Research Article

Release Characteristics of Quetiapine Fumarate Extended Release Tablets Under Biorelevant Stress Test Conditions

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Abstract. The aim of the present work was the investigation of robustness and reliability of drug release from 50 to 400 mg quetiapine extended release HPMC matrix tablets towards mechanical stresses of biorelevant intensity. The tests were performed under standard conditions (USP apparatus II) as well as under simulated gastrointestinal stress conditions. Mechanical stresses including pressure and agitation were applied by using the biorelevant dissolution stress test apparatus as it has been introduced recently. Test algorithms already established in previous studies were applied to simulate fasting gastrointestinal conditions. The dissolution experiments demonstrated striking differences in the product performance among standard and stress test conditions as well as dose strengths. In USP apparatus II, dissolution profiles were affected mainly by media pH. The dissolution experiments performed in biorelevant dissolution stress test device demonstrated that stress events of biorelevant intensity provoked accelerated drug release from the tablets.

KEY WORDS: biorelevant dissolution testing; burst release quetiapine; dissolution stress test; dose dumping.

INTRODUCTION

Quetiapine is an atypical antipsychotic, which is indicated for treatment of schizophrenia and bipolar disorders (1). The dibenzothiazepine structure with two basic nitrogen atoms is responsible for its higher solubility under acidic conditions. At a pH above 4, the water solubility is poor; towards pH 2, an increase in solubility is noticeable. However, below pH 2, solubility is decreasing owing to the ion effect (2). Due to its poor solubility over the physiological pH range but its high permeability, quetiapine is classified as a BCS class II drug (1).

Quetiapine is available as fumarate salt in immediate release and extended release (ER) formulations. The ER formulation was introduced several years ago and is intended to release the drug in a controlled way with the aim to increase compliance of schizophrenia patients and to reduce side effects. The most common adverse drug reactions of quetiapine are somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, ALT increased, and dyspepsia (3). Overall, quetiapine has an excellent risk/benefit profile and is a suitable first-line option for the treatment of schizophrenia (4). The administration of once-daily formulations is one of the possibilities to increase the drug adherence.

It was the aim of our study to investigate the robustness of ER tablets (SEROQUEL XR) containing either 50 or 400 mg quetiapine towards mechanical stresses of biorelevant intensity. The resistance towards physical stresses of biorelevant fortitude can be investigated using our biorelevant dissolution stress test device (5). This dissolution test system enables the *in vitro* evaluation of the robustness of formulation principles of modified release dosage forms under conditions of biorelevant stresses (5–7). The system is intended to depict the impact of GI-specific mechanical stresses on drug delivery processes of the formulation. These include the application of mechanical pressure and episodes of acceleration as they occur during gastrointestinal transit using physiology-based test algorithms. Particularly, the high stresses that may occur in the pyloric region and the ileocecal region are considered (8–12). By this, the stress test device enables the simulation of GI conditions as they are present in the fasted state in a biorelevant manner.

MATERIAL AND METHODS

SEROQEL XR tablets containing 50 and 400 mg quetiapine were investigated. Dissolution experiments were performed using 0.1 mol/L HCl (pH 1.0) solution as an artificial medium representing the conditions in the fasted stomach and phosphate buffer pH 6.8 (USP) as dissolution medium for simulation of fasting intestinal conditions.

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Standard Dissolution Test

The dissolution behavior of the tested tablets was investigated using USP apparatus II (DT80 Erweka, Heusenstamm, Germany) at a stirring rate of 50 rpm and a volume of the dissolution medium of 1,000 mL at a temperature of 37°C. The tests were performed for $n=6$ tablets per test conditions using single-dissolution medium over the entire test with a duration of 24 h.

The amount of drug dissolved was determined using a UV spectrophotometer (UV1650, Shimadzu, Duirchsburg, Germany) in off-line mode. Samples of each time 5-mL volume were withdrawn via a filter (Poroplast, 0.2-μm pore size, Eweka, Heusenstamm, Germany) at preselected time points. The withdrawn volume was replaced immediately with blank dissolution medium.

Stress Test Device

The dissolution stress test apparatus (PhysioStress) has been introduced by Garbacz *et al.* in 2008 (5). In the dissolution stress test apparatus, solid oral dosage forms like tablets or capsules can be exposed to sequences of agitation including transport events and pressure waves. The device consists of a central apparatus axis with six steel wire netting spheres, in which the dosage forms are hosted. Each chamber is divided into two parts. The bottom part is screwed onto the central pipe by a PVC bush and by a nozzle. The axle is connected to the deck plate of the device close above the top edges of the row of standard dissolution vessels in their symmetry plane. Consequently, each sphere operates in a separate vessel. One end of the central axis is connected with a pressure regulation unit and the opposite end with a stepping motor. Pressure waves are generated by pulsatile inflation and deflation of balloons located inside the chambers. The inflation and deflation is controlled by synchronized switching of solenoid valves, whereas the pressure value is regulated by a computer controlled pressure-reducing device. A programmable stepping motor drives the central axis. All test parameters are controlled by custom-made software. The dissolution medium (1,160 mL) was mixed by a separate paddle stirrer operated at 100 rpm during the entire test (5,13). This stirrer is required to mix the dissolution medium in order to achieve homogenous samples. The media flow generated by this stirrer does not influence drug release, as the netting steel wire shields the samples that are located inside the chamber (Fig. 1).

Test Algorithms

The test algorithms used for the investigation of the ER tablets are intended to mimic fasting intake conditions. Two different test programs have been developed that are aimed to reflect the variability of residence time of solid dosage forms in human stomach under fasting conditions. The arrangement of the test programs is summarized in Table I.

In program 1, a gastric residence time of 30 min was simulated, while in program 2 a gastric residence time of 60 min was assumed. In both programs, gastric emptying was simulated as a stress phase of high intensity. This stress phase was performed as three consecutive inflations of the balloons each with a duration of 6 s and a fortitude of 300 mbar

mimicking peristaltic pressure waves. These pressure events were followed by 1 min of intense rotation of the apparatus axle at 100 rpm corresponding to tablet velocities ranging from 15 up to 60 cm/s mimicking accelerated tablet transport as observed during gastric emptying of tablets in humans (12,14). Small intestinal transit was simulated as discrete events of tablet movement simulated as each time five rotations of the apparatus axle at a velocity of 10 rpm that were looped every 10 min. The ileocecal passage of the dosage forms was simulated after 5 h as the identical high stress phase that was applied for mimicking gastric emptying. The timing of this phase was intended to mimic the ileocecal reflex induced by meal intake [16]. Accordingly, the small intestinal transit phase mimicked in program 1 lasted 4.5 h while it lasted 4.0 h in program 2. Owing to its high variability, colon passage was simulated only roughly as the identical high stress phases as applied for mimicking gastric emptying and ileocecal passage that were repeated every 3-h simulating events of mass transport.

Three dissolution stress test experiments were performed. In the first experimental setup, program 2 (gastric emptying simulated after 60 min) was applied using USP phosphate buffer as the only dissolution medium throughout the entire test. In the second and third experiment, the milieu of the stomach under fasting conditions was simulated by using 0.1 N HCl (pH 1) for the first 30 (program 1) or 60 min (program 2). After simulated gastric emptying, the medium was in both settings changed to USP phosphate buffer pH 6.8.

The amount of drug dissolved in the experiments carried out with the biorelevant dissolution stress test device was determined by UV–vis spectroscopy. The absorbance was measured in intervals of 5 min in differential mode at 290 (signal) and 450 nm (background). The averaging time amounted to 1 s per wavelength. Data acquisition and processing was performed with commercial software (UV Probe, Shimadzu, Duisburg, Germany; WinUV Varian Inc., Palo Alto, USA). The loss of dissolution media due to evaporation (typically <5%) was determined and considered in the calculations.

Evaluation of the Dissolution Data

Dissolution rates were calculated as the percent of the dose dissolved within sampling interval. The dissolution profiles obtained under the various test conditions were compared using the statistical method developed by Pillay and Fassihi (15). Mean times for dissolution of 30% ($MDT_{30\%}$), 50% ($MDT_{50\%}$), and 80% ($MDT_{80\%}$) of the drug linearly extrapolated based on the mean dissolution profiles. The equality of variances within the data groups was investigated using the Brown–Forsythe test for $p>0.05$. The statistical significance of the observed differences of the dissolution profiles was determined by multivariate analysis of variance (ANOVA/MANOVA) with the post hoc test NIR (both $p>0.05$).

RESULTS AND DISCUSSION

Standard Dissolution Test

The standard dissolution profiles obtained for the 50 and 400 mg ER tablets are given in Fig. 2a, b. Both tablets show
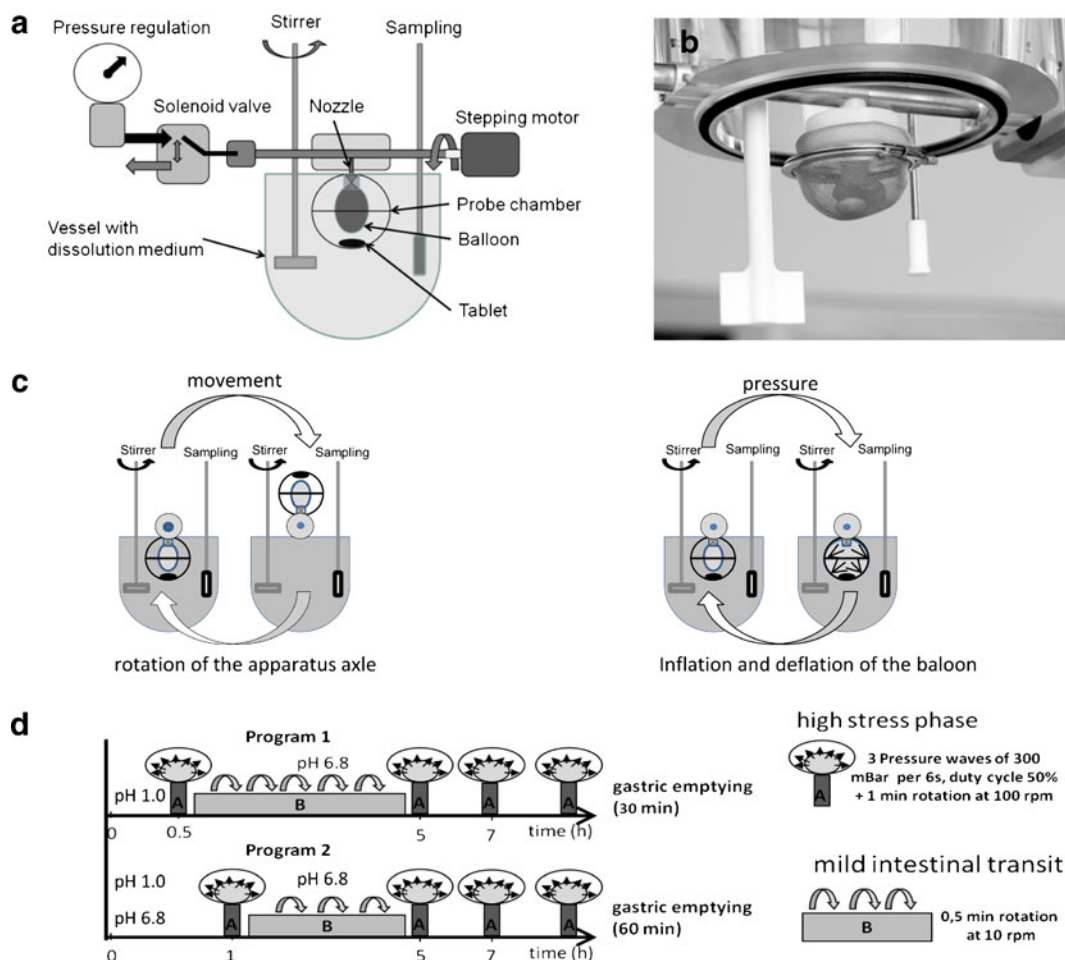
Fig. 1. Dissolution stress test device. **a** Schematic description of the apparatus, **b** photograph of one opened chamber with the paddle stirrer, **c** schematic representation of the agitation phases (*site view*), **d** arrangement of the test program

pH-dependent drug release. In 0.1 N HCl, the dissolution rates are about 12.3% per hour in case of the 50-mg tablets and 12.1% per hour in case of the 400-mg tablets. At pH 1, the dissolution process was completed after 8 h for both dose strengths. In USP phosphate buffer pH 6.8, significantly slower dissolution was observed. The dissolution rate of the 50-mg tablets amounted to about 5.7% per hour with

complete drug release after approximately 18 h. In the case of the 400-mg tablets, a dissolution rate of approximately 3.4% per hour was observed and quetiapine release was not complete within 24 h. The mean dissolution times are summarized in Table II. The statistical analysis confirmed that the dissolution profiles of the 50 and 400 mg ER tablets in the USP phosphate buffer pH 6.8 differed significantly.

Table I. Arrangement of the Test Programs Applied in Stress Test Apparatus

| Program-number	Gastric residence time	Gastric emptying	Intestinal passage	Ileocecal passage	Colon passage
1	0–0.5 h No agitation	0.5 h Three pressure waves of 300 mbar fortitude+1 min rotation at 100 rpm	0.5–5 h Five rotation at 10 rpm (30 s duration) looped every 10 min	5 h Three pressure waves of 300 mbar fortitude+1 min rotation at 100 rpm	5–12 h Three pressure waves of 300 mbar fortitude+1 min rotation at 100 rpm looped every 3 h
2	0–1 h No agitation	1 h Three pressure waves of 300 mbar fortitude+1 min rotation at 100 rpm	0.167–5 h One pressure wave of 100 mbar fortitude followed by four rotation at 20 rpm (16 s duration) looped every 10 min		
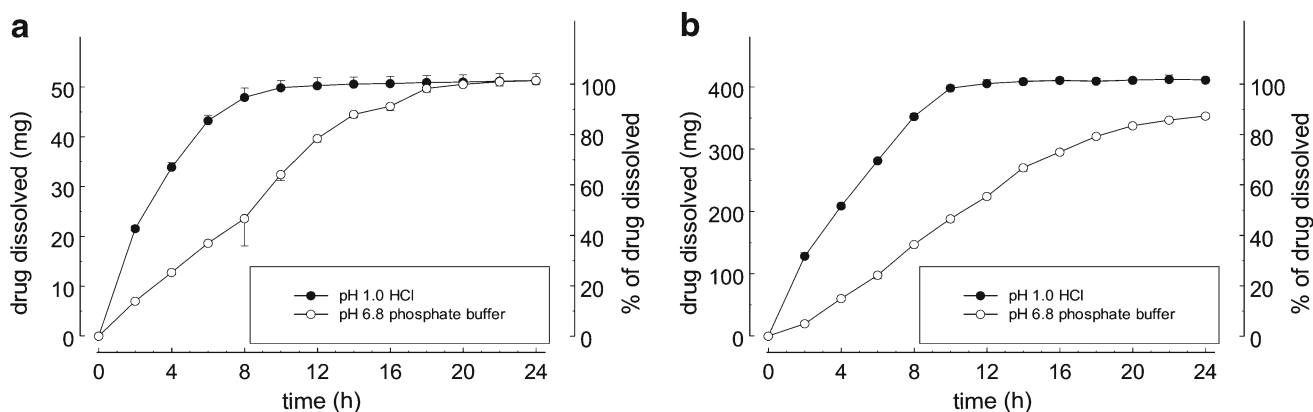
Fig. 2. Dissolution profiles of quetiapine 50 mg ER tablets (**a**) and quetiapine 400 mg ER tablets (**b**) in the USP apparatus II at 100 rpm, 37°C, 1,000 mL fill volume, using HCL pH 1.0 and USP phosphate buffer pH 6.8 as dissolution media. Given are means of $n=6$, the standard deviation is indicated by the *error bars*

Dissolution Stress Test

Using the stress test device, both products yielded strongly differing dissolution characteristics compared to USP apparatus II. The results of the tests performed for both formulations using phosphate buffer as dissolution media are shown in the Fig. 3a, b. The results of the statistical evaluation of the dissolution data are given in Table II. Within the first 5 h of dissolution, the release profiles of the 50-mg tablets did not differ significantly from the test results obtained with the USP apparatus. Gastric emptying simulated after 60 min had only a minor influence on dissolution behavior. However, the simulated ileocecal passage simulated after 5 h resulted in burst release of at least 20 mg of quetiapine, i.e., about 40% of the total drug load (Fig. 3a). Using phosphate buffer pH 6.8, the release profiles of the 400 mg ER tablets obtained with the USP apparatus II and the dissolution stress test apparatus are only comparable until the simulated gastric emptying after 60 min (Fig. 3b). The stress event after 60 min provoked a burst release of about 30 mg of quetiapine. The second stress event after 5 h yielded a further burst release of about 120 mg of quetiapine within 15 min.

The results of the dissolution experiments applying the stress test apparatus including media change are shown in the Fig. 3c, d. For the 50-mg tablets, dissolution was accelerated by the acidic conditions applied until simulated gastric emptying compared to the release rates obtained in phosphate buffer pH 6.8. Furthermore, the extent of burst release caused by the stress simulating gastric emptying was also intensified. The release rates after media change were well comparable to those obtained without media change. The stress event at 5 h simulating ileocecal passage resulted again in burst release. By applying the media change procedure, a decrease of MDT$_{30\%}$ and MDT$_{50\%}$ was observed. The release was completed within 8 h.

The dissolution profiles of the quetiapine 400 mg ER tablets were also clearly influenced by the simulated stresses of physiological intensity; however, media change had no significant effect on dissolution rates. Under the tested conditions, release was completed within approximately 11 h.

DISCUSSION

The resistance of oral solid dosage forms towards GI specific stresses is particularly important for modified release formulations. This is due to the fact that their therapeutic advantages are in many cases only present as long as they provide non-fluctuating drug plasma levels within the

Table II. Comparison of Mean Times for Dissolution (MDT) of 30, 50, and 80% of Quetiapine 50 and 400 mg ER Tablets Under Various Test Conditions

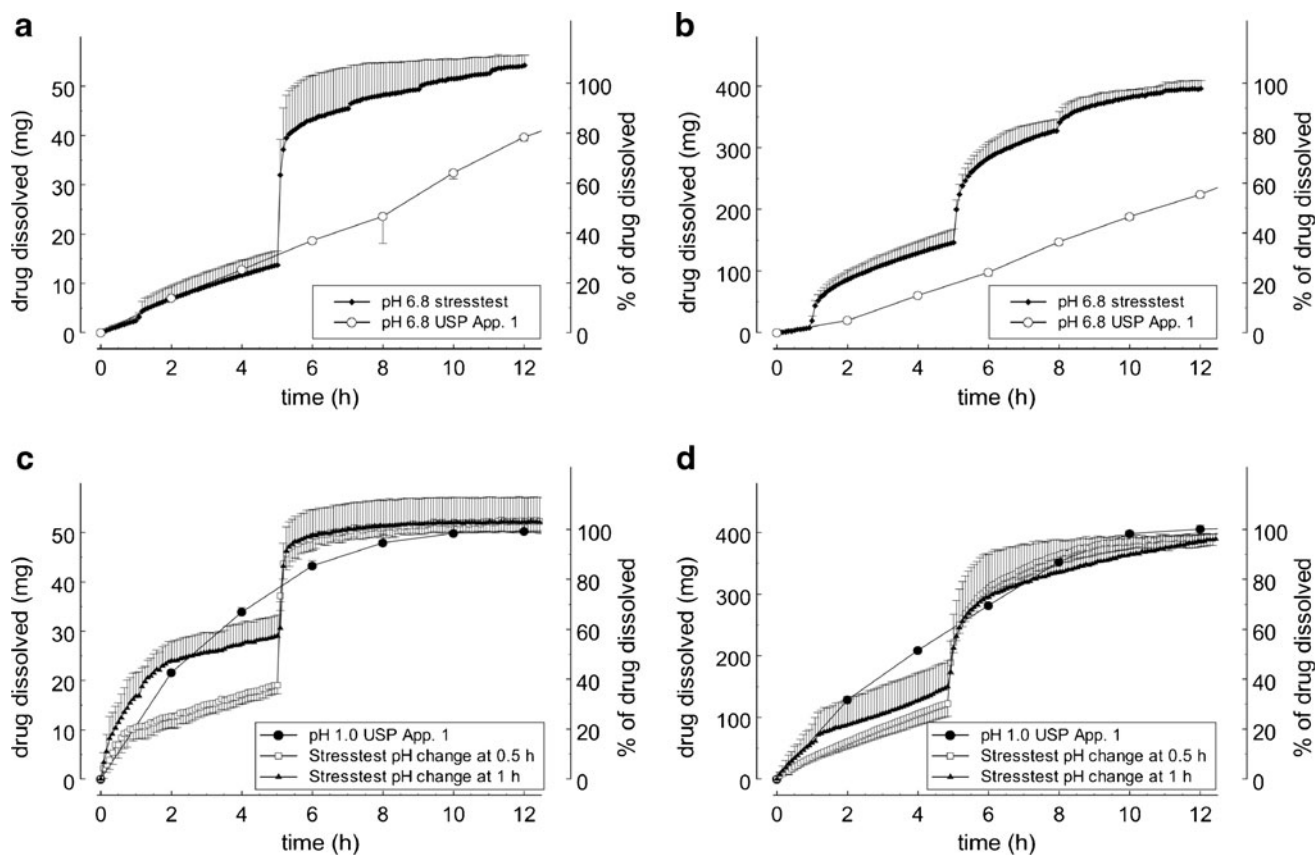| Test setup	Dose (mg)	Mean time for dissolution (h)		
		MDT30%	MDT50%	MDT80%
USP App. 2 at pH 1.0	50 mg	1.2	2.4	5.7
	400 mg	1.8	3.9	6.2
USP App. 2 at pH 6.8	50 mg	6.1	8.2	12
	400 mg	6.4	10.1	18
Stress test program 2 at pH 6.8 without media change	50 mg	5	5.1	5.3
	400 mg	3.1	5.1	7.1
Stress test program 1 (pH change at 30 min)	50 mg	2.2	5.1	5.2
	400 mg	4.1	5.1	7.2
Stress test program 2 (pH change at 60 min)	50 mg	0.6	1.9	5.1
	400 mg	3.9	5.1	7.1

Fig. 3. Dissolution profiles of quetiapine 50 mg ER tablets (**a**) and quetiapine 400 mg ER tablets (**b**) in the dissolution stress test device under test program 2 and the USP apparatus II at 100 rpm, 37°C, 1,000 mL fill volume, using USP phosphate buffer pH 6.8 as dissolution media quetiapine 50 mg ER tablets (**c**) and quetiapine 400 mg ER tablets (**d**) tablets in the dissolution stress test device under test programs 1 and 2 and the USP apparatus II at 100 rpm, 37°C, 1,000 mL fill volume, using HCl pH 1.0 as dissolution media. Given are means of $n=6$; the standard deviation is indicated by the *error bars*

therapeutic concentration range. Thus, the reliability of the applied formulation principle has to be investigated intensively during development and preclinical evaluation of new dosage forms. Problems and risks related to medication can be minimized by this procedure. If compendial dissolution methods are applied, reliable product characterization with respect to identification of possible undesired drug delivery *in vivo* may be often limited. It should be kept in mind that the standard dissolution apparatuses are potent tools for quality control, but their usability for a biorelevant simulation of the broad spectrum of physiological parameters affecting the dissolution process of solid oral dosage forms is often limited. However, to date, several attempts were made to develop *in vitro* tests capable of simulating GI-specific hydrodynamic or mechanical conditions. These novel dissolution devices are used to investigate the robustness of formulation principles towards biorelevant physical stresses. The systems available are characterized by strikingly different construction, degree of complexity, and spectrum of covered factors (16,17). In contrast to the other test setups, the biorelevant dissolution stress test device, which was used in the present study, enables straightforward evaluation of the dosage form robustness towards GI-specific mechanical stresses (6,16). Different test programs were applied to mimic the fasting state. The usability of test algorithms for the prediction of drug delivery behavior and identification of unwanted release characteristics of ER dosage forms

was demonstrated already on numerous examples (5–7,13,16). It should be emphasized that the design of the test programs does not reflect the whole variability and complexity of the *in vivo* situation. Nevertheless, the test arrangement enables the estimation of the impact of physiologically relevant stress events on drug delivery behavior of the tested quetiapine fumarate ER tablets.

Considering the variability of the pH conditions in the upper GI, the pH dependency of the dissolution profiles of ER formulations may be the first hint of undesired release behavior *in vivo*, which could be at least partly observed in the individual drug plasma levels obtained for quetiapine 300 mg ER originator tablet under postprandial conditions (18). In the case of the tested SEROQUEL XR tablets, the pH dependency of the dissolution profiles was observed for both dose strengths. However, the impact of media pH was more distinct in case of the low dose 50-mg tablets. This can be explained with the higher ratio of tablet surface to tablet volume that enabled faster water uptake of the 50-mg tablets (19–21). This was probably the reason for higher dissolution rates observed in our experiments. The dissolution profiles of 400-mg tablets were less influenced by environmental pH under both stress and standard test conditions which may be related to the relatively slower water uptake than in the case of 50-mg tablets (22–24).

The resistance of both dose strengths of the tested ER tablets towards mechanical stresses changes within the

experiment and was only slightly influenced by the media change pattern. The water uptake and swelling of the HPMC tablet matrices led to slow texture softening and as a consequence, the susceptibility towards mechanical stresses increased. When gastric emptying is simulated within the first hour of test duration, the swelling process was only limited and, thus, the dosage forms were characterized by higher mechanical resistance. In contrast, after 5 h, the dosage forms could not withstand the mechanical stresses of the simulated ileocecal passage since texture softening progressed considerably. This resulted in accelerated dissolution of 25–40% of quetiapine. Our observations were at least partly supported by a MRI study of quetiapine fumarate ER tablets that was performed using the flow through cell. This study indicates a low degree of water uptake and swelling as well as the presence of a dry tablet core of 400-mg tablets within the first 60 min (25). However, the test setup applied by Kulinowski *et al.* does not allow simultaneous tablet imaging and simulation of biorelevant stresses. Considering the dissolution data shown in Fig. 3, it is likely that the stress especially at later time points may induce changes of the geometry of the swollen tablet matrices and provokes a burs release of the API, which cannot be depicted using the flow through cell. The mechanical resistance of the swollen tablets can also be estimated by texture analysis (26,27). However, due to the test specificity, the simultaneous exposition of the tablets to mechanical stresses and the determination of its effect on dissolution behavior seem unlikely. Therefore, the usability of the texture analysis for the identification of undesired drug delivery behavior of ER formulations may be often limited.

In the case of the 400-mg tablets, we observed incomplete dissolution in USP phosphate buffer pH 6.8. This can be explained with the loss of sink conditions in the late stage of the dissolution test and the incomplete dissolution of the tablets during the test. Consequently, as indicated by the Noyes–Whitney equation, the solubility kinetic is known to limit the dissolution rate. Therefore, more attention has to be paid in further experiments to the assurance of sink conditions throughout the whole test duration. This can be realized by the addition of artificial surfactants to simple dissolution media, or the utilization of simplified or regular biorelevant media containing physiological surfactants such as FaSSIF and FeSSIF media as well as their modifications (28–31). The use of dissolution media with higher physiological relevance with regard to osmolality and surface tension would enable the biorelevant evaluation of drug dissolution. It is well recognized that these media characteristics may affect swelling, matrix formation, as well as dissolution processes of ER tablets. Moreover, surfactants may impact the robustness of tablets matrices towards mechanical stresses and, thus, change the tablets drug delivery behavior. Therefore, the utilization of biorelevant media as well as media change patterns adjusted to the GI transit is recommendable and would enable characterization of the dosage form performance under more realistic test conditions. Additionally, the impact of quetiapine on the GI transit conditions, namely the prolongation of GI transit times and suppression of GI motility and the overall motoric activity of the patients, needs to be considered in the design of test algorithms (32,33).

It should be kept in mind that the applied test procedures simulate only chosen aspects of the complex GI physiology and require further development in order to enable the testing of dosage forms under conditions simulating the GI transit of the dosage forms in more realistic manner. Recommendable are the modifications with the aim to reduce the volume of the applied dissolution media in order to reflect the physiological conditions (34). Moreover, the application of novel biorelevant dissolution media and test algorithms for simulation of pre- and postprandial conditions is also advisable (29,35,36).

CONCLUSION

The study indicated that the tested quetiapine 50 and 400 mg ER originator tablets are characterized by susceptibility towards mechanical stresses of biorelevant intensity. Furthermore, the results indicate that two investigated tablet dose strengths were characterized by different dissolution behavior under standard as well as biorelevant test conditions. The suspected susceptibility of the tablets towards biorelevant stresses needs to be verified in clinical studies.

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