

Research Article

Development of an *In Vitro* Dissolution Method for Novel Formulation: A Systematic and Scientific Approach

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India**Received:** October 21, 2014; **Accepted:** October 30,
2014; **Published:** November 01, 2014**Abstract**

The development of a discriminatory dissolution method for novel drug formulations has been a challenge to the pharmaceutical industry. Most of the times official dissolution method is not available for newly developed dosage forms. Parameters such as saturation solubility in different pH medium, dissolution behavior of formulations, influence of sink conditions, stability, and discriminatory effect of dissolution testing need to be studied for the selection of a proper dissolution medium for novel formulations. The present paper suggests a simple, scientific and systematic approach for development of an *in vitro* dissolution method for such novel formulations. In-house developed Metoprolol tartrate matrix tablet and Captopril sustained release beads were used as a model formulation. The developed methods were successfully applied for *in vitro* dissolution study of in-house developed novel formulations.

Keywords: Novel drug; Dissolution method; Captopril; Metoprolol tartrate; Quality Control**Introduction**

Dissolution study is very important test for various pharmaceutical dosage forms especially for those administered orally. The incorporation of adjuvant (e.g., diluents, lubricants, and surfactants) into the formulation of a solid oral dosage form can cause significant effects on the dissolution rate of drugs, especially those that are hydrophobic and poorly soluble [1]. Dissolution is an official test routinely used in Quality Control (QC) and Research and Development (R and D) Laboratories for the evaluation of pharmaceutical products. The purpose of *in-vitro* dissolution studies in QC is to check batch to batch consistency and detection of manufacturing deviation while in R and D the focus is to provide some predictive estimate of the drug release in respect to the *in vivo* performance of a drug product [2]. In the case of Class 2 drugs in the Biopharmaceutics Classification System (BCS), dissolution may be the rate-limiting step for drug absorption, so suitable dissolution tests can be used to predict differences in bioavailability among different formulations [3]. The choice of dosage form is often of critical importance in establishing a successful product for oral administration of this class of drugs [4].

As a regulatory test, dissolution is used to approve minor changes in formulation, changes in the site of manufacturing and also to assess the scale-up of the bio-batch to the production batch.

The present paper suggests a scientific and systematic approach for development of an *in vitro* dissolution method for such novel formulations. In-house developed Metoprolol tartrate matrix tablet and Captopril sustained release beads were used as a model formulation.

Materials and Methods**Materials**

Metoprolol tartrate and Captopril were obtained as a gift sample

from Rubicon Research, Mumbai and Kwaliti Pharmaceuticals, Amritsar, India, respectively. Metolar-50 (Cipla) tablets were purchased from local market. All the chemicals and reagents used were of analytical grade.

Instrumentation

Dissolution test was performed in an Electro lab dissolution test system (TDT-08L), in accordance to USP Pharmacopoeia general method. A double-beam UV-Vis spectrophotometer (Shimadzu 1800, Japan) with 1.0 cm quartz cells was used for all absorbance measurements.

Formulation used for study

Two different formulations were used to conduct the study. The formulations were prepared in laboratory. The details of the formulation are as mentioned below:

a) Metoprolol tartrate matrix tablet: Labeled to contain 50 mg of the Metoprolol tartrate and prepared by wet granulation method using natural polymers. Three batches (Coded as F1, F2 and F3) were prepared with low, medium and high concentration of polymer.

b) Captopril sustained release beads: Labeled to contain 50 mg of the Captopril. The beads were prepared by ionic gelation technique using sodium alginate and filled in hard gelatin capsule. Three batches (Coded as F1, F2 and F3) were prepared with low, medium and high concentration of polymer.

Determination of analytical wavelength*a) Metoprolol tartrate*

A standard stock solution of drug was prepared by dissolving 100 mg of Metoprolol tartrate in pH6.8 phosphate buffer to obtain a solution of 1000 μ g/mL. From standard stock solution, 1 mL solution was pipette in 100 mL volumetric flask and the volume was made up to the mark with the same medium. The resulting solution (10 μ g/

mL) was scanned between 200 to 400 nm to determine the λ max against pH6.8 phosphate buffer as blank in UV spectrophotometer (Shimadzu 1800).

b) Captopril

A standard stock solution of drug was prepared by dissolving 100 mg of Captopril in 0.01N HCl to obtain a solution of 1000 μ g/mL. From standard stock solution, 1 mL solution was pipette in 100 mL volumetric flask and the volume was made up to the mark with the same medium. The resulting solution (10 μ g/mL) was scanned between 200 to 400 nm to determine the λ max against 0.01 N HCl as blank in UV spectrophotometer (Shimadzu 1800).

Preparation of standard calibration curve

a) Metoprolol tartrate

Appropriate aliquots were withdrawn from the standard stock solution prepared above into different volumetric flasks and diluted with pH6.8 phosphate buffer to obtain solution of 1, 5, 10, 15, 20, 25 and 30 μ g/mL. The absorbances of these solutions were taken at 275 nm using pH 6.8 phosphate buffers as blank.

b) Captopril

Appropriate aliquots were withdrawn from the standard stock solution prepared above into different volumetric flasks and diluted with 0.01 N HCl to obtain solution of 5, 10, 15, 20,25,50,75 and 100 μ g/mL. The absorbance's of these solutions were taken at 205 nm using 0.01NHCl as blank.

Dissolution method development

a) For Metoprolol Tartrate Sustained Release Tablets

In vitro drug release testing of Metoprolol tartrate marketed immediate release tablets (Metolar-50,Cipla) was performed in distilled water and different buffers of pH 1.2(0.1N HCl), 4.5, 6.8, 7.4 as dissolution mediums (500mL) using USP apparatus 2 (paddle) at 50 rpm for 60minutes. The selected dissolution parameters for the study were based on official dissolution method of Metoprolol Extended release tablets USP and the method reported in the literature [5].

b) For Captopril Sustained Release Beads

In vitro drug release testing of Captopril capsules (50mg,compounded in laboratory) was performed in distilled water and different buffers of pH 2.1 (0.01N HCl), pH 4.5, 6.8, 7.4 as dissolution mediums (900mL) using USP apparatus I (Basket) at 50 rpm for 60minutes. The selected dissolution parameters for the study were based on official dissolution media reported in USP for Captopril Tablets and the method reported in the literature [6].

The dissolution study was performed on in-house developed formulation (F1-F3) using above optimized conditions to test the discriminatory power of the method.

Results and Discussions

Determination of analytical wavelength

a) Metoprolol tartrate

The UV- spectrum of Metoprolol tartrate in 0.01 N HCl is represented in Figure 1. The λ maximal's were found to be at about

222 nm, 275nm and 281nm which were similar to the values reported in literature [7, 8].

c) Captopril

The UV- spectrum of Captopril in 0.01 N HCl is represented in Figure 2. The λ max was found to be about 205 nm which was similar to the value reported in literature [9].

Standard calibration curve

a) Standard curve of Metoprolol tartrate in pH 6.8 phosphate buffer

The concentration range of 1-30 μ g/ml of Metoprolol tartrate was selected for development of standard curve in pH 6.8 phosphate buffer. The standard curve is constructed by plotting absorbance against concentration (Figure 3). The value of R^2 was found to be 0.9991 indicating linear relationship of drug concentration and absorbance in the selected range. The regression equation obtained for the straight line was $y = 0.03x + 0.0137$; where 'y' is the absorbance and 'x' is concentration.

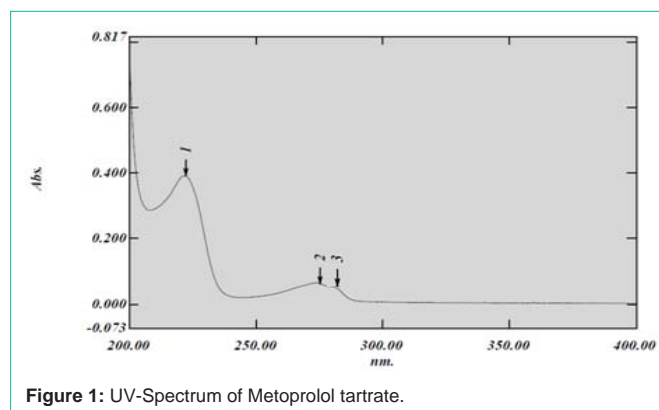


Figure 1: UV-Spectrum of Metoprolol tartrate.

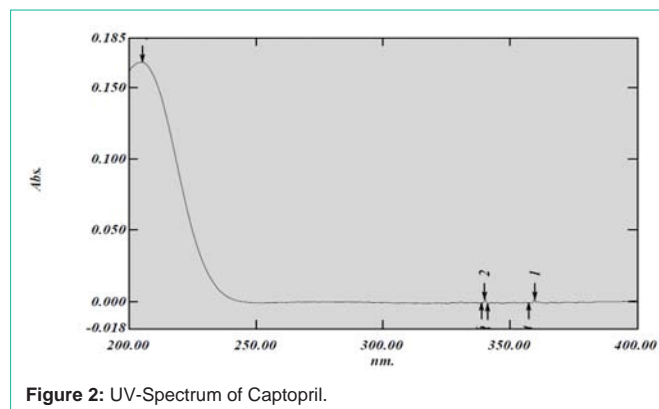


Figure 2: UV-Spectrum of Captopril.

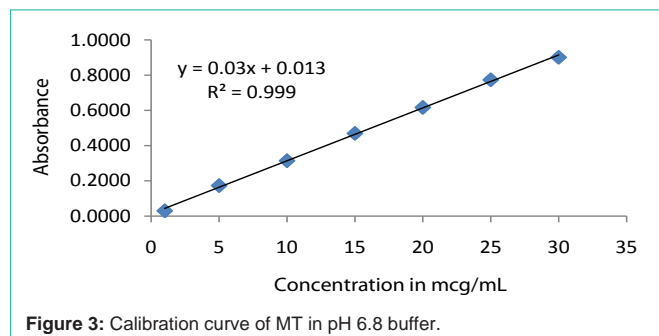


Figure 3: Calibration curve of MT in pH 6.8 buffer.

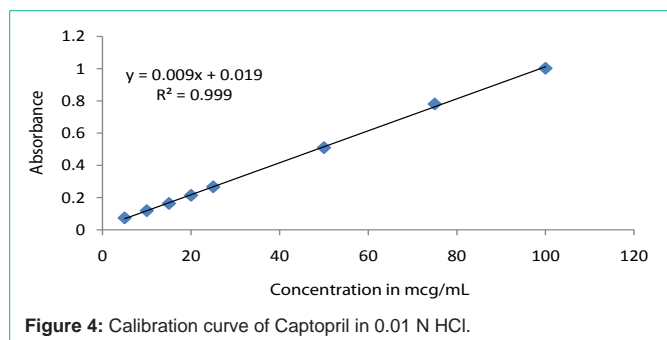


Figure 4: Calibration curve of Captopril in 0.01 N HCl.

b) Standard curve of Captopril in 0.01 N HCl

The concentration range of 5-100 µg/ml of Captopril was selected for development of standard curve in 0.01 N HCl. The standard curve is constructed by plotting absorbance against concentration (Figure 4). The value of R^2 was found to be 0.9994 indicating linear relationship of drug concentration and absorbance in the selected range. The regression equation obtained for the straight line was $y = 0.0099x + 0.0191$; where 'y' is the absorbance and 'x' is concentration.

In-Vitro dissolution method development

a) Dissolution method development for Metoprolol tartrate sustained release tablets

The results of the dissolution studies of the 50 mg Metoprolol tartrate marketed immediate release tablets with water and different buffers are given in Tables 1. The results indicated that less than 80 % of the drug released in 60minutes in the pH 1.2 and 4.5 buffer solution, whereas in buffer of pH 6.8 and water the dissolution is more than 80%. A less significant increase was observed between pH 6.8 and water. The dissolution is more than 90 % in pH 6.8 buffer and water. The dissolution is, however, optimal in pH 6.8 buffer at rpm 50 and this pH was, therefore, selected for further studies.

b) Dissolution method development for Captopril sustained release beads

The results of the dissolution studies of the 50 mg Captopril Compounded capsule with water and different buffers are given in Tables 2. The results indicated that less than 90 % of the drug released in 60 minutes in the water, pH 4.5, 6.8 and 7.4 buffer solutions. The dissolution is, however, maximum in 0.01N HCl at rpm 50 and this pH was, therefore, selected for further studies.

The discriminating power of the dissolution method is the method's ability to detect changes in the drug product [10-12]. The % cumulative drug release of formulation F1 to F3 of Metoprolol

Table 1: Dissolution results for conventional Metoprolol tartrate tablet (Metolar-50, Cipla, India) - Single time point.

S. No.	Medium	Parameters	Time (min)	% Dissolved*
1	Water	50rpm, Paddle	60	95.66±0.42
2	pH 1.2 buffer	50rpm, Paddle	60	73.89±0.61
3	pH 4.5 buffer	50rpm, Paddle	60	78.72±0.29
4	pH 6.8 buffer	50rpm, Paddle	60	97.94±0.52
5	pH 7.4 buffer	50rpm, Paddle	60	93.14±0.43

*The results are Average of six observations ± Standard deviation.

Table 2: Dissolution results for Captopril capsules (Compounded capsules) - Single time point.

S. No.	Medium	Parameters	Time (min)	% Dissolved*
1	Water	50rpm, Basket	60	88.65±0.68
2	pH 2.1 buffer (0.01 N HCl)	50rpm, Basket	60	97.98±0.46
3	pH 4.5 buffer	50rpm, Basket	60	77.56±0.25
4	pH 6.8 buffer	50rpm, Basket	60	69.77±0.61
5	pH 7.4 buffer	50rpm, Basket	60	67.31±0.33

*The results are Average of six observations ± Standard deviation.

tartrate sustained release tablets and Captopril beads are depicted in Figure 5 and Figure 6 respectively. The results are expressed as mean of six observations. Standard error calculated for six observations are represented in Figure 5 and Figure 6 as error bars. Formulation F1 contains low amount of retardant (Polymer), F2 contains medium amount of retardant and F3 contains high amount of retardant. The drug release was decreased from formulation F1 to F3 with increase in concentration of retardant. This indicated that the developed method is discriminatory dissolution method which can able to detect changes in the drug product.

Conclusion

This present study explains how to proceed for dissolution study of novel formulations if the dissolution test is not available in official compendium. The procedure consists of several steps like; Use of standard dissolution testing equipment such as the paddle (For tablets) / basket method (For beads) as per general USP guidelines, preliminary method development for the marketed product or compounded immediate release tablets by single point dissolution

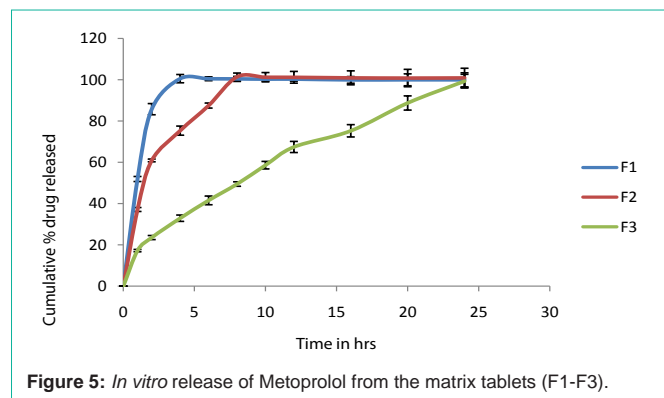


Figure 5: In vitro release of Metoprolol from the matrix tablets (F1-F3).

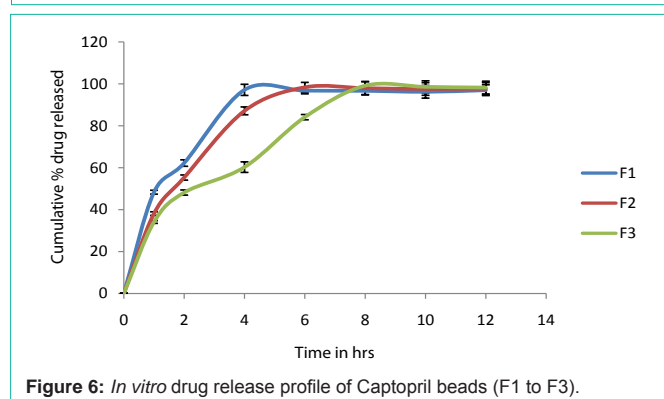


Figure 6: In vitro drug release profile of Captopril beads (F1 to F3).

for 60min., use of the distilled water and different buffers of pH 1.2, 4.5, 6.8, 7.4 as dissolution mediums, collection of samples and their analysis by suitable analytical method to obtain product dissolution profiles, analysis of data to determine the influence of the media on the dissolution (and solubility) of the drug and to ascertain the medium in which greater than 85 % dissolution in a reasonable amount of time (60 minutes) is possible, and dissolution of in house developed tablets using above optimized dissolution conditions. This is simplest scientific and systematic approach for development of an *in vitro* dissolution method for novel formulation.

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