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Short communication

Determination of dissolution rate of prolonged-release tablets in bio-relevant media using USP apparatus III

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Introduction

Dissolution testing is broadly used as analytical technique for evaluating the drug release characteristics of a pharmaceutical product. As a powerful tool, it is used for quality control in the development phase as well as throughout the whole life cycle of the finished product assuring that the patients continuously receive safe and effective treatments. (Mwila et al., 2016)

The traditional approach for dissolution method development is usage of USP apparatus I - baskets and USP apparatus II - paddles with agitation speed from 50 to 100 rotations per minute. Dissolution testing can be affected by various factors that can originate from the dissolution apparatus, the testing environment, the analyst's performance and the tested sample. Therefore, the solubility of the product will not be identical through the GIT (gastro-intestinal tract) and the conventional methods with baskets or paddles may not provide the correct estimation of the performance of the finished product. Novel trends in dissolution testing include implementation of bio-relevant media that will provide broader information for the influence of different physiological media compositions that the dosage form will encounter upon GIT transition. (Klein and Dressman, 2006)

To overcome these challenges, the USP apparatus III could be implemented to obtain more accurate data regarding the dissolution process of the drug product. The design of USP apparatus III provides good agitation of the product by moving the inner glass cylinders in the outer cylinders filled with media. During the dip of the cylinder, the dosage form moves freely in the interior of the inner cylinder hence simulating the movement of the dosage form in the GIT. (Mwila et al., 2016). The aim of our study was development of dissolution method using USP apparatus III for determination of the rate and extent of active substance release from prolonged-release tablet under fasted physiological environment.

Materials and methods

Materials

The test and reference products formulated as prolonged-release formulations were tested to evaluate similarity between their dissolution profiles in bio-relevant media. For preparation of biorelevant media simulating the GIT fluids, FaSSIF/FESSIF/FaSSGF reagent was purchased from Biorelevant.com Ltd. and Scof (simulated colon fluid) media was prepared in laboratory. The dissolution tests were performed on Agilent BioDIS III DSS with automated sampling station. Samples obtained after dissolution testing were analyzed on Thermo Dionex 3000 HPLC system.

Dissolution test conditions

The USP III apparatus system consists from an automated sampling station, heater and dissolution bath. In the dissolution bath, there are seven rows with vessels, each row is filled with media with different composition to simulate the GIT transit, and the dips per minute are adjusted to simulate the peristaltic movements in fasted state. The temperature of the media is set to 37.0°C and the media volume is 250 mL. The media, dips per minute and time points in each row are as follows:

1) Fasted State Simulated Gastric Fluid (FaSSGF) - pH 1.6) - 30', 60' - 20 DPM;

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2) Fasted State Simulated Intestinal Fluid (FaSSIF-pH 6.5) - 15'-15DPM;

3) FaSSIF* (pH 6.8) - 15'-15DPM;

4) FaSSIF** (pH 7.2) - 30'-15DPM;

5) FaSSIF Blank (pH 7.5) 120'-15DPM;

6) Simulated Colon Fluid (pH 5.8) 480' - 10DPM.

Overall, the length of the test is twelve hours with ten time points (30', 60', 75', 90', 120', 240', 360', 480', 600', 720').

Media FaSSIF - pH 6.5 was prepared according to manufacturer's prescription. For FaSSIF - pH 6.8 the pH was adjusted while the bile salts concentration remained the same while for FaSSIF - pH 7.2 both pH and bile salts concentration were adjusted. In FaSSIF blank, bile salts are not present.

* Adjusted pH; ** Adjusted pH and bile salts.

Chromatographic conditions and sample preparation

After specified time, 5 mL sample was automatically collected from each vessel and no media was replaced since every row has different media. Sample solutions as well as standard solutions were analyzed on HPLC system under the following conditions:

Mobile Phase: Mixture of phosphate buffer solution pH 3.0 and acetonitrile (95%: 5%, *V/V*); *Column*: Sun Fire (C8), 150 mm x 4.6 mm i.d; 5-µm or equivalent. The run time was 5 minutes.The detection wavelength 230 nm and the injection was 10 µL. The flow rate was 1.0 mL/min and the column temperature was kept at 25 ^{o}C.

Results and discussion

The advantage of using USP apparatus III in this case is that it can automatically perform complete media change that occurs in the body and with the reciprocating movements it can imitate the peristaltic movements. The bio-relevant media can be prepared using different pH values but also using different bile salts concentration of since this factor may differ in different parts of the intestines.

The percentage of dissolved active substance after one hour was between 20% and 40%, after four hours between 55% and 75%, and after twelve hours above 90%. From the generated data, it is evident that the active substance is not immediately released from the dosage form but with controlled rate.

To be precise, the lowest concentration of active substance was released and dissolved in the stomach after one hour. Then, over half of the active substance was dissolved throughout the different parts of the intestines and again the lowest concentration was dissolved in the colon. Hence, there was continuous controlled-release and dissolution of the active substance from the dosage form.

The comparison between dissolution profiles of the test and the reference product was performed with model independent approach using similarity factor (*f2).* When *f2* value is above 50, products can be considered similar. The curves for both products were almost identical and the similarity factor was 82.96.

During the development of this dissolution method, the pH and composition of the media, time points, dips per minute should be carefully chosen and/or evaluated in order to accurately mimic the environment the dosage form will encounter in GIT after oral administration.

Conclusion

Even though dissolution tests using USP apparatus III cannot be used for quality control of finished drug products, they are very powerful tool for prediction of product behavior in the GIT. The possibility of application of different media fin different time points, different dips of the cylinders greatly mimic the peristaltic movements of the GIT in different states - fasted or fed. The *in vitro* conditions obtained with this apparatus simulate the *in vivo* conditions, providing almost identical environment. , The overall benefit of assessing the dissolution properties using USP apparatus III with bio-relevant media would be gaining superior knowledge about the product and its possible behavior *in vivo*. Therefore, the decision for candidate bio-batch for bioequivalence would be more scientifically based and the outcome would be easier to predict thus saving significant amount of resources.

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