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Short communication

Investigation of the effect of different flow-through cell design on the release of prolonged release tablets

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Introduction

The dissolution test is an essential tool for characterization of the performance characteristics of solid oral dosage forms and evaluation of its bioavailability.

Although basket and paddle methods are currently the most popular methods for many drug products, they do not provide a detailed picture about the in vivo behavior of the drug product.

The flow-through cell (FTC) method permits continuous extraction of the drug, simulating absorption into the systemic circulation, generating an intermittent flow of the dissolution medium into the cell where the dosage form is placed (Emara et al., 2014). It can be used as an open system, allowing release under sink conditions, which facilitates the dissolution of poorly water-soluble drugs, as well as a change of the dissolution medium within a pH range of physiological relevance (Fotaki & Reppas, 2005).

The advantage of dissolution using FTC apparatus with open loop configuration is that it provides an environment potentially closer to that of the digestive tract (Gao, 2009).

The aim of this study was evaluation of the effect of different dissolution and hydrodynamic conditions of the FTC, on the release rate of the active pharmaceutical ingredient (API) from prolonged release tablets.

Materials and methods

Materials

Prolonged release tablets containing BCS III class component from two different manufacturers were used. All products used in this study contained 80 mg of active ingredient. All reagents used were of analytical grade.

Dissolution method

Dissolution testing using FTC apparatus has been performed according to current Ph. Eur. requirements (2.9.3. Dissolution test for solid dosage forms). The FTC, USP Apparatus 4 was a Sotax CE 7smart equipped with a CP 7-35 digital piston pump (Sotax, Switzerland). A built in filtration system with 0.7 Whatman glass microfiber (GF/F) and manual filtration with Phenex 0.45 µm regenerated cellulose (RC) was used throughout the study. The temperature of the dissolution medium was kept at 37 ± 0.5 °C.

Media used were: simulated gastric fluid without enzymes (SGF-Medium 1), pH 4.5 acetic (Medium 2) and pH 6.8 phosphoric (Medium 3) prepared according to current Ph. Eur. requirements (5.17.1. Recommendations on dissolution testing).

Different cell sizes, flow rates of dissolution medium and time intervals within the FTC were considered.

The dissolution studies were performed with the tablet secured on a tablet holder, without glass beads (turbulent flow) or in the presence of glass beads, each 1 mm in diameter (laminar flow). Two flow-through cells having internal diameters of 12 (small cell) and 22.6 mm (large cell) were used. The dissolution media were pumped at flow rates of 2, 4, 8, 16 mL/min.

Medium intervals were the following: 1) 1 hour in medium 1, 1 hour in medium 2, up to 12 hours in medium 3; 2) 30 minutes in medium 1, 30 minutes in medium 2, up to 12 hours in medium 3; 3) 30 minutes in medium 1, 1 hour in medium 2, up to 12 hours in medium 3.

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Chromatographic method

Quantification was performed using HPLC method. The mobile phase was comprised of sodium heptansulfonate solution adjusted to pH 2.0, acetonitrile and methanol in ratio 70: 10: 20 (v/v/v), at a flow rate of 0.8 mL/min. Kromasil C18 150 mm x 4.6 mm i.d; 5µm column was used, maintained at 55 °C. Detection was at 230 nm wavelength. Run time of 12 min is utilized with injection volume of 50 µL from the sample and the standard solution.

The amount dissolved was calculated with the following formula:

$$Amount\ dissolved\ (mg) = Concentration\left(\frac{mg}{ml}\right) * flow\left(\frac{ml}{\min}\right) * time\ interval(min)$$

The cumulative release profile of API has been evaluated with f_2 statistics between the test and reference product.

Results and discussion

In order to assess the influence of FTC on drug release profile, dissolution data from the test and reference product were compared. The concentration (mg/mL) of API has been determined using standard calibration curve with 4 concentration levels (0.00444-0.17776 mg/mL).

According to the obtained results, the dissolution profiles of the test and reference product was similar, but the reference product releases the API faster than the test product in the first time points. The f_2 factor demonstrates no significant difference between the products (it ranges from 64.04 to 80.26 between different experiments) showing that all evaluated effect does not significantly influence the release rate of API.

In this study, the cell size had almost no effect on API dissolution rate, as the use of glass beads in the cells. When 2 mL/min flow was applied there was a slight decrease in API release rate. Highest f_2 factor was observed when 4 ml/min was employed.

Lowest f_2 factor was observed when media intervals were set as 30 minutes in medium 1, 30 minutes in medium 2, up to 12 hours in medium 3. The other two sets had high f_2 values with no difference between them. Lower release rate of API, after the last pH change, was demonstrated with the following conditions: 30 minutes in medium 1, 1 hour in medium 2, up to 12 hours in medium 3.

Investigation of the effect of FTC parameters on the release of API from prolonged release tablets show that the most significant affect has the flow rate.

Conclusion

Evaluation of the effect of different factors in this study showed that cell size and presence of glass beads do not have significant effect on API dissolution rate. From all investigated factors, only the flow rate has demonstrated considerable effect on the release rate.

In general, the similarity between the test and reference product is maintained throughout all evaluated experiments with apparatus FTC.

When observing the cumulative release profile graphs, up to 2 hours, both products have same dissolution profiles and after 2 hours, the test product exhibits slightly faster release profile than the reference product. Concentration / time profiles, demonstrate that the reference product releases the API faster than the test product in the first time points.

References

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