In vitro Dissolution Studies of Different Brands of Sustained Release Metformin Hydrochloride Matrix Solid Dosage Forms Available in the Pharmaceutical Market of Bangladesh

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ABSTRACT

This study was designed to investigate the in vitro dissolution profile of ten brands of Metformin hydrochloride sustained release matrix tablets that are commercially available in the pharmaceutical market in Bangladesh in order to evaluate the quality standard of the available marketed product. The study was carried out on the ten brands of Metformin hydrochloride matrix tablets using dissolution test-t method apparatus –2 (paddle) at 100 rpm in 1000 ml simulated intestinal medium (pH 6.8 ± 0.1) for 10 hours time period according to the guideline of United States Pharmacopeia (USP). In this study, all the brands except two brands (Code: MH-5 and MH-8) complied with the USP in vitro dissolution specification of 85% drug release at 10th hour in simulated intestinal medium. Drug release of 81.6 % and 79.7 % were showed by the brand code of MH-5 and MH-6 respectively within the specified time period which did not meet the terms of the USP guideline. To reveal the release kinetics of sustained release tablets of Metformin hydrochloride, release profiles were analyzed for zero order, first order and Higuchi model and found that first order and Higuchi model showed high linearity with correlation coefficient (r) value of 0.98 or more. In conclusion, our results indicated that all the brands of Metformin hydrochloride sustained release matrix tablets included in this study apart from MH-5, MH-8 showed high dissolution profile and hence good bioavailability.

Key words: Metformin hydrochloride, Sustained release matrix tablet, Release kinetics, In vitro dissolution study.

INTRODUCTION

Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide class oral anti-hyperglycemic (anti-diabetic) agent. It is used as monotherapy as an adjunct to diet and exercise for the management of non-insulin dependent diabetes mellitus (NIDDM) type-2 diabetes, in patients whose hyperglycemia cannot be controlled by diet alone.[1] A traditional oral multiple release formulation releases the drug with undesirable peaks and troughs. These drawbacks can be overcome by designing a suitable sustained release Metformin hydrochloride preparation. Recently several studies have been carried out to investigate the pharmacokinetic and pharmacodynamic advantages of oral sustained release products of Metformin hydrochloride.[2-5] The primary benefit of a sustained release dosage form, compared to a conventional dosage form is the uniform drug plasma concentration, and therefore uniform therapeutic effect.

The process of in vitro dissolution played a vital role in liberating a drug from the tablet matrix and marking whether it is available for subsequent gastrointestinal absorption. The in vitro dissolution of the tablet from the drug matrix depends on many factors, which include not only the physicochemical properties of drug, but also the nature of formulation and the process of manufacturing.[6] Hence in vitro dissolution analysis of pharmaceutical dosage form has emerged as a very important parameter that ensured product quality as well as for differentiating among formulations of the same therapeutic agent.[7] For sustained release tablets the role of in vitro dissolution becomes still more crucial as an additional coating step involve in manufacturing process.[8]

In vitro dissolution study is an important tool in the evaluation of the best formulation and also in understanding the possible risks related to specific gastrointestinal environment, dose dumping, and food effects on bioavailability and interaction with other drugs.[9] Today dissolution studies are the most frequently used tools in the development, characterization and utilization processes of controlled release formulations.[9,10]

In Bangladesh, there are number of pharmaceutical companies that are manufacturing and marketing sustained release Metformin hydrochloride matrix tablet. This paper deals with the comparative in vitro dissolution or in vitro bioavailability characteristic of sustained release matrix tablets of most commonly available brands of Metformin hydrochloride in Bangladesh in order to evaluate the quality standard of the products.

MATERIALS AND METHODS

Chemicals

References standard of Metformin hydrochloride powder BP (Wanbury, India), reagent, sodium hydroxide (Merk, Germany) and monobasic potassium phosphate (Merk, Germany) were collected from Beximco Pharmaceuticals Limited, Bangladesh.

Equipments

Shimadzu cu-1700 UV-visible Spectrophotometer (Kyoto, Japan), Metler Toledo MP-200 pH meter (UK), Erweka DT-700 Dissolution tester (Germany), Sartorius CPA 225D electronic balance (Germany) were used in this experiment.

Drug samples used in this study

Ten (10) brands of metformin hydrochloride sustained release matrix tablet were purchased from various medicine shops. They were randomly marked as MH-1, MH-2, MH-3, MH-4, MH-5, MH-6, MH-7, MH-8, MH-9, and MH-10. The samples were properly checked for their manufacturing license number, batch number, and date of manufacture and expiry dates before purchasing. The labeled active ingredient was 500 mg of metformin hydrochloride and all were packaged in strip or in blister packing. The samples were collected in such a way that the production date not more than four months ago from the time of purchase. The strip or blister packs stored at 25±2°C for four weeks before the dissolution study, in order to evaluate any organoleptic changes.

Dissolution study

The dissolution tests were carried out using the type-2 apparatus (paddle), at 100 rpm (rotation per minute) in 1000 ml in simulated intestinal medium for 10 hours at temperature 37 ± 0.5°C ( test method -1), according to US pharmacopeia (USP) guidelines[11]. For in vitro dissolution study simulated intestinal medium (pH 6.8 ± 0.1) was required.

Preparation of simulated intestinal medium (buffer pH 6.8 ± 0.1) 6.8 g monobasic potassium phosphate was dissolved in 1000 ml water and pH was adjusted by adding 0.2 N sodium hydroxide Solution. For system, equilibration paddles were rotated for 15 minutes. One tablet chosen randomly from each
Table 1: multiple coefficients (r²) of different brands (marked as MH-1 to MH-10) sustained release metformin hydrochloride matrix tablets

<table>
<thead>
<tr>
<th>Code</th>
<th>Multiple coefficient of determination (r²)</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
</tr>
</thead>
<tbody>
<tr>
<td>MH-1</td>
<td>0.8624</td>
<td>0.9904</td>
<td>0.9914</td>
<td></td>
</tr>
<tr>
<td>MH-2</td>
<td>0.8516</td>
<td>0.9682</td>
<td>0.9835</td>
<td></td>
</tr>
<tr>
<td>MH-3</td>
<td>0.8489</td>
<td>0.9686</td>
<td>0.9849</td>
<td></td>
</tr>
<tr>
<td>MH-4</td>
<td>0.8696</td>
<td>0.9905</td>
<td>0.9933</td>
<td></td>
</tr>
<tr>
<td>MH-5</td>
<td>0.8771</td>
<td>0.9876</td>
<td>0.9904</td>
<td></td>
</tr>
<tr>
<td>MH-6</td>
<td>0.816</td>
<td>0.9837</td>
<td>0.9755</td>
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<tr>
<td>MH-7</td>
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<td>0.9836</td>
<td>0.9911</td>
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</tr>
<tr>
<td>MH-8</td>
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<td>0.9821</td>
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</tr>
<tr>
<td>MH-9</td>
<td>0.8047</td>
<td>0.9788</td>
<td>0.9708</td>
<td></td>
</tr>
<tr>
<td>MH-10</td>
<td>0.8093</td>
<td>0.9838</td>
<td>0.9728</td>
<td></td>
</tr>
</tbody>
</table>

MH = Metformin hydrochloride

Analysis of released data
To analyze the in vitro release data, various kinetic models were used to describe the release kinetics. The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), and Higuchi (cumulative percentage of drug released versus square root of time) equation model. The zero order equation described the system where the drug release rate was independent of its concentration. The first order equation described the release pattern where release rate was concentration dependent. Higuchi release kinetics describes the release of drugs from insoluble matrix as a square root of time dependent process.

RESULTS AND DISCUSSION

Most of the commercially available brands of the Metformin hydrochloride sustained release matrix tablet in Bangladesh met the official USP specification. All of the ten brands of Metformin hydrochloride sustained release matrix tablets were investigated to find out whether they complied with the USP in vitro dissolution specification of 85% drug release at 10th hour. The two brands coded MH-5 and MH-8 were failed to fulfill the USP in vitro dissolution specification of 85% drug release at 10th hour. The amount of drug present in each tablet was determined by spectroscopic method.

The dissolution data (from the values of 1st, 3rd and 10th hour) according to USP specification of all batches were best fitted to first order and Higuchi models. The model that best fitted the release data was evaluated by multiple coefficients (r²) mentioned in Table 4. For all ten brands, first order and Higuchi release kinetics were predominant than the zero order release kinetics. From these release kinetics, it might be revealed that the drug release of those brand followed concentration dependent and diffusion controlled release method from the matrix of tablet.

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REFERENCES:

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