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DEVELOPMENT OF DISCRIMINATORY DISSOLUTION METHOD OF EXTENDED RELEASE FORMULATION CONTAINING HIGHLY SOLUBLE DRUG

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ABSTRACTS

The aim of this work is to develop discriminating dissolution test methodology for metoprolol extended release tablets. LC Method was applied to test dissolution profile for extended release tablets containing 190 mg of metoprolol succinate. The appropriate conditions were determined after testing sink conditions in dissolution medium, rotation speed, pH of the dissolution medium, apparatus type and rotational speed. Dissolution profile was compared by model independent method. Based on studies conditions for this extended release formulation, the best dissolution conditions were achieved using a USP apparatus II, 900 ml of medium of pH 6.8 Phosphate buffer at a rotation speed of 150 rpm. Since there is monograph for this drug in tablets which is based on multiparticulate drug delivery system, the dissolution method presented here can be used as a quality control test for metoprolol extended release tablet matrix formulation with special emphasis to understand in a batch to batch evaluation.

KEYWORDS: Metoprolol, Discrimination, dissolution, extended release.

INTRODUCTION

Dissolution testing has emerged in the pharmaceutical field as a very important tool to characterize drug product performance. The significance of this test is based on the fact that the rate and extent of drug absorption depend on its dissolution from the dosage form. Therefore, dissolution test is used not only for quality control of the final dosage form, but also to assess several stages of formulation. Moreover, when an in vitro/in vivo correlation is demonstrated, dissolution can be used as a surrogate test to predict the in vivo bioavailability of pharmaceutical formulations.

The interest in the in vitro dissolution of highly soluble drugs in extended release formulation has increased over the years due to the fact that this class of drugs is more likely to present a meaningful correlation between dissolution and absorption. Difficulties are usually encountered in selecting a dissolution medium of acceptable volume and composition that also presents a good discriminating power.

Metoprolol is a cardioselective beta-blocker and it is used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, and heart failure. The half-life of the metoprolol is stated to be 3-4 h. Metoprolol tartrate, with its incomplete oral bioavailability (due to extensive first-pass metabolism), short half-life, and multiple daily dosing, is appropriate for a formulation in a once-a-day extended-release dosage form. Therefore, metoprolol tartrate is the ideal candidate for sustained release system because it is water-soluble and has a short half-life.

Metoprolol being classified as class I, according to the Biopharmaceutical Classification System where its dissolution is the not rate-limiting step for absorption. But when formulated as extended release formulation its becomes rate-limiting steps for absorption. A dissolution method for extended release metoprolol tablets was reported in US Pharmacopeia for generic drug formulation which is based on mutliparticulate drug delivery system. However, we developed matrix extended release formulation for metoprolol as previously published.

In this context, the purpose of the present study is to develop discriminating dissolution test for metoprolol extended release tablets, based on extended release characteristics of formulation. Additionally, the method was tested in by varying rotational speed (RPM), pH Conditions and dissolution apparatus type, similarity of dissolution was determined using model independent methods.

MATERIALS AND METHODS

Chemicals

Metoprolol Succinate powder was purchased from FTF Pharma. The excipients used to simulate those found in the dosage forms (Carbopol971P® NF, Eudragit L100-55, Eudragit S100, PolyoxWSR301, Sodium Hydrogen Carbonate, Magnesium stearate and cellulose

microcrystalline) were all of pharmaceutical grade and acquired from different distributors. LC-grade Solvents was obtained from Merck India. Purified water (Milli-Q Plus, Millipore®, MA, USA) was used throughout the analysis. All other reagents and solvents used for the preparation of buffer solutions were of analytical grade. The 0.1N and Sodium acetate buffer (pH 4.5) and monobasic potassium phosphate USP buffers (pH 6.8) were prepared as described in USP-NF.

Instrumentation

Dissolution test conditions and discrimination of media

The development of the dissolution test was performed using a VANKEL® VK 8000 dissolution auto-sampling station consisting of a VK type bidirectional peristaltic pump, VK 750D digitally controlled heater/circulator, VK 7010multi-bath dissolution testing station (n = 8) with automated sampling manifold. Discrimination of Dissolution was performed using 900 ml of dissolution medium pre-heated at 37 ± 0.5◦C. Influence of rotation speed, dissolution medium pH and different apparatus (USP basket and paddle) were evaluated. Sample aliquots were withdrawn at 1, 4, 8, and 20 hours replaced with an equal volume of fresh medium to maintain a constant total volume. An auto sampler was used to withdraw aliquots through a 0.45 m filter. All the dissolution samples were analyzed by HPLC.

HPLC analysis

The HPLC system consisted of a Shimadzu LC model (Kyoto, Japan) composed of a LC-10AD pump, a SPD-M10ADVP photodiode array (PDA) detector, a SLA-10ADVP system controller, a DGU-14A degasser, a column thermostat oven CTO-10AS and an autoinjector SIL-10AD. Data were acquired and processed using CLASS-VP software (version 6.1).

Determination of Sink Conditions

Metoprolol is Succinate salts with pH-independent solubility. In both acid and alkaline solutions, its solubility is high. Because of high solubility sink conditions is established in 0.1N HCl, pH 4.5 Buffer and pH 6.8 Buffered solutions. Vessels (n=3) containing 250 ml of medium were preheated in a thermostatically controlled water bath at 37±0.5°C, before adding a 190mg of metoprolol. The solution was found clear based on physical observation because of high solubility of drug.

Comparison of dissolution profiles by a model-independent method

This study utilized a model-independent approach in which the dissolution profiles of two drug products are compared using the fit factor. This fit factor directly compares the difference between percent drug dissolved per unit time for a test and a reference product. The fit factor, f2, is defined by the following:

$$f_2 = 50 \times \log \left[(1 + 1/n \sum_{t=1}^{n} (R_t - T_t)^2)^{-0.5} \times 100 \right]$$

Where, n is the number of dissolution sampling times, and Rt and Tt are the individual or mean percent dissolved at each time point for the reference and test dissolution profiles, respectively. f2 values greater than 50 (50–100) would indicate sameness or equivalence of the two curves. The drug release profile for metoprolol extended release tablets at different dissolution conditions were using f 2 values.

RESULTS AND DISCUSSION

Determination of discrimination Conditions of dissolution media

For extended release formulation containing high soluble drug, medium selection for dissolution tests is an important step in discriminations dissolution method development. Discrimination power of the dissolution media studied by changing pH of dissolution media, apparatus type, RPM of the apparatus. Among the media tested, sink condition was observed for all dissolution medium studies because of high pH independent solubility of drug.

Effect of pH of the dissolution media

Table 1: Dissolution profile of metoprolol Extended Release tablets at different pH conditions.

Apparatus II, 150 RPM, Volume 900ml (n=6)			
Time in Hours	**0.1 N HCl,**	**4.5 pH Acetate Buffer,**	**6.8 pH Phosphate Buffer**
1	18	11	7
4	45	27	24
8	69	44	57
20	98	91	89

The above dissolution profiles show that the dissolution of Metoprolol succinate extended tablets is higher in 0.1 N HCl than in buffer pH 4.5 and in buffer pH 6.8. Therefore, the choice of dissolution media is 6.8 pH Phosphate buffer. In addition, the dissolution medium buffer pH 6.8 has been chosen because this is the most appropriate one for simulating the in-vivo conditions for extended release formulation containing high soluble drug.

Effect of the paddle vs. Basket on the dissolution profile

Dissolution apparatus paddle and basket have different hydrodynamics which affect dissolution rate of high

soluble drug in extended release formulation. Discrimination power of dissolution medium was studied by carrying out dissolution in paddle and basket apparatus. Dissolution profile shows that there is no remarkable difference in the dissolution profile of the product whether paddle or basket is used.

Table 2: Dissolution profile of metoprolol Extended Release tablets for paddle vs. Basket apparatus.

6.8 pH Phosphate Buffer, 150 RPM, Volume 900ml (n=6)		
Time in Hours	**Apparatus I (Paddle)**	**Apparatus II (Basket)**
1	7	7
4	24	23
8	57	44
20	89	89

Effect of the speed of the paddle on the dissolution profile of the tablets

Hydrodynamics of dissolution medium are based on rotational speed which affect dissolution rate of high soluble drug in extended release formulation. Change in dissolution profile by changing hydrodynamics of dissolution medium was studied by varying rotational speed of dissolution apparatus II. The metoprolol extended tablets show slow release profile at lower speed and show higher release at higher speed. The high dissolution rate at higher speed might be because change in hydrodynamics around the tablet surface.

Table 3: Dissolution profile of metoprolol Extended Release tablets (effect of paddle speed).

Intervals	RPM	% Drug Dissolved
1 Hours	150	9%
	100	8%
	50	7%
4 Hours	150	27%
	100	22%
	50	18%
8 Hours	150	60%
	100	37%
	50	30%
20 Hours	150	103%
	100	82%
	50	56%

Based on the Studied parameters for development of discriminating dissolution media following dissolution conditions were finalized as a optimum dissolution condition as a quality control dissolution media.

Table 4: Optimum Conditions for dissolution study of metoprolol Extended Release tablets.

Sr. No	Parameters	Conditions
1	Dissolution Media	6.8 pH Phosphate buffer
2	Time	1, 4, 8 and 20 hours
3	Apparatus	II (paddle)
4	Volume	900ml
5	RPM	150

Discriminatory power of chosen dissolution test method

For demonstrating the discriminatory power of chosen dissolution test method a non acceptable development batch of Metoprolol extended release tablets was determined by optimum dissolution conditions (main change in formulation: change in polymer concentration). With these changes in composition discrimination power of media proved.

Table 4: Discriminatory power of dissolution medium by changing the polymer concentrations.

Time in Hours	Optimum Composition	Change in Composition (Polymer Concentration)
1	8	12
4	25	36
8	57	75
20	89	100

CONCLUSION

Dissolution testing plays a very important role as an in vitro test for evaluating drug products. In the present study, an attempt has been made to develop discrimination dissolution medium for metoprolol extended release tablets. Which provide the discriminatory results when different pH condition, RPM and apparatus were varied.

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