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Short Communication

Development and validation of dissolution test for Metoprolol sustained release capsules

K. Kannan[1]*, T. Subburaj[2], R. Manavalan[1], P. K. Karar[1]

[1]Department of Pharmacy, Annamalai University, Annamalai Nagar, Tamilnadu State India - 608 002.
[2]Micro Labs Limited, Bangalore, INDIA.

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Dissolution test for sustained release capsules of Metoprolol 125 mg was developed and validated according to FDA and ICH guidelines. Metoprolol coated pellets were coated with microcrystalline wax and glyceryl distearate for slow release of drug. The dissolution method which uses USP apparatus I (Basket) with rotating at 100 rpm, 900 ml of different dissolution medium, ultra violet spectroscopy for quantification was demonstrated to be robust, discriminating and transferable. Dissolution tests conditions were selected after it was demonstrated that the Metoprolol rapidly dissolved in the aqueous media over the pH range of 1.2 to 7.4

Key words: Metoprolol, validation.

INTRODUCTION

Metoprolol is a β-blocker clinically used in the treatment of hypertension, angina pectoris and arrhythmia. The chemical structure of Metoprolol is shown in Figure 1. This study describes the development and validation of a dissolution test for Metoprolol sustained release capsules 125 mg. Dissolution method was developed and validated according to current ICH and FDA guidelines.

Metoprolol sustained release capsules 125 mg were prepared by filling the sustained release pellets in hard gelatin capsules. The average fill weight of one capsule is 169 mg. Dissolution test was conducted in USP XXV dissolution test apparatus type I with basket rotation at 100 rpm. The dissolution medium was 900 ml 0.1 N hydrochloric acid (pH 1.2) for 2 h and phosphate buffer pH 7.4 for 6 h and temperature was maintained at 37 ± 5˚C. One capsule was taken in each basket. 5 ml of samples were withdrawn at 1, 2, 3, 4, 5, 6, 7 and 8 h. 5 ml of dissolution medium was replaced in each sampling. Ultra Violet method was used to determine the drug content. Absorbance was measured at 223 nm and calculated the percentage release.

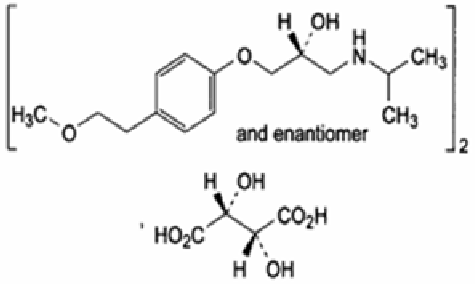

Figure 1. Chemical structure of Metoprolol.

RESULTS AND DISCUSSION

The dissolution test was developed based on the physiccochemical properties of the Metoprolol, the gastro intestinal conditions that the capsule is to encounter, and drug delivery characteristics of the dosage form. The chemical name of Metoprolol is Bis [(2*RS*)-1-[4-(2-methoxyethyl) phenoxy]-3-[(1-methylethyl) amino] propan-2-ol](2*R*,3*R*)-2,3-dihydroxybutanedioate. The molecular weight is 685 and the molecular formula is $(C_{15}H_{25}NO_3)_2$, $C_4H_6O_6$. Metoprolol is freely soluble in water. The spectrophotometer was used to analyze the dissolution samples and

*Corresponding author. E-mail: egkkannan@yahoo.co.in. Tel: +91 9842391373

Table 1. Linear regression parameters with 95% confidence limits[a].

Parameters	Values
R^2	0.9988
Slope	1.6 (±0.03)x10^4

[a]Standard concentrations were 2, 4, 5, 7.5, 10, 11, and 12.5 µg/ml.

Table 2. Accuracy results (% recovery).

Sample	% Nominal concentrations		
	50	100	125
1	99.2	100.6	101.5
2	99.8	100.4	101.3
3	100.1	101.3	101.4
4	99.6	100.8	101.6
5	99.5	100.2	101.3
6	99.4	100.7	101.4
Average	97.7	100.6	101.4

Table 3. Screening study results for Metoprolol sustained release capsules 125 mg (cumulative % released)[a].

Parameter	Time (h)							
	1	2	3	4	5	6	7	8
0.1 N HCl (pH 1.2)								
50 rpm Baskets	34 (3.4)	45 (4.3)	55 (3.7)	64 (5.4)	73 (2.9)	80 (3.3)	87 (2.8)	95 (4.1)
75 rpm Baskets	33 (3.5)	46 (4.4)	54 (5.6)	65 (3.6)	72 (2.2)	79 (5.1)	86 (3.9)	94 (3.9)
100 rpm Baskets	35 (4.9)	44 (3.2)	53 (4.6)	64 (2.3)	73 (1.9)	80 (4.2)	87 (2.4)	96 (1.8)
Phosphate buffer (7.4)								
50 rpm Baskets	33 (2.9)	45 (3.4)	54 (3.2)	64 (4.9)	73 (2.4)	78 (3.7)	85 (3.6)	94 (4.4)
75 rpm Baskets	36 (5.4)	47 (4.1)	56 (3.5)	65 (4.3)	74 (3.3)	81 (2.2)	90 (3.7)	96 (3.2)
100 rpm Baskets	35 (4.1)	45 (3.7)	54 (2.2)	64(3.4)	75 (2.8)	82 (4.3)	91 (2.3)	97 (3.4)

[a]The average result is reported followed by the standard deviation in parentheses.

validated according to FDA and ICH guidelines. The validation included specificity, linearity, accuracy and reproducibility.

Specificity of this method was determined by measuring the absorbance of the following (1) a sample solution prepared from blending of the API and excipients (2) a solution containing API at nominal concentration (3) a placebo solution prepared from a synthetic blend of the excipients. Those results demonstrate the specificity of the method.

Linearity of the method was evaluated from 20 - 125% of the nominal assay concentration for Metoprolol. Solutions of known concentration were prepared from stock solutions and measured the absorbance. Calibration plot was constructed by plotting area of the main peak versus concentration of the API and calibration lines were calculated using ordinary least square method. As shown in Table 1, these regression lines had co-efficient of determination (R^2) that were ≥ 0.9988 and y-intercepts that were not significantly differ from zero at the 95% confidence level. These results indicate that the method is linear.

Accuracy of this method was evaluated at 50, 100 and 125% of the nominal assay concentration of Metoprolol. As indicated in Table 2 the average recoveries ranged form 97.7 to 101.4%. The accuracy of the method was acceptable based on its intended use.

The dissolution test conditions of the Metoprolol sustained release capsules were selected based on a screening study with apparatus I. The capsules were tested on 900 ml of 0.1 N hydrochloric acid (pH 1.2), pH 4.5 and pH 6.8. The release of Metoprolol from the pellets was given in the Table 3. These data show that no premature drug release and 94% and more of the dose are released over 8 h.

The reproducibility of the method was evaluated by

Table 4. Reproducibility results (% cumulative release)[a,b].

Time (h)	Lot 1		Lot 2		Lot 3	
	Lab A	Lab B	Lab A	Lab B	Lab A	Lab B
1	33 (3.7)	36 (4.3)	34 (3.3)	33 (3.2)	35 (4.1)	34 (4.4)
2	44 (3.2)	47 (2.2)	45 (4.3)	44 (4.1)	45 (3.3)	45 (2.9)
3	53 (5.4)	56 (3.6)	54 (2.4)	53 (4.3)	55 (3.3)	54 (3.2)
4	64 (4.1)	65 (3.7)	64 (3.2)	63 (4.4)	64 (3.2)	66 (2.2)
5	73 (4.3)	74 (2.4)	75 (3.3)	74 (3.2)	73 (2.8)	74 (2.4)
6	79 (4.1)	80 (3.3)	82 (2.4)	80 (4.3)	81 (2.2)	81 (3.7)
7	86 (3.2)	89 (4.1)	90 (2.8)	89 (2.4)	90 (4.1)	91 (4.3)
8	95 (2.4)	96 (2.8)	97 (4.3)	96 (3.2)	97 (3.3)	97 (2.4)

[a]Laboratory A tested six capsules.
[b]The Average result is reported followed by the standard deviation in parentheses.

means of an inner-laboratory study, where two laboratories used the dissolution test to assay the capsules from three different lots. As shown in Table 4, the results from the two laboratories were considered as equivalent since the average values differed by 5% at each time point.

In conclusion, a perceptive dissolution method was developed for Metoprolol sustained release capsules 125 mg. Screening study was conducted to select the dissolution apparatus, dissolution medium and rotation speed. This method was validated successfully to current ICH and FDA guidelines, and the transferability of the method was demonstrated during an inner laboratory trial. This method will be used to optimize the formulation process and to determine the quality and performance of each lot.

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REFERENCES

Food and Drug Administration (2000). Draft Guidance for Industry on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation; Availability, Fed. Regist. 65(169): 52776 – 52777.

Food and Drug Administration (1997). Guidance for Industry on Dissolution Testing of Immediate Release Solid Oral Dosage Forms; Availability, Fed. Regist. 62(164): 52138 – 52139.

Food and Drug Administration (1995). International Conference on Harmonisation; Guideline on Validation of Analytical Procedures: Definitions and Terminology; Availability, Fed. Regist. 60(40): 11260-11262.

Food and Drug Administration (1997). International Conference on Harmonisation; Guideline on Validation of Analytical Procedures: Methodology; Availability, Fed. Regist. 62(96): 27464 – 27467.

Food and Drug Administration (1997). Guidance for Industry on Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations; Availability, Fed. Regist. 62(187): 50619.

Varma RK, Garg S (2001). Current status of drug delivery technologies and future directions. Pharm. Technol. 25: 1-14.

United States Pharmacopoeia, XXV NF XX, United State Pharmacopoeial Convention, INC., Rockville, MD, 20852, p. 1144.