International Journal of Pharmaceutics 484 (2015) 235–245

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

An understanding of modified release matrix tablets behavior during drug dissolution as the key for prediction of pharmaceutical product performance – case study of multimodal characterization of quetiapine fumarate tablets

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ARTICLE INFO

Article history:
Received 6 December 2014
Received in revised form 11 February 2015
Accepted 16 February 2015
Available online 18 February 2015

Keywords:
Pharmaceutical generic product
Quality by design (QbD)
Magnetic resonance imaging (MRI)
X-ray microtomography (μCT, Micro-CT)
Texture analysis
Biorelevant dissolution

ABSTRACT

Motivation for the study was the lack of dedicated and effective research and development (R&D) *in vitro* methods for oral, generic, modified release formulations. The purpose of the research was to assess multimodal *in vitro* methodology for further bioequivalence study risk minimization.

Principal results of the study are as follows: (i) Pharmaceutically equivalent quetiapine fumarate extended release dosage form of Seroquel XR was developed using a quality by design/design of experiment (QbD/DoE) paradigm. (ii) The developed formulation was then compared with originator using X-ray microtomography, magnetic resonance imaging and texture analysis. Despite similarity in terms of compendial dissolution test, developed and original dosage forms differed in micro/meso structure and consequently in mechanical properties. (iii) These differences were found to be the key factors of failure of biorelevant dissolution test using the stress dissolution apparatus.

Major conclusions are as follows: (i) Imaging methods allow to assess internal features of the hydrating extended release matrix and together with the stress dissolution test allow to rationalize the design of generic formulations at the *in vitro* level. (ii) Technological impact on formulation properties *e.g.*, on pore formation in hydrating matrices cannot be overlooked when designing modified release dosage forms.

1. Introduction

Medicinal products differ significantly from other ordinary consumer products. First of all, there are no medicines that are completely safe and patients cannot evaluate the risks and benefits of their application. Therefore, the process of registration of drugs, also referred to as product authorization is a multistage, highly regulated procedure that focuses on the quality, safety and efficacy of the drug product (Rägo, 2008).

The common technical document (CTD) that organizes the modern structure of registration dossiers is based on more than fifty specific guidelines prepared and recommended by the International Conference of Harmonization (ICH), which describe the content and structure of particular sections of the drug product dossier. The pharmaceutical development – an important aspect of drug product quality – is characterized by the ICH Q8 (R2) guideline (ICH, 2009). The pharmaceutical development is focused on designing "a quality product and its manufacturing process to consistently deliver the intended performance of the product" (ICH, 2009). The guideline emphasizes the gaining of scientific knowledge necessary to ensure the highest possible quality of the drug product and to establish the methods of its constant control. The concept of systematic approach to pharmaceutical development is called quality by design (QbD). It assumes that the quality of drug products should not be tested *post hoc*, but should be designed and built into the product.

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http://dx.doi.org/10.1016/j.ijpharm.2015.02.040
0378-5173/

The most important aspects of the pharmaceutical development are the determination of the quality target product profile (QTPP) and identification of critical quality attributes (CQA) that affect the product quality, safety and efficacy. Comprehensive knowledge of the mechanistic relationship between processing parameters and drug CQA lead to reduction of variability and achievement of desired quality in a repeatable manner. The optimization process through understanding of technological attributes of drug product as well as structural and functional consequences of the composition and manufacturing process gives obvious benefits for both, patients and industry, and may create a basis for reducing the overall risk and implementing flexible regulatory approaches.

In 2004, the US Food and Drug Administration (US FDA) initiated the implementation of the process analytical technology (PAT) in the pharmaceutical industry through "GMPs for the 21st Century" (Hinz, 2006; PAT, 2010). The PAT approach introduced a number of tools for enabling scientific understanding of drug formulation. Since drug formulae are considered a complex, multifactorial systems, the use of statistical design of experiments (DoE) is recommended for studying the effects of process variables on drug product attributes.

The above-mentioned strategies of pharmaceutical development could be applied equally for innovative medicines as well as to multisource (generic) products. However, in the case of generics, QTTP is predefined by the quality of the originator.

The drug dissolution test is one of the most important tools applied in the pharmaceutical development procedures. In the last few decades, dissolution testing has become equally a routine tool for quality control as well as a prerequisite for biopharmaceutical characterization of different products (Dickinson et al., 2008). The compendial dissolution tests have a relatively simple construction and provide well-definable conditions by implying continuous exposition of the dosage form to a sufficient amount of dissolution medium and mechanical agitation (Garbacz and Klein, 2012; Garbacz et al., 2010). The dissolution equipment represents highly standardized tools for quality control and with appropriate experimental settings the simulation of the physicochemical conditions in the gastrointestinal tract (GIT) is also possible. However, these well definable and continuous conditions during the dissolution test do not reflect the physiological circumstances along the gastrointestinal (GI) tract. The design of the official dissolution test apparatus does not provide the possibility of simulating GI mechanical stress conditions in a realistic way and does not reflect the volumes, discontinuous distribution and flow patterns of the gastro-intestinal fluids (Garbacz and Klein, 2012; Schiller et al., 2005).

For modified release dosage forms the application of compendial dissolution methods that reliably allow comparing the formulations, brings additional challenges. It is known that the release behavior of solid oral dosage forms during the GI transit may be affected by physicochemical conditions and mechanical stress (Garbacz and Klein, 2012). It has been recognized that the GI transit is characterized by highly variable conditions with long rest phases and short but intensive events of transport (Weitschies et al., 2005). During GI transport events, dosage forms are moved with high velocities of up to 30–50 cm/s for short periods. Such intensive movements are mainly triggered by gastric emptying and transition through the ileocaecal junction as well as colonic mass movement. During GI transit, monolytic dosage forms such as capsules or tablets are also exposed to mechanical pressure caused by GI motility events. Maximum pressures are registered in the antropyloric region of the stomach and reach up to 350 mBar in the case of monoliths like modified release tablets (Kamba et al., 2000; Kuo et al., 2008). It has already been demonstrated that the release behavior of modified release formulations can be affected by mechanical stress in the GIT (Garbacz and Klein, 2012; Garbacz et al., 2010, 2008). Due to the complex physiology of the GIT, standard dissolution methods are not necessarily capable to simulate realistically the GI transit conditions of solid oral dosage forms. By use of the bio-relevant dissolution methods, such as the stress test device, the impact of mechanical stress on drug release of modified release products can be investigated (Garbacz et al., 2014, 2010; Garbacz and Klein, 2012). The device provides the simulation of essential physiological stress parameters including discontinuous dosage form movement and GI motility forces using physiology-based test algorithms. By this, the stress test device can demonstrate the mechanical conditions of the GI transit in a rational way (Garbacz and Klein, 2012).

In physiological conditions, the structural and compositional factors play an important role in the drug release during the passage throughout the whole gastrointestinal tract hence selection of appropriate methodology reflecting the physiological conditions may be problematic (Dickinson et al., 2008). The need of scientific characterization of processes occurring during drug release from modified release dosage forms induces the increasing demand for techniques that could provide additional information about the mechanism of action of the dosage form and the temporal changes of its properties during the drug delivery (Chen et al., 2010). Even biorelevant dissolution testing gives only indirect information concerning structural/morphological and physicochemical properties of the modified release matrices. For this reason, during the last two decades, various, new analytic and imaging methods were introduced to investigate hydrated polymeric matrices (Dorożyński et al., 2012). It was shown that they have great potential, but they were not used as a tool for a rational dosage form development so far. These methods, some of them destructive, were mainly used to study properties of model dosage forms. Moreover, most of the methods have restrictions concerning size and shape of the matrix and their application is often limited to the characterization of modified release monolithic dosage forms such as tablets and capsules. Some previously performed studies on swelling dosage forms have drawn attention to important new aspects of matrix properties and structure evolution during hydration *e.g.*, to matrix porosity (Karakosta et al., 2006; Laity and Cameron, 2010; Laity et al., 2010), potential presence of drug depletion zone (Chen et al., 2014), formulation dependent differences in physicochemical properties of matrices and different layer formation (Kulinowski et al., 2014).

Magnetic resonance imaging (MRI) and X-ray microtomography (micro-CT) can be used to study intact hydrated matrix dosage form, virtually of any size and shape. Most of the MRI methods are sensitive to water proton properties inside the hydrated polymeric matrix – images reflect directly or indirectly molecular dynamics and proton density (Dorożyński et al., 2012; Mantle, 2011, 2013). MRI of dosage forms in flow-through cell was found to be a very promising tool for evaluation of matrix systems (Dorożyński et al., 2012). However, it inherently suffers from relatively low spatial resolution (0.2–0.5 mm) (Chen et al., 2014; Kulinowski et al., 2011; Zhang et al., 2011). X-ray microtomography offers better resolution and mainly density based contrast, but cannot be performed during dissolution (Laity and Cameron, 2010; Laity et al., 2010). To date, only few studies were performed on commercial products using MRI and/or X-ray computed microtomography (micro-CT) (Chen et al., 2014; Dorożyński et al., 2014; Kulinowski et al., 2011; Yin et al., 2013; Zhang et al., 2011).

The first and only micro-CT studies during matrix tablet hydration combined with an MRI study was reported by Laity et al. (2010). In the subsequent work, the authors applied a synchrotron X-ray source to achieve shorter scan time and higher spatial resolution (Laity and Cameron, 2010). They studied placebo tablets composed of hydroxypropylmethylcellulose