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Research Article

The Improvement of the Dissolution Rate of Ziprasidone Free Base from Solid Oral Formulations

Daniel Zakowiecki,[1,8] Krzysztof Cal,[2] Kamil Kaminski,[3] Karolina Adrjanowicz,[4] Lech Swinder,[1] Ewa Kaminska,[5] and Grzegorz Garbacz[6,7]

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Abstract. This work aims at increasing solubility and dissolution rate of ziprasidone free base—Biopharmaceutics Classifaction System (BCS) class II compound. The authors describe a practical approach to amorphization and highlight problems that may occur during the development of formulations containing amorphous ziprasidone, which was obtained by grinding in high-energy planetary ball mills or cryogenic mills. The release of ziprasidone free base from the developed formulations was compared to the reference drug product containing crystalline ziprasidone hydrochloride—Zeldox® hard gelatin capsules. All preparations were investigated using compendial tests (USP apparatuses II and IV) as well as novel, biorelevant dissolution tests. The novel test methods simulate additional elements of mechanical and hydrodynamic stresses, which have an impact on solid oral dosage forms, especially during gastric emptying. This step may prove to be particularly important for many formulations of BCS class II drugs that are often characterized by narrow absorption window, such as ziprasidone. The dissolution rate of the developed ziprasidone free base preparations was found to be comparable or even higher than in the case of the reference formulation containing ziprasidone hydrochloride, whose water solubility is about 400 times higher than its free base.

KEY WORDS: amorphization; dissolution stress test device; enhanced dissolution; solubility improvement; ziprasidone free base formulations.

INTRODUCTION

The literature data indicate that in this day and age about 40% of the drug products available on the market contain hydrophobic, poorly soluble substances. This number is constantly growing, and it is estimated that among all currently developed substances 90% are characterized by poor aqueous solubility (1–4).

Many of the poorly soluble substances belong to Biopharmaceutics Classifaction System (BCS) class II, which means that they are characterized by poor solubility and good permeability. They usually demonstrate poor bioavailability after oral administration. Consequently, the solubility and dissolution rate in the gastrointestinal tract are limiting factors for bioavailability of such compounds. Despite such problems, the oral route of administration is still the most preferred one, among others, due to the ease and comfort of use and relatively low production costs of solid oral dosage form, such as tablets or capsules (5–7).

It is well known that the dissolution rate of drug substances strongly depends on their particles' dimensions. Particle size reduction is often achieved by milling performed in different types of mills. Depending on the applied micronization technique, it is possible to obtain materials with different particle size distribution, physicochemical properties (*e.g.* stability, polymorphism) or functional features (*e.g.* flowability, compressibility). Using for example high-energy mills, it is possible to obtain material in the amorphous state (8–12).

Recently, amorphous drug substances have attracted a lot of interest in the pharmaceutical industry because of their specific properties such as improved solubility, increased dissolution rate and in consequence biological availability. Numerous papers pointed out significant increase in dissolution rate of many highly hydrophobic, practically insoluble

[1] Pharmaceutical Works Polpharma SA, Pelplinska 19, 83-200, Starogard Gdanski, Poland.
[2] Department of Pharmaceutical Technology, Medical University of Gdansk, Hallera 107, 80-416, Gdansk, Poland.
[3] Institute of Physics, University of Silesia, Uniwersytecka 4, 40-007, Katowice, Poland.
[4] NanoBioMedical Centre, Adam Mickiewicz University, Umultowska 85, 61-614, Poznan, Poland.
[5] Department of Pharmacognosy and Phytochemistry, Medical University of Silesia in Katowice, ul. Jagiellonska 4, 41-200, Sosnowiec, Poland.
[6] Institute of Pharmacy, University of Greifswald, Felix-Hausdorf-Strasse 3a, 17489, Greifswald, Germany.
[7] Physiolution GmbH, Walther-Rathenau-Strasse 49 a, 17489, Greifswald, Germany.
[8] To whom correspondence should be addressed. (e-mail: daniel.zakowiecki@gmail.com)

drugs as well as improving their functional properties (13–15). This may allow the reduction or even elimination of certain excipients, *e.g.* binders or lubricants from pharmaceutical composition (16).

In the present work, we investigated ziprasidone and its preparations in the form of hard gelatin capsules. Ziprasidone is an antipsychotic substance and belongs to the indole derivatives group. It is used to treat mental disorders such as schizophrenia and manic symptoms of bipolar disorder (17–19).

Ziprasidone is chemically described as 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one. Its empirical formula is $C_{21}H_{21}ClN_4OS$ and molecular weight stands at 412.9 g/mol. Ziprasidone is a weak organic base, and it is classified as a BCS class II compound. This means that the substance is highly permeable, and bioavailability is limited only by its solubility (20). Because of ziprasidone free base's poor aqueous solubility (about 0.5 μg/mL), the drug is usually administered as hydrochloride salt with enhanced solubility in water (about 210 μg/mL). Ziprasidone hydrochloride monohydrate is available on the market as Zeldox® (Geoden®) capsules of different strength, manufactured by Pfizer (21,22).

The aim of the present study was improving solubility and dissolution rate of a poorly water-soluble drug, ziprasidone free base, as well as finding the optimal way of relevant comparison of these two parameters which can substantially affect the bioavailability of the drug. The authors present the way of preparation of hard gelatin capsules containing amorphous ziprasidone free base prepared by cryomilling as well as grinding in high-energy planetary ball mill. Dissolution of ziprasidone from developed preparations was analyzed and finally compared with commercially available drug product containing ziprasidone hydrochloride monohydrate (23,24). For these purposes, the authors utilized pharmacopoeial methods, *i.e.* paddle and flow-through cell, as well as novel biorelevant dissolution stress test devices (25).

The devices realistically simulating the gastrointestinal (GI) transit conditions are based on simple and straightforward working principles and can prove to be useful during the rational development of solid oral dosage forms. An example of such a device is the biorelevant dissolution stress test device developed by Garbacz and Weitschies and currently routinely applied by Physiolution GmbH. The device is able to simulate the relevant physicochemical and mechanical parameters of the GI transit. Moreover, these devices provide the opportunity to simulate essential parameters like intermitted dosage form movement and motility forces by physiology based algorithms to investigate their impact on drug release of solid oral dosage forms in a biorelevant way. The physiology-based algorithms contain phases of rest and sequences of movement and pressure which are in accordance to the *in vivo* situation. The further improvements of the equipment led to development of the "dynamic open flow through test apparatus" which is designed as an accessory to the dissolution stress test apparatus. The device enables the systematic and deductive refinement of biorelevant factors determining the product performance and the design of test protocols that allow product discrimination within the range of physiological variability of the transit conditions through the proximal gastrointestinal tract. The novel apparatus allows us to perform the dissolution tests in volumes of ≤50 mL which represents a realistic volume of the gastric fluid under fasting conditions. To this is added 250 mL of water which is heated to body temperature at an appropriate rate. In addition, the device offers the opportunity for simulation of intragastric media flow and gastric emptying kinetics under fasting conditions (26,27).

MATERIALS AND METHODS

Active pharmaceutical ingredient, ziprasidone free base, was supplied by the Pharmaceutical Works Polpharma SA (Starogard Gdanski, Poland). Purity of the material was higher than 99.5%.

Ball Milling of Ziprasidone

Crystalline ziprasidone free base was ground in the high-energy planetary ball mill PM100 (Retsch GmbH & Co KG, Haan, Germany) using six 30-mm diameter zirconium oxide balls. The grinding balls were placed in a 250-mL volume cylindrical container made of the same material. The substance was milled for 24 h in 15 min cycles with 5-min intervals at a speed of 400 rpm.

Cryogrinding of Ziprasidone

Cryogrinding of ziprasidone free base was performed using cryogenic impact mill 6750 Freezer/Mill (SPEX SamplePrep, Metuchen, NJ, USA). The substance was placed in tightly closed stainless steel vessel and immersed in liquid nitrogen. Grinding was done by stainless steel rod which vibrates by means of magnetic coil in the mode: 10 min of initial precooling of sample at the liquid nitrogen temperature followed by 15 grinding cycles of 6 min each, separated by 3 min cool-down periods. The total milling time was 3 h. After milling, the grinding vial was immediately transferred to a vacuum oven and allowed to warm up to room temperature.

Identification of the Amorphous Ziprasidone Free Base by XRPD and DSC Techniques

X-ray analysis was performed using the powder diffractometer in Bragg-Brentano geometry X'Pert PRO MPD (PANalytical, Almelo, Holland) equipped with Cu anode, X'Celerator real-time multiple strip (RTMS) detector. The samples were placed in the non-reflective sample holders. Diffraction patterns were registered in the scan range of 2–40° 2θ with step size of 0.0167°.

Thermal analysis was performed using simultaneous thermal analyzer TG-DSC Luxx STA409PG (Netzsch-Gerätebau GmbH, Selb, Germany). The measurements proceeded in an atmosphere of inert gas (He) in the temperature ranging from 20 to 150°C with heating rate of 10°C/min.

Solubility Study

In this work, the solubility is presented as concentration of ziprasidone in solution obtained after 2 h of test performed at the temperature of 37°C with a traditional shake-flask technique (28). During tests, around 25 mg of the substance was shacked with about 50 ml of solvent. The excess of

undissolved ziprasidone was filtered out through Syringe Filters 0.45 μm (Pall Poland Ltd, Warsaw, Poland) and obtained solution was analyzed using the ultra-performance liquid chromatography (UPLC) method developed and validated by Zakowiecki and Cal (29).

The solubility was investigated in compendial dissolution media prepared in accordance with Ph.Eur. Monograph 2.9.3. representing the physiological pH range of the human gastrointestinal (GI) tract. Dissolution media such as 0.1 M hydrochloric acid (pH 1.2), phosphate buffer solution (pH 4.5), acetate buffer solution (pH 4.5), phosphate buffer solution (pH 6.8), purified water (pH≈6.9–7.0) and phosphate buffer solution (pH 7.5) were used.

Analysis of Particle Size Distribution

Particle size distribution of ziprasidone free base was analyzed using the automated particle characterization system Morphologi G3a (Malvern Instrument Ltd., Worcestershire, Great Britain). Each substance analysis was performed in two independent repetitions, and during the analysis, pictures of 10^5 particles were recorded. Two types of lens zoom were used, *i.e.* ×10 and ×50. This allowed registration of the particles in the wide range, from about 400 μm to below 1 μm.

Preparation of Ziprasidone Solid Dosage Forms

Amorphous ziprasidone free base obtained by either ball milling or cryogrinding was used to prepare solid oral dosage preparations in the form of hard gelatin capsules. Powders contained in capsule shells consisted of ziprasidone free base (29.5%), tartaric acid (10.0%), carbomer-carbopol 974P (1.0%), lactose monohydrate (44.0%), croscarmellose sodium (7.5%), pregelatinized cornstarch (7.5%) and magnesium stearate (0.5%). Powders were obtained using high-shear granulation and, as a reference, physical mixtures prepared by dry mixing in a laboratory V blender.

Wet granulation was performed in laboratory by high-shear granulator GMX-LAB (Freund-Vector, Marion, IA, USA). The process consisted of a few steps, such as:

a) Dispersing mixture of ziprasidone free base and tartaric acid in acetone using an ultrasonic bath LBS2 4.5Lt (Falc Instruments Treviglio (BG), Italy) for 5 min at a frequency of 59 kHz
b) Adding lactose and croscarmellose sodium to high-shear granulator bowl and blending under the following conditions: initial mixing for 1 min followed by wetting step during which suspension of ziprasidone and tartaric acid in acetone is added (impeller speed—100 rpm, chopper speed—300 rpm) and finally, general granulation for 3 min (impeller speed—1500 rpm, chopper speed—3000 rpm)
c) Drying of the obtained blend in a vacuum dryer SalvisLAB VC-20 (E. Renggli AG, Rotkreuz, Switzerland) at a temperature of 60°C to obtain the humidity of less than 0.5%
d) Homogenisation of the granules by sifting through a sieve with a mesh size of 0.5 mm
e) Extragranular addition of carbomer and cornstarch followed by mixing in laboratory V blender ML-B1109 for 15 min at 15 rpm
f) Addition of magnesium stearate and final mixing in the same blender for 5 min at 15 rpm
g) Filling the obtained powders into hard gelatin capsule shells, white colour, size "1" (Capsugel, Morristown, NJ, USA).

Physical mixtures were prepared in the following steps:

a) Initial mixing of ziprasidone free base with tartaric acid in laboratory V blender ML-B1109 (Kates, Olsztyn, Poland) for 5 min at 15 rpm
b) Addition of other excipients apart from magnesium stearate, *i.e.* carbomer, lactose, croscarmellose sodium and cornstarch and mixing in laboratory V blender for 15 min at 15 rpm
c) Addition of magnesium stearate and final mixing in the same blender for 5 min at 15 rpm
d) Placing the obtained powders in aforementioned hard gelatin capsule shells

Dissolution in Paddle Apparatus

The analysis was performed using paddle dissolution apparatus (USP apparatus II) DT 70 (Erweka GmbH, Heusenstamm, Germany) at 75 rpm and 37°C; 900 mL of 0.1 M hydrochloric acid (pH 1.2) containing 0.05 M NaCl (according to Ph.Eur. 2.9.3.) and 1.5% sodium lauryl sulphate was used as a dissolution medium. Analysis took 60 min with sample acquisition time after 10, 20, 30, 45 and 60 min. At particular points of time, sample solutions were withdrawn through a membrane filter Syringe Filters 0.45 μm (Pall Poland Ltd, Warsaw, Poland) and analyzed with UPLC method (29).

Dissolution in Flow-Through Cell Apparatus (Apparatus IV)

Flow-through cell dissolution apparatus (USP apparatus IV) DFZ 720 (Erweka GmbH, Heusenstamm, Germany) was used. The dissolution conditions are given in Table I. The samples were withdrawn through a membrane filter Pall Acrodisc Syringe Filters 0.45 μm Premium GHP (Pall Poland Ltd., Warsaw, Poland) and analyzed with the UPLC method (29).

Dissolution Stress Test Device Type I

The schematic representation of the device is given in Fig. 1a. Exact description of dissolution stress test device (DSTD) type I apparatus and principle of its work are described elsewhere (25,30–32). The test parameters applied in the present study aimed at simulation of conditions in the upper GI tract in the fasting state. The probe chamber containing the dosage form was placed in 1160 mL of simulated gastric fluid pH 1.2 without enzyme containing 1% Tween20 (according to Ph.Eur. 2.9.3). The dissolution medium was stirred with 100 rpm speed, and the temperature was maintained at 37°C. After 30 min, three 6-s symmetrical pressure waves of 300 mbar each were applied. They were then followed by 1 min rotatory movement of the apparatus axle at 100 rpm. This combination mimics the gastric emptying stage. Subsequently,

Table I. Dissolution Conditions in Flow-Through Cell Apparatus

Cell size	22.6 mm
Configuration	Open loop
Flow rate	8 mL/min
Pulsation	120 pulses/min
Time/dissolution medium	
For 30 min	0.1 M hydrochloric acid (pH 1.2) containing 0.05 M NaCl[a] and 1% Tween20
For 15 min	Acetate buffer pH 4.5 containing 1% Tween20
For 415 min	Phosphate buffer pH 6.8 containing 1% Tween20
Temperature	37±0.5°C
Total analysis time	460 min
Sample acquisition time	10, 20, 30, 40, 70, 100, 160, 220, 340, 460 min

[a] Dissolution medium according to Ph.Eur. 2.9.3

the test was continued under the initial conditions for a further 16 min. The whole analysis time was 46 min with sample acquisition interval equal to 2 min. The determination of the amount of the drug dissolved was performed using UV–vis spectroscopy at the wavelength of 315 nm with Agilent 8453 (Agilent Technologies Inc., Santa Clara, CA, USA) equipped with flow-through quartz cuvettes of 5 mm path length (Hellma GmbH & Co KG, Müllheim, Germany).

Dissolution Stress Test Device Type II

The diagram of the system used during analyses is presented in Fig. 1b. The exact description of DSTD type II

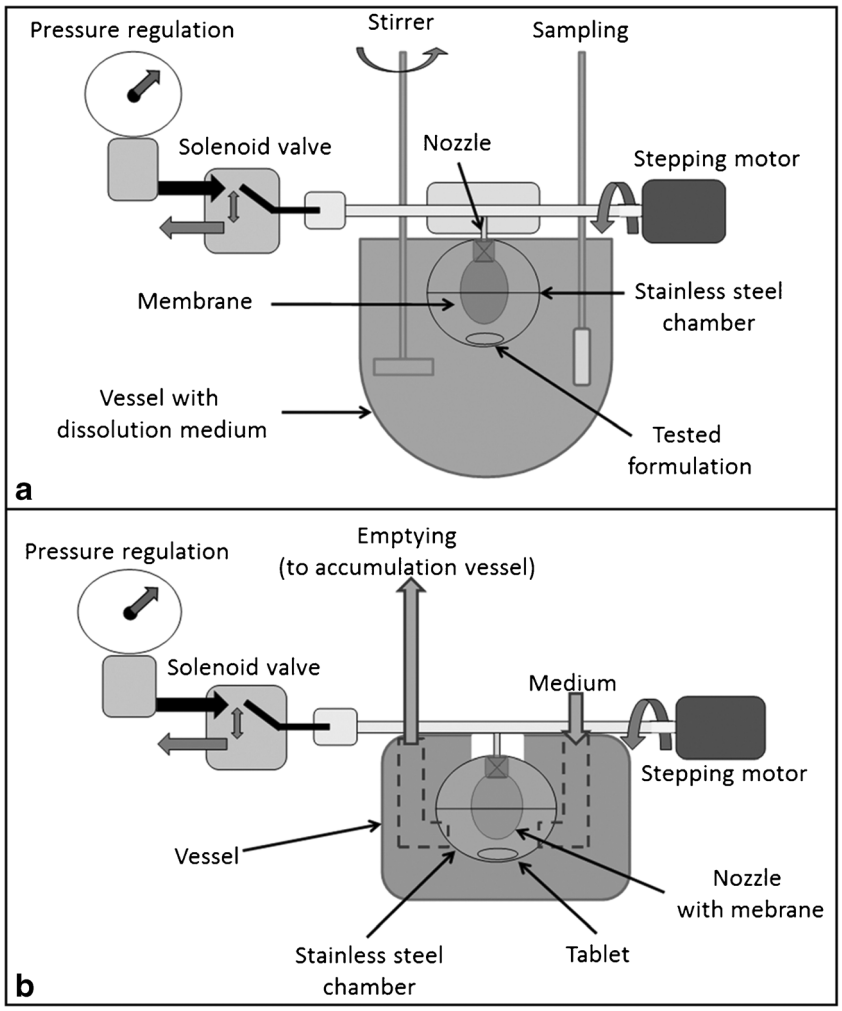

Fig. 1. Comparison of the biorelevant dissolution stress test device type I (DSTD type I) **(a)** and type II (DSTD type II) **(b)** (adopted from (28–32))

apparatus and principle of its work are described elsewhere (27). The tested dosage form was placed in a spherical basket and immersed in flow-through cell containing 50 mL of dissolution medium which simulated gastric fluid, *i.e.* 0.1 M hydrochloric acid pH 1.2 without enzyme containing 1% of Tween20 prepared according to Ph.Eur. 2.9.3. In order to simulate the possible conditions, which are experienced by the dosage forms during the passage through the gastrointestinal tract under fasting conditions, two different stress test programmes were applied. During the first 30 min of experiment, flow rate of dissolution medium amounted to 8.33 mL/min. Such conditions were applied to simulate the zero order gastric emptying kinetics. Within this time preparation was in contact with 250 ml of the liquid. Thereon, a sequence of three 6-s symmetrical pressure waves, of 300 mbar each, was applied, which simulated the gastric emptying. This was followed by a 1-min pendulum-like movement of the apparatus axle at an amplitude of 90° and velocity corresponding to 100 rpm. At that time, the liquid was pumped with flow rate of 24 mL/min. Then, another 50 mL of dissolution medium was introduced into the cell and examination was continued for another 16 min with a flow rate of 4 mL/min. In the second programme, after 10 min of the test, additional 1-s symmetrical pressure wave of 100 mbar was applied. The concentration of the released substance was analyzed using Cary-50 UV–vis spectrophotometer (Varian Inc., Palo Alto, USA) equipped with a multicell holder and fibre optics (2 m length and 1 cm light path) at 315 nm. Analysis time was 46 min with sample acquisition intervals every 2 min.

RESULTS AND DISCUSSION

Confirmation of the Ziprasidone Free Base Amorphisation

During grinding, both in the high-energy planetary ball mill and cryogenic mill, crystalline ziprasidone free base underwent gradual amorphisation. Complete amorphisation of ziprasidone was confirmed with X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) techniques. Figure 2a shows XRPD patterns of milled ziprasidone free base with broad amorphous halo peak and no evidence of sharp diffraction peaks which are indicative for crystalline material. Furthermore, both cryomilled and ball-milled ziprasidone showed a glass transition temperature (Tg) which is characteristic for amorphous substances at about 70–71°C, followed by recrystallization starting from about 102–104°C (Fig. 2b).

Solubility Study

The comparison of solubility of crystalline and amorphous ziprasidone is presented in Table II. It can be observed that amorphous substances demonstrated improved solubility in comparison to their crystalline counterpart. This effect is the most prominent when distillate water and hydrochloric acid solution were used as dissolution media (11). Moreover, it can be observed that in the presence of carboxyl groups (in acetate buffer), solubility of ziprasidone free base improved significantly. In phosphate buffer solutions with pH above 6.8, ziprasidone free base is practically insoluble.

Amorphous form of ziprasidone base, as many other active substances, is markedly more soluble and dissolves faster as compared to the crystalline equivalent (14). In particular, this is true in the environment of pH analogic to the first part of the gastrointestinal tract, *i.e.* the stomach and to some extent the duodenum. Together, these properties give an interesting perspective of increased dissolution rate and in consequence, biological availability, which is particularly important for many drugs BCS class II compounds with a narrow absorption window located in the duodenum such as ziprasidone (33).

Particle Size Distribution—Influence of Grinding Process

The aim of this analysis was to compare particle size distribution of amorphous ziprasidone obtained by ball milling (BM) and cryomilling (CR) as well as to examine the impact of dispersing in acetone and the solvent evaporation on the size distribution and morphology of the drug. The results of the analyses are presented in Fig. 3. It can be observed that upon mechanical milling at both conventional mill and cryomill, micronized particles of ziprasidone are being compressed into larger aggregates (curves depicted as “BM dry dispersion” or “CR dry dispersion”, respectively). As a result, the substances’ particle size is similar to the starting, crystalline material. Such substances contained in solid formulations have significantly reduced surface areas which can further impact their dissolution.

This spontaneous aggregation of ziprasidone can be overcome by dispersing ziprasidone in acetone and evaporation of the suspending agent. In such a way, the substance’s aggregates break down and small individual particles are fully exposed (curves depicted as “BM dispersion in acetone” or “CR dispersion in acetone”).

In the present work, formulations containing amorphous ziprasidone free base were prepared by initial suspension in acetone followed by blending with other excipients. Finally, the suspending agent was evaporated under vacuum. Acetone, used during the process, is regarded as a solvent with low toxic potential (34).

Impact of Applied Technological Unit Operations on Amorphous Ziprasidone

The physical stability of a drug substance is particularly important in the case of amorphous material as it can have a significant impact on the dissolution of these substances from pharmaceutical formulations. The impact of the applied technological unit operations on physical stability of amorphous ziprasidone free base was assessed with XRPD technique. The results of the analyses are presented in Fig. 4. Sharp Bragg peaks characteristic for crystalline ziprasidone free base are not visible on diffraction patterns representing formulations containing cryomilled or ball-milled ziprasidone. The results confirmed that applied unit technological process such as high-shear granulation followed by vacuum drying, mixing and capsulation have not caused crystallization of ziprasidone contained in drug preparations. Furthermore, comparison of XRPD diffraction patterns of analytical placebo and ziprasidone free base showed no interference of peak characteristic

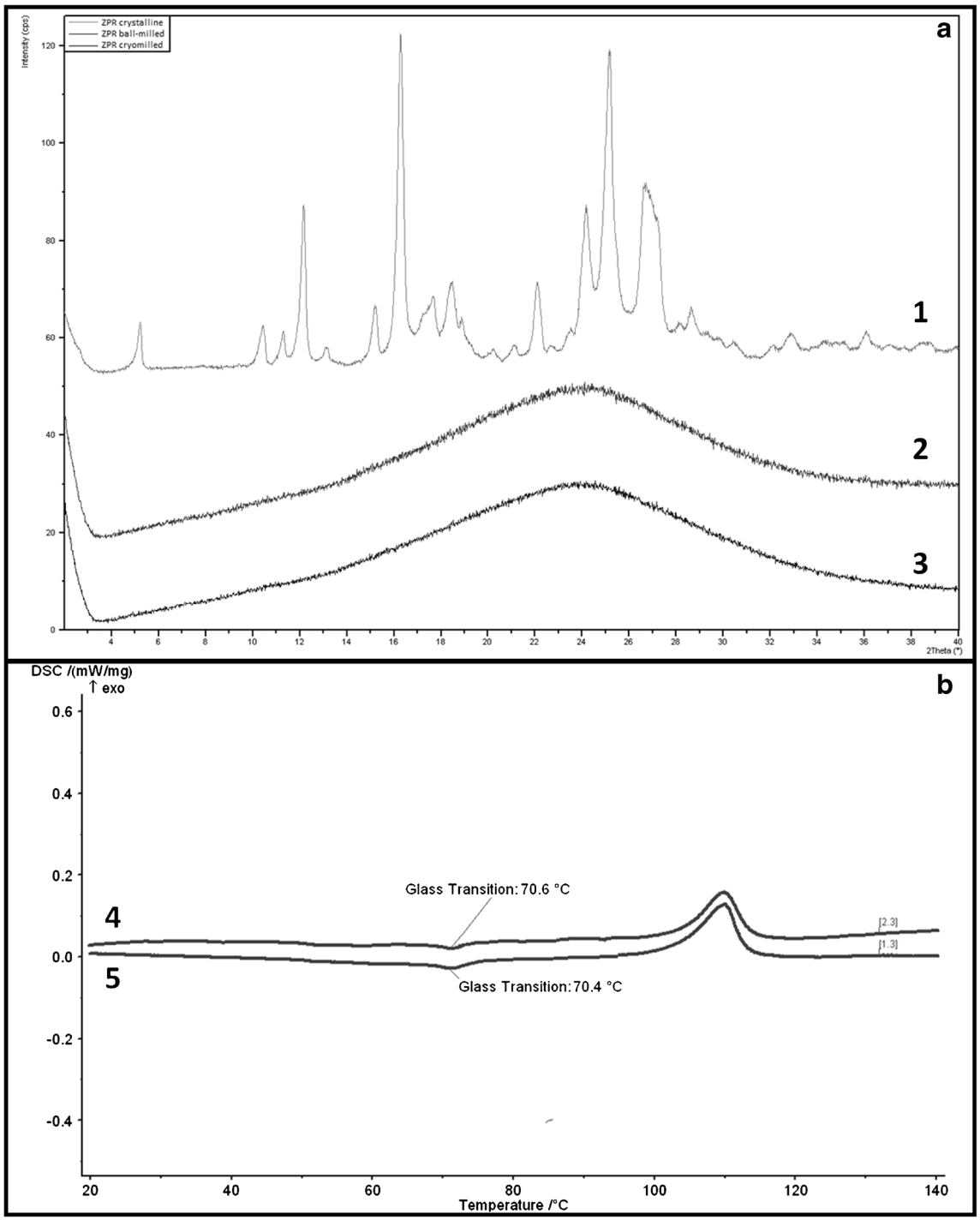

Fig. 2. Confirmation of the ziprasidone free base amorphisation. **a** comparison of XRPD patterns in the scan range 2–40° 2θ of crystalline ziprasidone free base with sharp diffraction peaks (*1*), ball-milled (*2*) oraz cryomilled with broad halo peak characteristic for amorphous substances (*3*). **b** comparison of DSC thermograms of cryomilled (*4*) and ball-milled (*5*) ziprasidone with marked T_g starting from 70–71°C as well as exothermic recrystallization peak starting at about 102–104°C

for excipients used in formulations with diagnostic peaks of the crystalline drug substance.

Dissolution in Paddle Apparatus

The results of the dissolution tests are presented in Fig. 5. The amount of the drug dissolved is given as the percentage of the total amount of the drug contained in the preparation. The obtained dissolution profiles were compared with reference drug product by calculating the similarity factors (f_2) which is commonly used to establish similarity of two dissolution profiles. An f2 value between 50 and 100 indicates similarity between two dissolution profiles (35).

Table II. Comparison of Solubility of Crystalline and Amorphous Ziprasidone Free Base in Aqueous Media in Physiological pH Range at Temperature of 37°C (Mean of Three Measurements±Standard Deviation)

Medium	pH	Solubility [ρ, mg/ml]±SD		
		Crystalline	Cryomilled	Ball-milled
0.1 M Hydrochloric acid[a]	~1.2	$0.006\pm0.045\cdot10^{-2}$	$0.012\pm0.062\cdot10^{-2}$	$0.023\pm0.106\cdot10^{-2}$
Acetate buffer[a]	~4.5	$0.156\pm0.120\cdot10^{-2}$	$0.178\pm0.181\cdot10^{-2}$	$0.184\pm0.198\cdot10^{-2}$
Phosphate buffer[a]	~4.5	$0.006\pm0.053\cdot10^{-2}$	$0.008\pm0.036\cdot10^{-2}$	$0.011\pm0.069\cdot10^{-2}$
Phosphate buffer[a]	~6.8	<0.0001[b]	<0.0001[b]	<0.0001[b]
Phosphate buffer[a]	~7.5	<0.0001[b]	<0.0001[b]	<0.0001[b]
Distilled water	~6.9	$0.0005\pm0.002\cdot10^{-2}$	$0.003\pm0.025\cdot10^{-2}$	$0.004\pm0.036\cdot10^{-2}$

SD standard deviation
[a] Recommended dissolution media according to Ph.Eur. method 2.9.3
[b] Limit of quantification of analytical method according to (27)

Hard gelatin capsules containing physical mixtures of either ball-milled or cryomilled ziprasidone dissolved at a slower rate than the reference drug product. Calculated similarity factor f_2 was very low and amounted to 33. In comparison, formulations prepared by wet granulation, which included amorphous ziprasidone initially suspended in acetone, demonstrated faster dissolution rate. Their release profiles resembled those obtained from the reference product. Values of similarity factor f_2 calculated for ball-milled and cryomilled substance were high and amounted to 55 and 63, respectively. It should be kept in mind that the formulations in the form of physical mixtures contained ziprasidone with relatively big particle size (aggregates) and consequently reduced surface area. During wet granulation process comprising dispersion of the ground substance in acetone, these aggregates were broken down. Consequently, small particles with significantly increased surface area and therefore higher dissolution rate were produced.

Dissolution in Flow-Through Cell Apparatus

In the present study, the dissolution of the amorphous ziprasidone formulations in variable pH conditions, similar to those prevailing in the gastrointestinal tract, was investigated. It should be noted that only preparations with similarity factor f_2 greater than 50 were chosen to be investigated. Similarly to the previous analysis, the results were compared with those obtained for reference hard gelatin capsules.

A study in flow-through cell apparatus was performed by changing the dissolution media (and consequently of pH) in the way that mimics the different sections of the gastrointestinal tract. In the first 30 min of the test, 0.1 M hydrochloric acid at a flow rate of 8 mL/min was applied. Under such conditions, the preparation was in contact with about 240 mL of dissolution medium. This volume reflects the conditions during the bioavailability study, when drug is administrated with one glass of water, *i.e.* about 200–250 mL (35,36). Subsequently, the dissolution medium was changed to acetate buffer solution

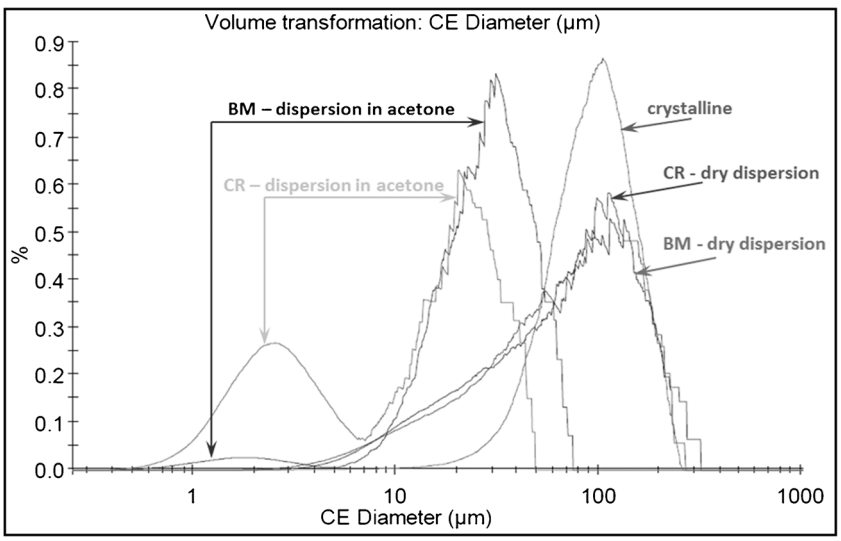

Fig. 3. Comparison of PSD of amorphous ziprasidones (*CR* cryomilled, *BM* ball-milled) and crystalline one analyzed as dry or acetone dispersion (CE Diameter in volume distribution)—for each substance the representative curve of two repeated measurements is given

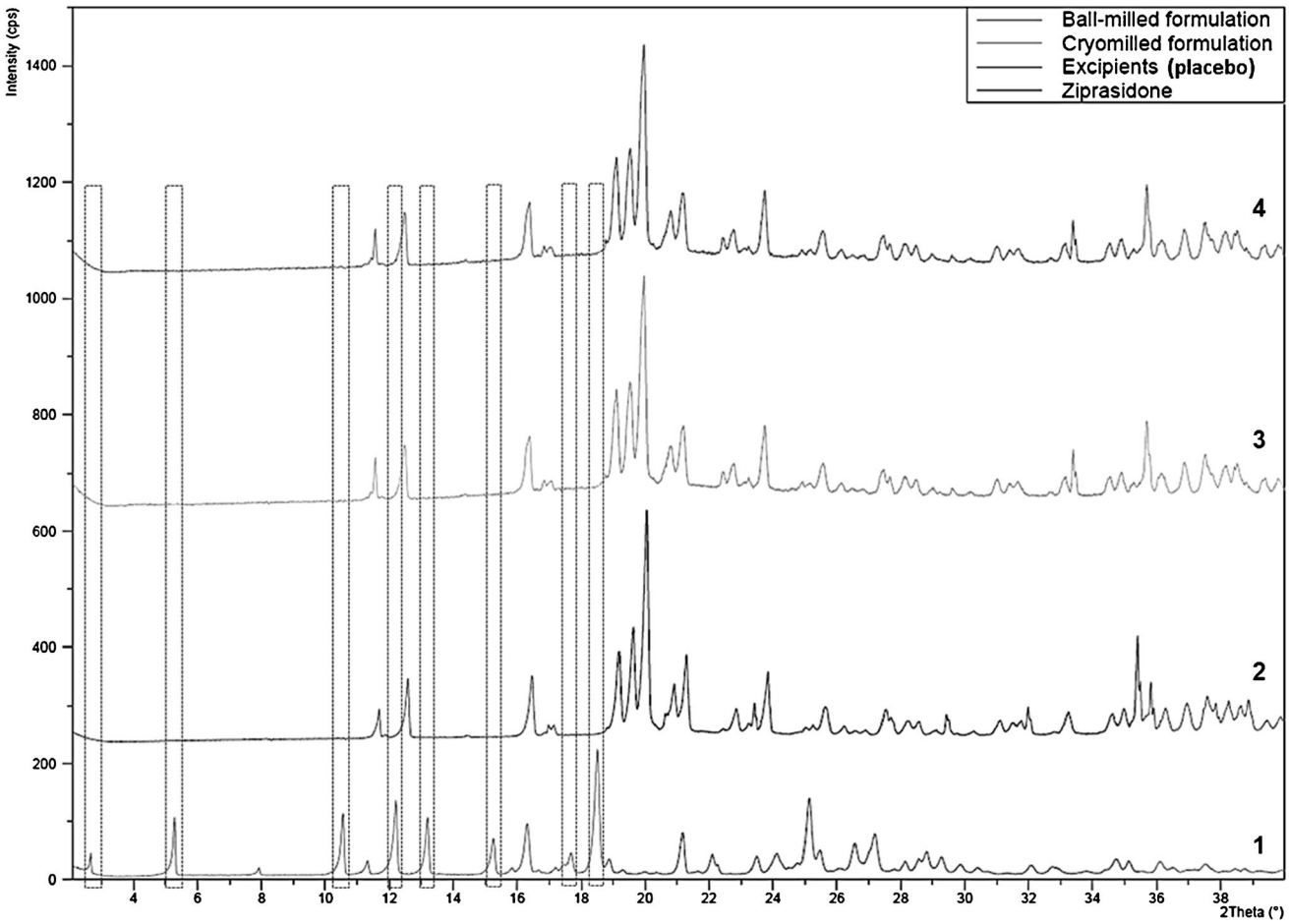

Fig. 4. Comparison of XRPD diffraction patterns of crystalline ziprasidone free base (*1*), mix of excipients–analytical placebo (*2*) and formulations containing cryomilled or ball-milled substance (*3* and *4*, respectively) with the most intensive peaks characteristic for crystalline ziprasidone highlighted

pH 4.5 and the test was continued for another 15 min. Ultimately, in the last stage of the test, phosphate buffer solution pH 6.8 for around 7 h was employed. Based on the literature, we established the time (t_{max}) during which the

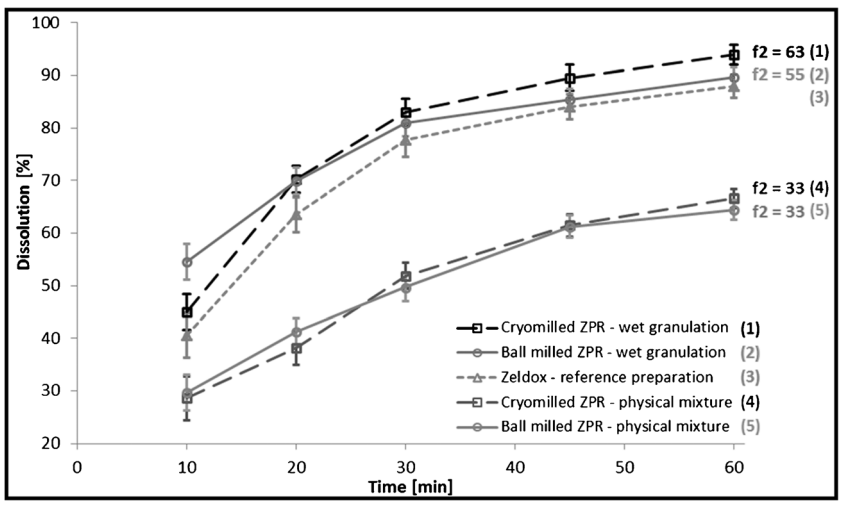

Fig. 5. Comparison of dissolution profiles of different ziprasidone free base formulations tested in paddle apparatus at 75 rpm (0.1 M HCl with 0.05 M NaCl and 1.5% SLS as dissolution medium); results are means of six measurement, SD is given by the *error bars*, the f2 factors are indicated by the *labelling*

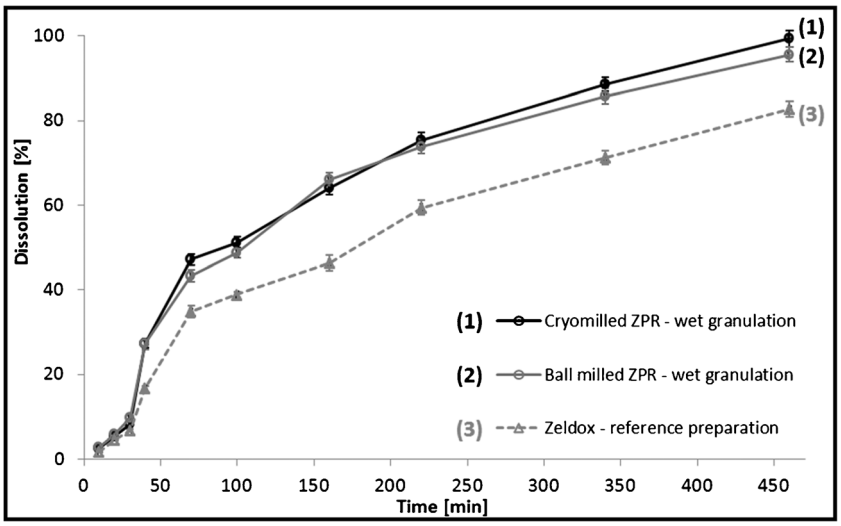

Fig. 6. Comparison of dissolution profiles of different ziprasidone free base formulations tested in flow-through cell apparatus in variable environment (first 30 min pH=1.2, next 15 min pH=4.5, last 415 min pH=6.8); results are means of six measurement, SD is given by the *error bars*

maximum plasma concentration (C_{max}) of ziprasidone was achieved during the bioavailability studies (37,38). The comparison of dissolution profiles obtained for tested amorphous ziprasidone formulation and reference hard gelatin capsules are presented in Fig. 6.

The flow-through cell apparatus tests revealed a large dependence of the ziprasidone dissolution rate on the chemical properties of the dissolution media, simulating the nature of the environment which prevails in different parts of the gastrointestinal tract. In order to compare dissolution rates quantitatively, the slope function of the tangent line to the curves determined in each pH was utilized.

In acidic condition, similar to those in an empty stomach, slope value fell within the range of 0.24–0.35 mg/min. A rapid increase in the dissolution speed can be observed in medium with a pH of 4.5, which imitate conditions in the duodenum. In this environment, the highest value of slope function was recorded (0.68–0.90 mg/min). In the USP phosphate buffer pH 6.8, which was intended to mimic the intestinal pH value, the dissolution proceeded gradually with a rate that was slower than in other media and amounted to 0.13–0.14 mg/min.

Furthermore, it can be observed that the rate of release of amorphous ziprasidone formulations in an acidic environment (pH 1.2) is similar to the reference drug product. When pH of the dissolution medium is increased to 4.5, the dissolution rate of amorphous ziprasidone formulations is higher (slope function value for ball-milled material reached 0.77 mg/min, for

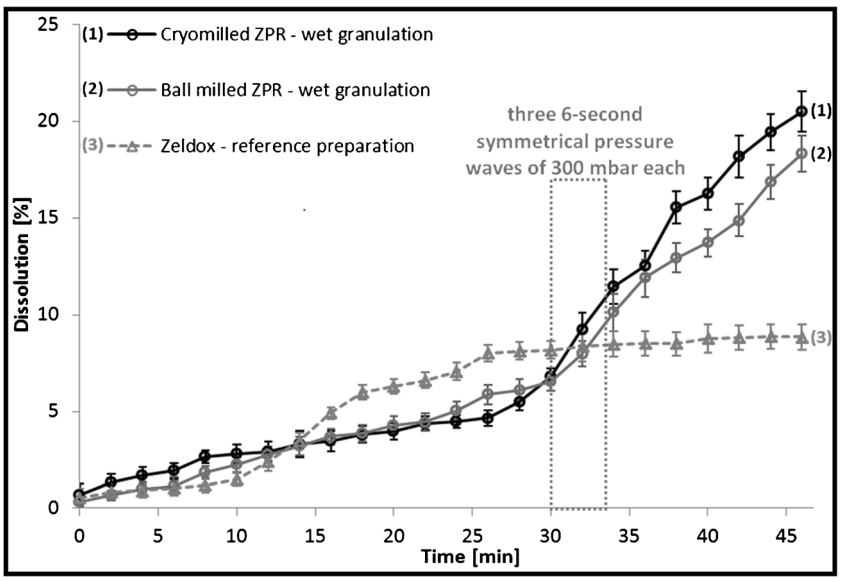

Fig. 7. Comparison of dissolution profiles of amorphous ziprasidone formulations with reference capsules tested in DSTD type I apparatus; results are means of six measurement, SD is given by the *error bars*

cryomilled 0.90 mg/min and for reference product only 0.68 mg/min). In the phosphate buffer pH 6.8, the dissolution rate of all tested preparation is again similar.

Dissolution Stress Tests

The behaviour of the developed formulation and reference drug product in acidic conditions, similar to these prevailing in the stomach (hydrochloric acid medium) was verified thoroughly by means of biorelevant dissolution stress tests.

The results of analyses performed using the DSTD type I apparatus are presented in the Fig. 7. Furthermore, Fig. 8 shows test results obtained using the DSTD type II apparatus. The test results indicate that in the initial phases of dissolution process, under conditions mimicking the fasting stomach, the amount of the drug dissolved in the case of reference preparation is slightly higher than that released from the developed formulations. The mechanical agitation during the simulated gastric emptying increased the dissolution rate of formulations with amorphous ziprasidone. Collating the results obtained both for the reference drug product and amorphous ziprasidone formulation using the biorelevant stress test devices as

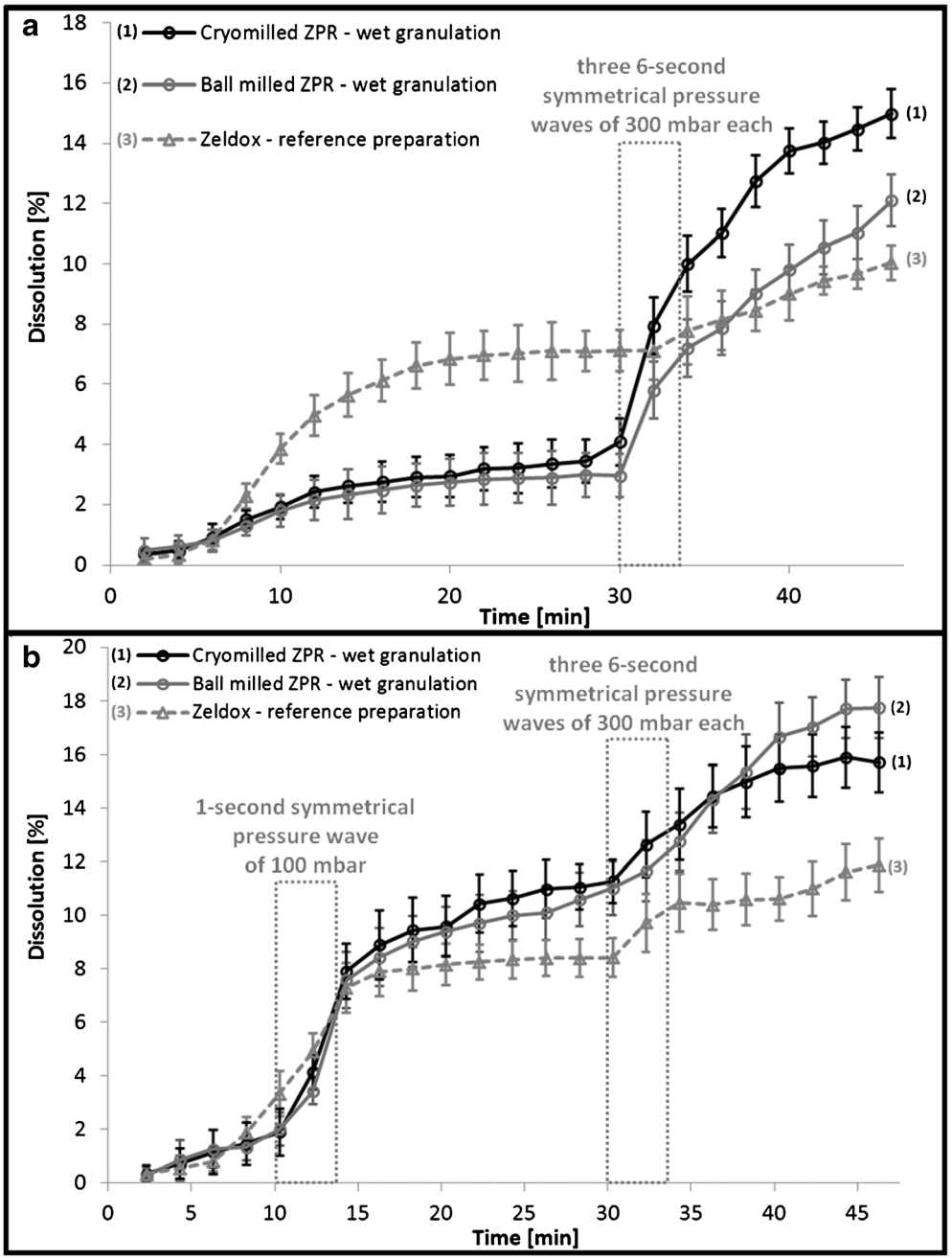

Fig. 8. Comparison of dissolution profiles of amorphous ziprasidone formulations with reference capsules tested in DSTD type II apparatus, programme A (*upper*) and B (*bottom*); results are means of six measurement, SD is given by the *error bars*

well as of the results obtained using the flow-through cell apparatus suggest that the developed formulations are characterized by higher dissolution rate than the originator. Moreover, the pH and mechanical agitation such as movement, mechanical pressure forces and media flow pattern simulating the fasting intragastric conditions cause faster release of amorphous ziprasidone from the formulations.

Therefore, it is likely that *in vivo*, in the duodenum, where the absorption of ziprasidone is the highest (absorption window) and in subsequent parts of the gastrointestinal tract, the bioavailability of the developed formulations containing amorphous ziprasidone free base may be similar or even higher than the one obtained from the reference drug product.

The results presented in this paper suggest that the poor water solubility of ziprasidone free base may be overcome by its amorphisation followed by combining it with a suitable excipient such as tartaric acid. However, we found out that amorphous material obtained by means of milling techniques had a tendency to form agglomerates, which in consequence led to the decrease of surface area and subsequently to slow dissolution rate. Such adverse phenomenon may bring about poor efficiency of amorphous ziprasidone in *in vivo* tests. We found that the crucial issue to overcome this inconvenience is suspending ziprasidone free base in acetone (suspending agent) for the wet granulation.

The dissolution profiles obtained from acidic conditions (pH ~1.2) using the paddle apparatus and corresponding similarity factor f2 (higher than 50) indicate that some of the ziprasidone base formulations and the reference drug product dissolution profiles are comparable. Nevertheless, test simulating the fluctuations of the pH along the gastrointestinal tract revealed that the dissolution rate of amorphous ziprasidone base formulations increased more rapidly than reference capsules when changing the media pH from 1.2 up to 4.5. It should be pointed out that this fact is very important for ziprasidone whose absorption window is located in the duodenum and thus this stage of dissolution (during simulated gastric emptying) was investigated using the dissolution stress test devices. The test results demonstrated how far the drug delivery behaviour of the tested formulations can be impacted by mechanical agitation. As opposed to analyses performed using paddle apparatus, at the beginning of the test, the reference drug product had higher dissolution rate, however, the mechanical agitation simulated as a combination of pressure waves as well as movement increases the dissolution rate of the tested formulations. This effect was predominant in the tests in which an additional pressure wave was simulated at 10 min. It is well recognized that similar forces may act on the formulations during their GI transit. Therefore, they should be taken into account in the comprehensive assessment of the dissolution behaviour of solid oral dosage forms. The results obtained with different dissolution test methods suggest that it is possible to obtain formulations containing ziprasidone free base, whose drug delivery rate will be similar or even faster than product containing ziprasidone hydrochloride salt.

In this study, the authors focused mainly on solubility and dissolution issues, nevertheless short-term stability tests were also performed. During the tests carried out under accelerated conditions (40°C/75% RH), amorphous ziprasidone base proved to be physically unstable and after 3 months, started to crystallize. However, decreasing temperature and relative humidity during storage significantly improved stability of the amorphous material which is a well known phenomenon (39,40). Tested formulations containing amorphous ziprasidone free base stored in refrigerator at a temperature of 5°C were stable for 6 months. Nonetheless, the research concerning physical stabilization of amorphous ziprasidone in pharmaceutical formulations is a further, extensive topic that shall be undertaken.

CONCLUSION

The present work demonstrates the possibility of developing a ziprasidone formulation using free base form with comparable dissolution performance as the commercial product containing hydrochloride salt. Poor water solubility of ziprasidone free base may be overcome by its amorphisation followed by combining it with suitable excipient such as tartaric acid. Nonetheless, it should be taken into account that amorphous material obtained by grinding can form agglomerates which can influence dissolution rate and cause poor efficiency. Such adverse phenomenon may be overcome by application of suitable technological unit processes during drug products preparation.

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