0.6463
	AIC	81.6505	74.4225
	MSC	-0.3335	0.8392
First-order	R^2_{adj}	0.6654	0.9514
	AIC	69.3675	54.5802
	MSC	0.8948	2.8235
Higuchi	R^2_{adj}	0.9083	0.9933
	AIC	56.4209	34.8081
	MSC	2.1895	4.8007
Korsmeyer-Peppas	R^2_{adj}	**0.9767**	**0.9940**
	AIC	**43.5273**	**34.4443**
	MSC	**3.4789**	**4.8371**
Hixson-Crowell	R^2_{adj}	0.4721	0.8927
	AIC	73.9281	62.4901
	MSC	0.4388	2.0325
Hopfenberg	R^2_{adj}	0.6235	0.9451
	AIC	71.3710	56.6117
	MSC	0.6945	2.6203

Korsmeyer-Peppas dissolution model explains the exponential relationship of dissolved drug fraction versus time. This model is frequently used to identify the drug release mechanism of various modified-release pharmaceutical dosage forms.

$$F = k_{KP}.t^n \quad (1)$$

In the Korsmeyer-Peppas model, F is the cumulative quantity of drug released at time t, t is the dissolution time (minute), k_{KP} is the release constant associated with structural and geometric characteristics of the dosage form; n is the diffusional exponent related to the drug-release mechanism [23]. The exponent n is related with the nature and geometries of the drug delivery system and can be used to explain the mechanisms involved in the dissolution. According to Table 7, the drug release mechanisms can be evaluated in three different cases:

(1) Fickian diffusion: This mechanism can be observed in nonswelling systems or where the polymer relaxation time is much shorter than the characteristic solvent diffusion time for water transport;
(2) Case II transport: This mechanism refers to the polymer chain erosion;
(3) Anomalous transport: This mechanism involves both Fickian and Case II transport [24].

Table 7. Exponent n and drug release mechanism of different geometries

Exponent n			Drug Release Mechanism
Thin Film	**Cylinder**	**Sphere**	
0.50	0.45	0.43	Fickian diffusion
$0.50 < n < 1.00$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Anomalous transport
1.00	0.89	0.85	Case II transport

4. DISCUSSION

Due to its rapid absorption and elimination (3-4 h), MT needs to be administered as repeated doses up to 4 times in a day to maintain effective blood concentration during long-term treatment. Therefore, modified-release MT formulations were developed by different pharmaceutical companies. In the Turkish drug market, different bioequivalent and interchangeable extended release tablets containing MT have been approved. In this study, we investigated an original and a generic extended release MT tablets by performing QC studies to compare their pharmaceutical quality and evaluate interchangeability.

HPLC is the most widely used method for analysis of active ingredients in different formulations since it has a basic system and ease of use. There are many studies in the literature using HPLC methods to analyze MT [25-28]. Therefore, in this study, we used a reversed phase HPLC system to analyze MT with a fine peak shape within a short analysis time. All the experiments were carried out on an ACE C18 column (250 x 4.6 mm, 5 µm) with pH 3.0 acetonitrile-phosphate buffer (30:70, v/v) mixture pumped at 1 mL/min flow rate. UV detection wavelength was 234 nm. The method validated according to the ICH guidelines was found to be precise, accurate, specific and sensitive for determination of MT (Table 2 and Table 3).

Preparation methods can cause variations in unit tablets. The amount of the active ingredients among dosage units should be equivalent for the safety and efficacy of the pharmaceuticals and the homogeneity of dosing [29]. Weight variation and content uniformity are two most important QC parameters for evaluation of the consistency of dosage units in a batch or batch to batch. Pharmacopoeias have limitations for weight variations and content uniformity of the tablets. According to the USP [18], the amount of MT in the tablets has to be between 90.0-110.0%. Our results showed that weight variations and content uniformity of tablets were within the pharmacopoeia limits for both brands (Table 4 and Table 5).

Since the tablet dimension is related to the tablet weight, size measurements like diameter, thickness and width are necessary during and after the production to avoid possible problems related with tablet

weight and dosage uniformity. Moreover, tablet thickness is a parameter directly related with the tablet compression process [3, 30]. According to the results shown in Table 5, the diameter, thickness and width of the tablets from each brand have no significant differences.

The hardness and friability of tablets affect many properties of drugs from manufacturing to pharmacological behavior after use. Both hardness and friability are related with the mechanical strength of drug products which is important to withstand the compression forces, coating, packing, and shipping. In this study, it was found that the friability of tablets of both brands was less than 1% (Table 5). The hardness is also important for the disintegration time of tablets in the gastrointestinal system (GIS). If the tablets are too hard, tablets may not disintegrate during the required dissolution time due to the increase in disintegration time [31, 32]. In our experiments the average hardness of the tablets was between 144.01 ± 10.62 Newton for drug A and 193.89 ± 1.05 Newton for drug B (Table 5). Since the dosage forms used in this study are extended release tablets, the high hardness values are not important because disintegration of the tablets is not expected in the GIS before dissolution.

The dissolution test is designed to measure the time which is required for an oral solid dosage form to dissolve under the specified set of conditions. *In vitro* dissolution studies are useful to predict the *in vivo* performance of the active ingredient. Moreover, dissolution studies are very critical and determinant for biowaiver, bioequivalence and bioavailability studies especially for extended release tablets [33]. When the release profiles of the extended release MT tablets were examined, a prolonged release for 8 hours was observed (Figure 3). This situation reduces dosing frequency and increases patient compliance. Also, because of prevention of rapid increase in plasma concentration, adverse effects are reduced.

The dissolution data were evaluated by model independent and model dependent methods using DDSolver add-in program. The results showed that release kinetics of both drugs were well fitted with the Korsmeyer-Peppas model (Table 6). Drug A and drug B dissolution profiles with Korsmeyer-Peppas model also gave n values of 0.3766 and 0.5240 respectively. For cylindrical dosage forms (tablets) n=0.5240 indicates that dissolution occurs through the mechanism of anomalous transport. Thus, the release of drug B occurs through the combination of Fickian diffusion and polymer relaxation (Table 7). The exponent n for drug A is lower than 0.45 value. In this case 0.45≥n corresponds to a quasi Fickian diffusion mechanism for cylindrical tablets [34].

5. CONCLUSION

Based on the QC results, the extended release MT tablets were both fulfilled the pharmacopoeial requirements. Therefore, it was concluded that the investigated MT tablets produced by two different manufacturers in Turkey can be used safely. Additionally, the *in vitro* release profiles of two drugs were found to be similar and the extended release kinetics were well fitted with the Korsmeyer-Peppas model.

ACKNOWLEDGEMENTS

Ayse Gencer was supported by TUBITAK 2211-A grant. This study is the part of Ayşe Gencer's graduation project.

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