Screening the Dissolution Performance of the Modified Release Tablets Containing Insoluble Active Substance in Different Dissolution Media

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Objective: The aim of the present work was to examine a test and a marketed product containing indapamide in different dissolution media: hydrochloric acid, acetate buffer solution, phosphate buffer solution, fasted state simulated intestinal fluid and fed state simulated intestinal fluid.
Methods: Dissolution testing was performed in compliance with USP, using USP apparatus 2. In order to quantify the dissolution of indapamide from modified release tablets, a high liquid chromatographic method was developed.
Results: The dissolution profiles registered in different dissolution media were represented graphically and we calculated the difference factor f1 and the similarity factor f2 between the test and the marketed product's dissolution profiles obtained in different dissolution media. It can be observed that the dissolution behavior of the test and the marketed product is very similar in hydrochloric acid, phosphate buffer solution, in fasted state simulated intestinal fluid and fed state simulated intestinal fluid, but it is not similar in acetate buffer solution.
Conclusions: In case of poorly soluble active substances, such us indapamide, it is very difficult to develop a dissolution method in order to predict the in vivo behavior. It is necessary to investigate the dissolution profiles not only in the routine dissolution medium, and in three different pH solutions, but in biorelevant media, too.

Keywords: indapamide, dissolution profile, FaSSIF media, FeSSIF media, difference factor f1, similarity fit factor f2

Received: 3 November 2012

Introduction

In vitro dissolution testing is a useful tool in the drug development process. Formulation specialists use dissolution tests to assess the dissolution profiles of the active substance itself and thereby select appropriate excipients for the formulation. The problem is that if these tests are not performed under appropriate conditions, the prediction of the in vivo release profiles of the developed product may be erroneous. It is more difficult to develop a proper in vitro dissolution test if the examined active substance is poorly soluble or insoluble. This could be achieved if the conditions in the gastrointestinal tract are reconstructed as closely as possible in in vitro test systems.

The most important factors in the dissolution of the active substance from a dosage form in the gastrointestinal tract are: the composition, the volume and the hydrodynamics of the contents in the lumen. The luminal composition in the GI tract is: hydrochloric acid, bicarbonate, enzymes, surfactants, electrolytes, mucus, water, etc.

Values of gastric pH in the fasted state can fluctuate on a minute-to-minute basis in the range of 1 to 7, but in healthy Caucasians, gastric pH lies below 3 in fasted conditions. Intestinal pH values are higher than gastric pH values because of the neutralization of incoming acid with bicarbonate ion secreted by the pancreas. In the small intestine there is a pH gradient with values gradually rising from the duodenum to the ileum (4.4–7.4). The volume of fluids available in the gastrointestinal tract for drug dissolution depend on the volume of coadministered fluids, secretions and water flow. The hydrodynamics of the gastrointestinal tract or how well the luminal contents are mixed has an important role in in vivo dissolution [1,2,3,4].

Based on the physiological parameters of the gastrointestinal tract we have tested the dissolution of a marketed product and a test product containing indapamide in the following dissolution media: hydrochloric acid with pH = 1, acetate buffer solution with pH = 4.5, phosphate buffer solution with pH = 6.8, fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) [1,2,3,4,5]. From the technologists point of view it is very important to be absolutely sure that the in vivo behaviour of the developed product will be the expected one, so it is important to examine this behavior in different pH solutions and biorelevant medias, too.

Indapamide is the first representative of its antihypertensive/diuretics class, the indolines. It has an antihypertensive action causing a drop in systolic, diastolic and mean blood pressure, and an extrarenal antihypertensive action with a decrease in vascular hyperreactivity and a reduction in total peripheral and arteriolar resistance. There is also a direct renal diuretic action [6,7]. Indapamide is practically insoluble in water [8], and it is rapidly and almost completely absorbed after oral administration [7]. Based on these properties, indapamide belongs to class

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II in the Biopharmaceutics Classification System (BCS). The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability [9]. For Class II drugs the rate of dissolution is almost certain to be the main limitation of its oral absorption.

Methods

Indapamide (Bioindustria, Italy) was a high purity standard. The test product was developed in the laboratories of the Development Department of Gedeon Richter Romania S.A. The other chemical reagents were also analytical grade purity: potassium dihydrogen phosphate (Merck, Germany), disodium hydrogen phosphate dihydrate (Merck, Germany), sodium hydroxide (Merck, Germany), 1 octanesulfonic acid sodium salt monohydrate (Merck, Germany), glacial acetic acid (VWR BDH Prolabo), acetonitrile (VWR BDH Prolabo), sodium acetate (Merck, Germany), sodium taurocholate (Promochem, Germany), lecithin (Alfa Aesar, USA), sodium dihydrogen phosphate (Merck, Germany), sodium chloride (Merck, Germany), hydrochloric acid (Merck, Germany), sodium acetate (Merck, Germany).

In vitro dissolution study

Dissolution testing was performed in compliance with USP [10]. The dissolution test was performed with Erweka DT 800 LH multi-bath (n = 6) dissolution system with auto sampler (Heusanstamm, Germany), in brown dissolution test vessels to avoid indapamide photo degradation [8]. The dissolution test conditions were: apparatus 2, 900 ml dissolution media maintained at 37±0.5°C at a paddle speed of 75 rotations per minute.

Dissolution media:

a. Hydrochloric acid 0,1 N, pH = 1.2
   8.3 ml hydrochloric acid 37% was mixed with water, then completed to a volume of 1000 ml.
b. Acetate buffer solution, pH = 4.5
   2.99 g of sodium acetate was dissolved in water, then 14 ml of 2M acetic acid was added and it was diluted to 1000 ml with water [7]
c. Phosphate buffer solution pH = 6.8
   Potassium dihydrogen phosphate 0.2 mol/l and disodium hydrogen phosphate dihydrate 0.2 mol/l was mixed in a 510:490 volume ratio, then the pH was adjusted to 6.8±0.5% with sodium hydroxide 50% solution [7]
d. FaSSIF
   Preparation of blank FaSSIF: 1.74 g of sodium hydroxide, 19.77g of sodium dihydrogen phosphate and 30.93 g of sodium chloride was dissolved in 5L of purified water. The pH was adjusted to exactly 6.5 using sodium hydroxide solution 1 N.
   Preparation of FaSSIF solution: 3.3 g of sodium taurocholate was dissolved in 500 ml blank FaSSIF. 11.8 ml of a solution containing 100 mg/ml lecithin in methylene chloride was added to forming an emulsion. The methylene chloride was eliminated under vacuum, and a vacuum was drawn for thirteen minutes. The result was a clear, micellar solution, adjusted to 2L with blank FaSSIF [11].
e. FeSSIF
   Preparation of blank FeSSIF: 20.2 g of sodium hydroxide, 43.25 g of glacial acetic acid and 59.37 g of sodium chloride was dissolved in 5L of purified water. The pH was adjusted to exactly 5.0 using sodium hydroxide solution 1 N.
   Preparation of FeSSIF: 16.5 g of sodium taurocholate was dissolved in 500 ml of blank FeSSIF. 59.08 ml of a solution containing 100 mg/ml lecithin in methylene chloride was added to forming an emulsion. The methylene chloride was eliminated under vacuum, and a vacuum was drawn for thirteen minutes. The result was a clear, micellar solution, adjusted to 2L with blank FeSSIF [11].

In all cases a sample volume of 1.5 ml was taken out with auto sampler through 10 µm Poroplast and 0.45 µm PTFE filter in brown HPLC vials. The samples were collected at time points of 2, 4, 8, 16 hours.

HPLC analysis

Analysis of dissolution samples was performed on Elite LaChrom Merck Hitachi HPLC system equipped with a L2130 quaternary pump, L2200 auto sampler, L2455 DAD detector. Analytical separation was performed on Hypersil ODS2, 150 × 4.6 mm, 5 µm particles size. The mobile phase was a 1.08 g 1 octanesulfonic acid sodium salt monohydrate dissolved in 700 ml water, 10 ml glacial acid acetic 100% and 300 ml acetonitrile, and was pumped at a flow rate of 1.5 ml/min. The injection volume was 50 µl, the run time 10 minutes. Detection was achieved at 242 nm. Data integration was performed with EzChrom Elite 3.2.1 software.

Results

a. Dissolution profiles obtained in hydrochloric acid 0.1 N dissolution media

Based on the theory presented in the introduction section, suitable dissolution media for simulating the fasted state gastric conditions could be the hydrochloric acid with pH values between 1.2–2.0. We compared the dissolution profiles obtained from a test and a marketed product in hydrochloric acid 0.1 N (Figure 1).

b. Dissolution profiles obtained in acetate buffer solutions pH = 4.5

In order to simulate the small intestine conditions from the first part (duodenum-jejunum) we tested and compared the dissolution profiles of the test and the marketed product in acetate buffer solutions pH = 4.5 (Figure 2).

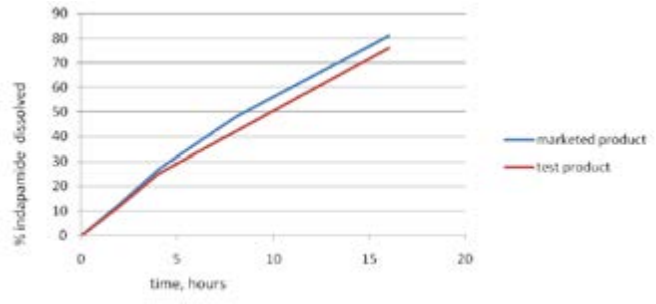

Fig. 1. Comparison of dissolution profiles of indapamide modified release tablets in hydrochloric acid, pH=1.2

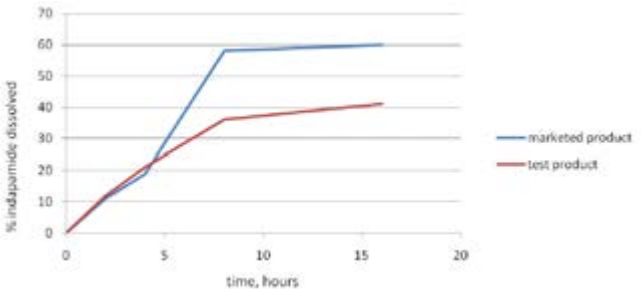

Fig. 2. Comparison of dissolution profiles of indapamide modified release tablets in acetate buffer solution, pH=4.5

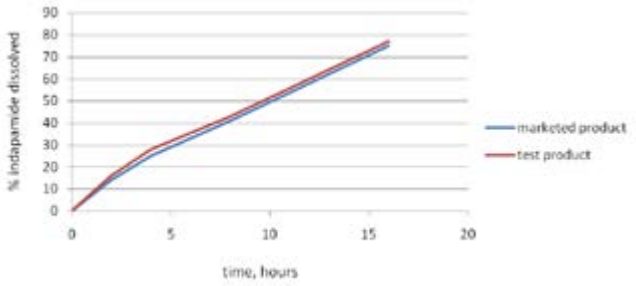

Fig. 3. Comparison of dissolution profiles of indapamide modified release tablets in phosphate buffer solution, pH=6.8

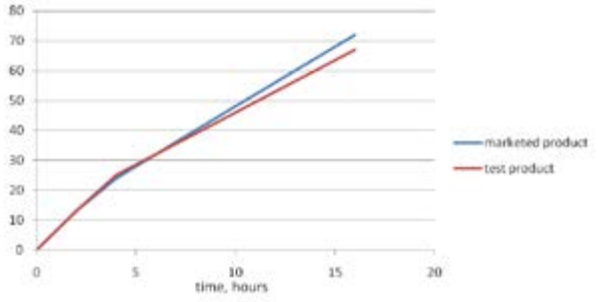

Fig. 4. Comparison of dissolution profiles of indapamide modified release tablets in FaSSIF conditions

c. Dissolution profiles obtained in phosphate buffer solutions pH = 6.8

We have tried to simulate the small intestine conditions from the ileum, too. We examined our product and the marketed product in phosphate buffer solutions pH = 6.8. (Figure 3).

d. Dissolution profiles obtained in FaSSIF conditions

In the small intestine not only the pH is higher than in te stomach, but there are bile salts and lecithin, too. Sodium taurocholate was chosen as a representative salt because cholic acid is one of the most prevalent bile salts in the human bile. Phosphate buffer is used as a substitute for the physiological buffer, bicarbonate to avoid instability in the pH value. The pH value is 6.8, which is generally representative for the mid-duodenum and the ileum [1]. Therefore, we registered the dissolution profiles in FaSSIF conditions (Figure 4).

e. Dissolution profiles obtained in FeSSIF conditions

Some of the drugs are better absorbed when given with a meal, than in the fasted state. The dissolution medium for FeSSIF conditions contains acetate buffer instead of phosphate buffer in order to achieve the higher buffer capacity and osmolarity, while maintaining the lower pH value representative of fed state duodenal conditions. The taurocholate and lecithin are present in higher concentrations because of meal-induced secretions [1]. We tested if in FeSSIF conditions (Figure 5) the release of the indapamide from dosage forms is different than in FaSSIF conditions (Figure 4).

Discussion

Data obtained from the dissolution profiles in different dissolution media data were also mathematically compared using the difference factor f1 and the similarity fit factor f2.

The difference factor f1 is proportional to the average difference between the two profiles.

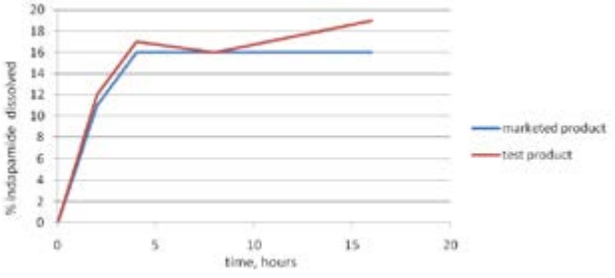

Fig. 5. Comparison of dissolution profiles of indapamide modified release tablets in FeSSIF conditions

Table I. f1 and f2 values obtained by comparing marketed and test product dissolution profile obtained in different dissolution media

Dissolution media	Difference factor f1	Similarity factor f2
Hydrchloric acid 0.1 N	9	69
Acetate buffer solution pH = 4.5	30	42
Phosphate buffer solution pH = 6.8	80	6
FaSSIF solution	5	78
FeSSIF solution	8	86
Limits	0–15	50–100

$$f1 = \left(\frac{\sum (Rt - Tt)}{\sum Rt} \right) x100$$

The similarity fit factor f2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time-points. The fit factor, f2, is defined by the following:

$$f2 = 50 \bullet \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} \left[\overline{R}_{(t)} - \overline{T}_{(t)} \right]}{n}}} \right]$$

where R_t and T_t are the average values of the two data sets at time point t and n is the total number of time points used for calculation. The concept of the f1 and f2 approach was described by Moore and Flanner [12].

The calculated f1 and f2 values for all examined situations are presented in Table I.

It can be observed than in hydrochloric acid and phosphate buffer solution the release of the active substance from the dosage form is linear, and it is almost complete in 16 hours. Based on the calculated f1 and f2 factors the marketed and the test product dissolution behavior is similar. In acetate buffer solution the release of the drug product is not complete in 16 hours and a considerable difference can be observed between the marketed and the test product.

Conclusions

In drug development there is a need to develop dissolution tests in order to select appropriate excipients for the formulation, and to predict the in vivo performance of drug products. When in vitro results fail to predict the in vivo performance of a drug product, more clinical studies are needed to assess bioavailability, thus increasing substantially the cost of product development.

But can we be sure that the developed dissolution method is "good"enough to predict in vivo performance? Probably not 100%, but we can test the developed product in different phases of the development not only with the routine dissolution test method, not only in three different pH-s indicated form regulatory point of view, but in conditions which simulate more appropriately in vivo conditions, like the biorelevant media.

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