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Research paper

Physicochemical properties of direct compression tablets with spray dried and ball milled solid dispersions of tadalafil in PVP-VA

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ABSTRACT

The aim of this research was to develop immediate release tablets comprising solid dispersion (IRSDTs) of tadalafil (Td) in a vinylpyrrolidone and vinyl acetate block copolymer (PVP-VA), characterized by improved dissolution profiles. The solid dispersion of Td in PVP-VA (Td/PVP-VA) in a weight ratio of 1:1 (w/w) was prepared using two different processes i.e. spray drying and ball milling. While the former process has been well established in the formulation of IRSDTs the latter has not been exploited in these systems yet. Regardless of the preparation method, both Td/PVP-VA solid dispersions were amorphous as confirmed by PXRD, DSC and FTIR. However, different morphology of particles (SEM) resulted in differences in water apparent solubility and disk intrinsic dissolution rate (DIDR). Both solid dispersions and crystalline Td were successfully made into directly compressible tablets at three doses of Td, i.e. 2.5 mg, 10 mg and 20 mg, yielding nine different formulations (D_1–D_9). Each of the lots met the requirements set by Ph.Eur. and was evaluated with respect to appearance, diameter, thickness, mass, hardness, friability, disintegration time and content of Td. IRSDTs performed as supersaturable formulations and had significantly improved water dissolution profiles in comparison with equivalent tablets containing crystalline Td and the marketed formulations. Tablets with both spray dried and ball milled Td/PVP-VA revealed the greatest improvement in dissolution depending on the investigated doses, i.e. 2.5 mg and 20 mg, respectively. Also, dissolution of Td from Td/PVP-VA delivered in different forms occurred in the following order: powders > tablets > capsules.

1. Introduction

Solid dispersions are one of the most promising approaches to the solubility improvement of poorly soluble drug substances, which represent the vast majority of currently investigated drugs [6]. Many research papers published in the last 40 years have described methods of preparation of solid dispersions [23], their physicochemical characteristics [30], classification [14], mechanisms for solubility enhancement [26] and issues related to thermodynamic and kinetic aspects of physical stability [16,11]. Nevertheless, a relatively few groups have moved beyond the preformulation focus of research and aimed to use solid dispersions in the formulation of immediate release oral solid dosage forms [4]. This has been also reflected in the pharmaceutical market where only eight commercial products classified as instant release tablets with solid dispersions (IRSDTs) have been registered to date [25,4].

Difficulty in the preparation of IRSDTs results from a number of obstacles including scale-up limitations, stability issues and changes in dissolution kinetics after compression [4]. While the first limitation is becoming of decreasing importance, as a result of the development of continuous, scalable and applicable processes such as melt extrusion and spray drying [3,20], the lack of physical stability during formulation processes is still a crucial limiting factor. Amorphous systems, which are the most advantageous type of solid dispersions, tend to crystallize not only when exposed to moisture during wet granulation and fluid-bed coating [10] but also under the influence of pressure force when dry compacted or compressed [5,1,12]. Spontaneous crystallization frequently leads to differences in dissolution profiles and might diminish the beneficial effect of amorphous drugs. No release improvement from tablets was observed despite enhancement of the dissolution rate and an increase in apparent solubility might also result from the high content of polymers in tablet cores and their unsuitable selection [9]. Swelling, which is desirable in sustained-release formulations, is a property of polymeric systems and must be reduced in the IRSDTs e.g. by using efficient disintegrants. Additional

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difficulties resulting from the mechanical properties of solid dispersions may be related to poor flowability and compressibility of powders [4].

The aim of this work was to develop directly compressible tablets comprising tadalafil (Td) amorphous solid dispersions prepared in two different processes i.e. spray drying and ball milling and to compare their dissolution profiles. While spray drying has become a well-established and commercially used step for the production of IRSDTs, milling has not been exploited to the same degree yet [4]. Discontinuity and considerable energy consumption of ball milling, depending on the crystal lattice energy of an active substance, can be compensated by lack of thermal degradation and no residual solvents arising from melt extrusion and spray drying, respectively. In this work dissolution profiles of IRSDTs were additionally compared to those of capsules filled with Td solid dispersions and non-encapsulated powders.

Td, a model drug selected for this study, is commonly used in the treatment of erectile dysfunction and pulmonary hypertension. It is a class II molecule of the Biopharmaceutical Classification System, which means that poor solubility in water is a limiting factor of its absorption. Scientific reports on Td solubility improvement include complexation with cyclodextrins [2], incorporation in microporous silica [17], nanoparticles [19], self-nanoemulsifying drug delivery systems [8] and amorphization [27]. The currently available marketed products of Td are conventional tablets containing surfactants and oral gels with extensive efforts being undertaken to develop orodispersible tablets and films. Despite significant efforts to provide appropriate bioavailability of Td the lack of pharmacological response may concern over 40% of patients, as demonstrated in the clinical trial of the first Td drug product – Cialis.

The polymer used for the preparation of spray dried and ball milled Td solid dispersions subjected to compression, as described in this manuscript, was selected based on the prior preformulation studies [28]. That screening, carried out on freeze dried Td solid dispersions prepared using six different polymers, implied that the vinylpyrrolidone and vinyl acetate block copolymer (PVP-VA, Kollidon VA64) is the most promising polymer. This choice was made based on physicochemical analysis of solid state properties and solubility studies of the solid dispersion, as PVP-VA significantly improved Td apparent solubility as well as did not inhibit its intrinsic dissolution rate by swelling. Utilization of Hansen solubility parameters and a film casting method allowed to confirm the good miscibility of these two components.

The weight ratio of Td to PVP-VA in solid dispersions (Td/PVP-VA) subjected to direct compression was chosen based on the work of Wlodarski et al. [29], which was conducted on Td/PVP-VA solid dispersions spray dried in nine different weight ratios and concentrated on investigations of stability of samples with respect to solubility of Td in PVP-VA. The solubility prediction was based on a modified calorimetric protocol [15], which uses the phenomenon of drug crystallization from the supersaturated solid dispersion as well as the Flory-Huggins theory. Thermodynamic solubility of Td in PVP-VA calculated at 25 °C was approximately 20%, which indicated no likelihood of crystallization during tablet formulation with solid dispersions containing 0–20% of Td. Physical stability of non-saturated Td/PVP-VA solid dispersions was subsequently confirmed in accelerated aging tests at elevated temperatures and 0% RH. However, the presence of moisture resulted in the instant crystallization of binary systems with the highest content of hydrophilic PVP-VA. Therefore, the weight ratio of Td to PVP-VA in the solid dispersion selected for tableting was set to 1:1 (w/w) as a compromise between its physical stability at higher temperatures and increased humidity.

Despite the supersaturated nature of Td/PVP-VA (1:1, w/w), this amorphous solid dispersion was not only kinetically stable at ambient conditions but also under the pressure force of 80 kN applied to the surface of 13 mm diameter, which was confirmed by PXRD. This relatively high content of Td prevents from unacceptably large size of tablets, considering doses of Td and necessary excipients. Moreover, lack of significant differences in apparent solubility profiles between Td/PVP-VA solid dispersions differing in quantitative composition supported validity of this selection [28].

This manuscript introduces a third method of preparation of Td/PVP-VA solid dispersions, i.e. ball milling, and extensively describes the formulation approach toward manufacturing of immediate release tablets made by direct compression. The main objective of this research was to develop supersaturable formulations of Td accentuating the influence of spray drying and ball milling processes on the properties of Td solid dispersions that in turn may have an impact on dissolution profiles of tablets.

2. Materials and methods

2.1. Materials

Tadalafil (Td, series 20211) was kindly donated by Polpharma S. A. (Poland) while Cialis 2.5 mg (series C413805) and 10 mg (series C417654), the marketed formulations of Td, were purchased from Eli Lilly (USA). Vinylpyrrolidone and vinyl acetate block copolymer (PVP-VA, Kollidon VA 64), polyvinylpyrrolidone (PVP, Kollidon K30), cross-linked polyvinylpyrrolidone with particle size of 110–130 μm (PVP CL, Kollidon CL), 20–40 μm (PVP CL F, Kollidon CL F) and 10–30 μm (PVP CL SF, Kollidon CL SF) were kindly donated by BASF SE (Germany). Agglomerated lactose (Tablettose 80), croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate (Vivastar) and potato starch were purchased from Meggle (Germany), FMC Biopolymer (USA), Rottenmaier (Germany) and BEST CFS SJ (Poland), respectively. Ultrapure water was produced by a Millipore Direct-Q 3UV-R water purification system while microcrystalline cellulose (Avicel PH 101), magnesium stearate, talc, acetone and all other chemicals of analytical grade were purchased from Sigma-Aldrich (Germany).

2.2. Methods

2.2.1. Preparation of samples

2.2.1.1. Preparation of tadalafil solid dispersion using spray drying. The Td/PVP-VA (1:1, w/w) solid dispersion was obtained by spray drying of a solution (acetone/water 9:1, v/v) containing Td and PVP-VA at a total concentration of 1% (w/v). The process was performed in a Mini Spray Dryer B-290 (Büchi, Switzerland) using an open, suction mode with nitrogen. The gas inlet pressure was 6 bar and set to 4 cm of the gas flow (rotameter setting). Spray dryer was equipped with a standard atomization nozzle with a 1.5-mm cap and a 0.7-mm tip. The pump speed was set to 25% (7 ml/min) and the aspirator was operated at 100%. The inlet temperature was set to 65 °C and such setup resulted in an outlet temperature of 52 °C. Additionally, Td 1% (w/v) solution (acetone/water 9:1, v/v) was spray dried following the above procedure. Spray dried powders were sieved through a Retsch sieve with 200 μm mesh diameter before all experiments.

2.2.1.2. Preparation of tadalafil solid dispersion using ball milling. The Td/PVP-VA (1:1, w/w) solid dispersion was obtained by milling in a planetary ball mill PM 100 (Retsch, Germany) at 3 °C. The effective grinding time was 5 h at 600 rpm with 10-min breaks every 0.5 h. A quantity of 2 g of powder was loaded to the stainless steel container, which had a volume of 50 ml, and three stainless steel balls (20 mm in diameter, 32 g each) were used for a milling

experiment. The powder was sieved through a Retsch sieve with 200 μm mesh diameter before all experiments.

For simplicity, the Td/PVP-VA abbreviation used in this work always refers to the 1:1 weight ratio of Td to PVP-VA in a solid dispersion.

2.2.1.3. Preparation of tadalafil physical mixtures. Td and PVP-VA (1:1 and 1:9, w/w) physical mixtures were prepared by milling in a planetary ball mill PM 100 (Retsch, Germany) at 400 rpm for 10 min. A quantity of 2 g of powder was loaded to the stainless steel container, which had a volume of 50 ml, and three stainless steel balls (20 mm in diameter, 32 g each) were used for milling experiments.

2.2.2. Solid-state characterization

Solid state characterization by powder X-ray diffraction analysis (PXRD), Scanning electron microscopy analysis (SEM) and Fourier transform infrared spectroscopy (FTIR) were performed according to the method described by Wlodarski et al. [29]. Differential scanning calorimetry (DSC) of samples was investigated in the temperature range of 25–350 °C at a heating rate of 10 °C/min according to the method described by Wlodarski et al. [29] for conventional DSC.

2.2.3. Solubility studies

2.2.3.1. Apparent solubility investigation. Apparent solubility of samples was investigated according to the method described by Wlodarski et al. [28].

2.2.3.2. Disk intrinsic dissolution rate (DIDR) study. The study of intrinsic dissolution rate was carried out according to the method described by Wlodarski et al. [28].

2.2.3.3. Standard dissolution test of capsules filled with tadalafil solid dispersions. The standard dissolution test was carried out on hard gelatine capsules (size 0) filled with either 5 mg or 20 mg of Td/PVP-VA solid dispersion and equivalent amounts of crystalline Td (2.5 mg and 10 mg, respectively). Capsules embedded in metal sinkers were placed in 900 ml of purified water at 37 °C in the dissolution basket apparatus (DIS 6000 Copley, Germany) with a paddle speed of 75 rpm. Samples were withdrawn at specified time intervals over 1 h, filtered and quantitatively diluted with acetonitrile (1:1, v/v). This study was carried out in triplicate for each sample and each replicate value was based on the averaged result of two HPLC injections, as described by Wlodarski et al. [28].

Additionally, dissolution studies on non-encapsulated powders were carried out using the dissolution paddle apparatus (DIS 6000 Copley, Germany) and following the procedure described above.

2.2.4. Preparation of tablet blends and the tableting process

2.2.4.1. Preparation of tadalafil tablet blends. Composition of each of seven tablet formulations (A-G) containing crystalline Td (2.5 mg dose) and different disintegrants as well as selected D formulations (D_1–D_9) with crystalline Td and Td/PVP-VA solid dispersions (Td doses of 2.5, 10 and 20 mg) are presented in Tables 1 and 2, respectively. Td, Td-PVP-VA solid dispersions and other excipients were sieved through a Retsch sieve with 200 μm mesh diameter and weighted. The material without lubricants was stirred in a porcelain dish for 5 min followed by further 2-min stirring upon the addition of talc and magnesium stearate.

2.2.4.2. Tableting process. Compression of tablet blends was performed using a single station tablet press XP1 (Korsch, Germany) using concave punches, 7 mm in diameter. The pressure force applied on an upper and lower punch was approximately 5 kN, while the tablet weight was set to 140 mg.

Table 1
Composition and disintegration time of seven tablet formulations containing crystalline Td and different disintegration agents.

Substance	Content (mg) of compounds in one tablet (140 mg)						
	A	B	C	D	E	F	G
Tadalafil	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tablettose 80	97.8	97.8	97.8	97.8	97.8	97.8	97.8
Avicel PH 101	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Potato starch	7.0	–	–	–	–	–	–
Vivastar	–	7.0	–	–	–	–	–
PVP	–	–	7.0	–	–	–	–
PVP CL	–	–	–	7.0	–	–	–
PVP CL F	–	–	–	–	7.0	–	–
PVP CL SF	–	–	–	–	–	7.0	–
Ac-Di-Sol	–	–	–	–	–	–	7.0
Talc	7.0	7.0	7.0	7.0	7.0	7.0	7.0
Mg stearate	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Disintegration time (s)	25	25	55	19	25	21	30

Table 2
Composition of nine tablet formulations comprising crystalline Td, spray dried and ball milled Td/PVP-VA solid dispersions at three different doses of Td, i.e. 2.5 mg, 10 mg and 20 mg.

Substance	Content (mg) of compounds in one tablet (140 mg)					
	D_1	D_2	D_3	$D_{4,7}$[a]	$D_{5,8}$[a]	$D_{6,9}$[a]
Tadalafil	2.5	10.0	20.0	–	–	–
Td/PVP-VA	–	–	–	5.0	20.0	40.0
Tablettose 80	97.8	90.3	80.3	95.3	80.3	60.3
Avicel PH 101	25.0	25.0	25.0	25.0	25.0	25.0
PVP CL	7.0	7.0	7.0	7.0	7.0	7.0
Talc	7.0	7.0	7.0	7.0	7.0	7.0
Mg stearate	0.7	0.7	0.7	0.7	0.7	0.7

[a] Formulations with spray dried (D_4, D_5, D_6) and ball milled (D_7, D_8, D_9) Td/PVP-VA solid dispersion.

2.2.5. Physicochemical properties of tablets

2.2.5.1. Weight, thickness and diameter uniformity of tablets. Weight uniformity of the tablets D_1–D_9 was measured based on the method described in Ph.Eur. 8. The thickness and diameter were measured on 20 randomly selected tablets to the nearest 0.01 mm using a hardness tester TBH 125 (Erweka, Germany). All measurements were followed by calculation of mean values and standard deviations (SD).

2.2.5.2. Hardness, friability and disintegration time of tablets. All measurements for the tablets D_1–D_9 were performed according to the methods described in Ph.Eur. 8. Hardness of tablets was measured using the hardness tester TBH 125 and expressed as a mean value with SD. The friability test was performed using a friability tester TAR 120 (Erweka, Germany), while the disintegration time was measured in distilled water at 37 °C using a disintegration apparatus ZT 221 (Erweka, Germany) at 30 strokes/min.

2.2.5.3. Uniformity of tadalafil content in tablets. Uniformity of Td content in the tablets D_1–D_9 was measured according to the method described in Ph.Eur 8. Briefly, each of randomly selected 10 tablets from the formulation was pulverized in a mortar, and an amount of powder nominally equivalent to 0.25 mg of Td (1.75, 3.5 and 14 mg of powder for tablets with 20, 10 and 2.5 mg Td dose, respectively) was transferred to a 5 ml volumetric flask and quantitatively dissolved in a mixture of acetonitrile and phosphate buffer pH 6.0 (55:45, v/v). The resulting suspension was sonicated for 15 min and filtered through a 0.45 μm membrane syringe filter. The concentration of Td was determined using

a developed and validated high performance liquid chromatography (HPLC) method, as described by Wlodarski et al. [28]. The content of Td in tablets was expressed as the mean percent of the declared dose and SD.

2.2.5.4. Release studies. The dissolution study for the tablets D_1-D_9 was conducted in 900 ml of purified water at 37 °C with a paddle speed of 75 rpm in the dissolution paddle apparatus DIS 6000. Samples were withdrawn at specified time intervals over 1 h, filtered and quantitatively diluted with acetonitrile (1:1, v/v). This study was carried out in sextuplicate for each formulation with each replicate based on the averaged result of two injections and HPLC analysis, as described by Wlodarski et al. [28]. Additionally, the marketed formulations, Cialis, at two different Td doses, i.e. 2.5 and 10 mg, were subjected to the same test conditions.

In addition to water, tablets D_1, D_4 and D_7 (containing 2.5 mg of Td each) were also subjected to dissolution studies in 0.1 M hydrochloric acid and phosphate buffer pH 6.8.

3. Results and discussion

3.1. Solid state characterization

Since the solid state of the spray dried Td/PVP-VA solid dispersion was already thoroughly characterized and presented in one of our previous works [29], the attention here was paid to the ball milled powder and a comparative evaluation of both systems. Spray drying efficiency in obtaining homogenous amorphous samples has been already repeatedly demonstrated [20], in contrary to milling, which has not been regarded as the process of choice for this purpose. Our intention was to obtain amorphous solid dispersions which could be subsequently used in the formulation of tablets.

Both processes implemented to prepare the Td/PVP-VA solid dispersion yielded amorphous binary systems as revealed by the disappearance of Bragg peaks characteristic of crystalline Td in the X-ray diffractometric analysis (Fig. 1). The 5-h milling time required to amorphize the blend of crystalline Td and PVP-VA was significantly shorter when compared to the 24-h amorphization time of crystalline Td without a polymer [27]. This means that the presence of PVP-VA contributed not only to the mechanical destruction of Td crystal lattice but also additional events such as dissolution of Td molecules in PVP-VA occurred. The Bragg peaks visible for a Td and PVP-VA physical mixture (1:9, w/w) indicated that at least 10% content of crystalline Td could be detected by the applied diffractometer (Fig. 1).

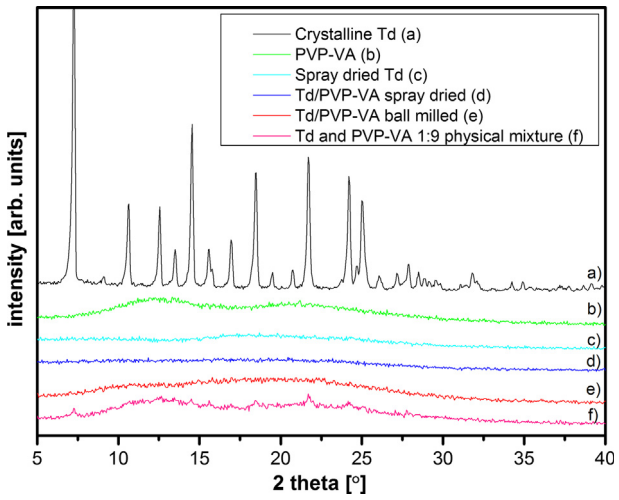

Fig. 1. X-ray powder diffraction patterns of crystalline Td (a), PVP-VA (b), spray dried Td (c), spray dried Td/PVP-VA solid dispersion (d), ball milled Td/PVP-VA solid dispersion (e), Td and PVP-VA (1:9, w/w) physical mixture (f).

The ball milled Td/PVP-VA solid dispersion took a form of a brown, free-flowing powder as opposed to the white fluffy spray dried Td/PVP-VA particles. The same color change from white to brown was previously observed for pure crystalline Td when subjected to a 24-h ball milling [27]. SEM confirmed the lack of Td crystals remaining in the ball milled Td/PVP-VA solid dispersion and revealed the presence of irregular particles characteristic of milled materials, much larger in size than those spray dried (Fig. 2).

A DSC thermogram of the ball milled Td/PVP-VA solid dispersion is presented in Fig. 3. Briefly, there was a single T_g at 129.5 ± 0.2 °C followed by the exothermic event of Td crystallization with an onset at 182.1 ± 0.3 °C and an endothermic peak of Td melting/dissolution in PVP-VA. A single T_g of this system, occurring between T_gs of neat PVP-VA and spray dried amorphous Td, reveals the existence of a molecular level amorphous solid dispersion [22], while the crystallization event confirms its supersaturated nature. A calorimetric measurement carried out on spray dried Td/PVP-VA solid dispersion revealed a similar thermal behavior as for the ball milled sample. The T_g located at the same temperature (129.3 ± 0.3 °C) indicated that homogenous Td/PVP-VA solid dispersions were formed in both processes. The only difference was a wide endothermic event observed in the range of 50–100 °C for the ball milled Td/PVP-VA solid dispersion, indicating a higher moisture content of this sample.

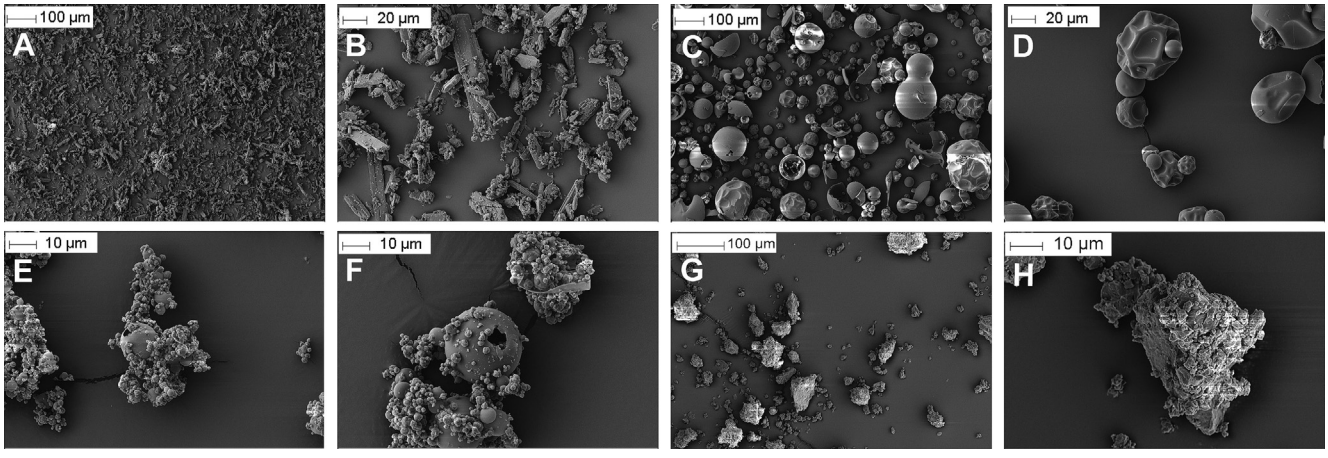

Fig. 2. SEM images of crystalline Td (A, B), PVP-VA (C, D), spray dried Td/PVP-VA solid dispersion (E, F) and ball milled Td/PVP-VA solid dispersion (G, H).

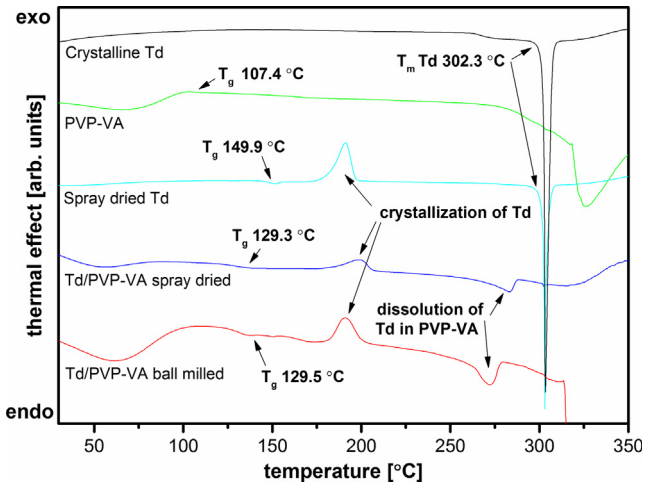

Fig. 3. DSC thermograms of crystalline Td, PVP-VA, spray dried Td, spray dried Td/PVP-VA solid dispersion and ball milled Td/PVP-VA solid dispersion obtained at a heating rate of 10 °C/min.

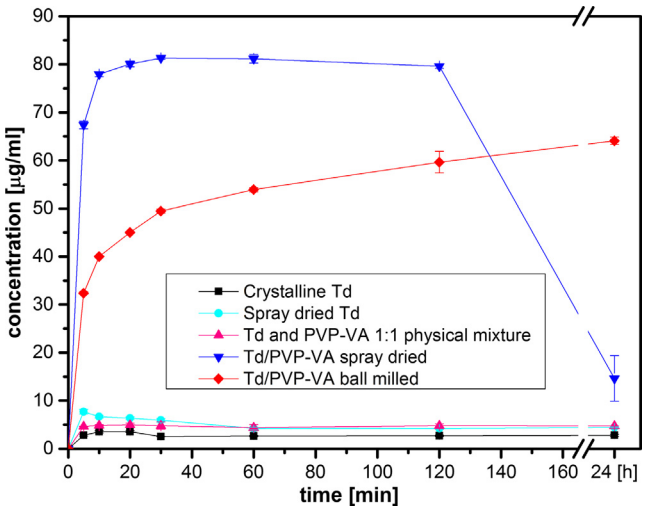

Fig. 5. Apparent solubility study of crystalline Td, spray dried Td, Td and PVP-VA (1:1, w/w) physical mixture, spray dried Td/PVP-VA solid dispersion and ball milled Td/PVP-VA solid dispersion.

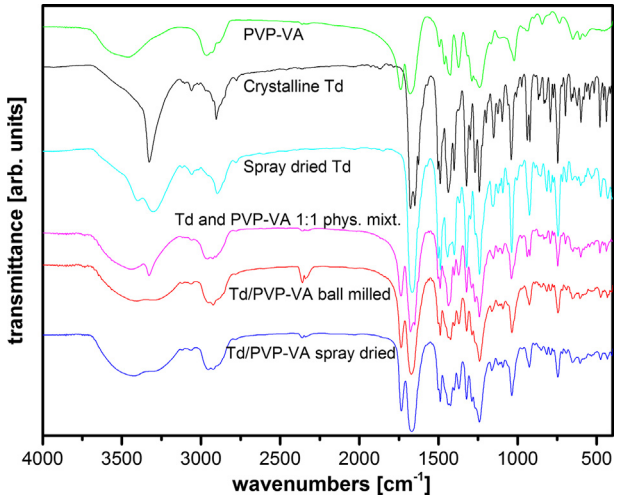

Fig. 4. IR spectra of PVP-VA, crystalline Td, spray dried Td, Td and PVP-VA (1:1, w/w) physical mixture, ball milled Td/PVP-VA solid dispersion and spray dried Td/PVP-VA solid dispersion.

The difference in the water content did not have a significant impact on FTIR spectra of both amorphous systems, similarity of which was ultimately confirmed by this spectroscopic method (Fig. 4). In both cases the signal of a stretching vibration of the Td amine group was broadened and shifted from 3326 cm^{-1}, characteristic of crystalline Td, toward lower wave numbers. The double signal of Td carbonyl groups observed at 1676 cm^{-1} and 1649 cm^{-1} for the crystalline drug was distorted indicating the possible formation of intra-hydrogen bonds between the amine and carbonyl groups of Td as well as inter-H-bonds between Td molecules and PVP-VA chains. These changes were not apparent in the corresponding physical mixture of Td and PVP-VA (1:1, w/w), confirming the formation of new physical entity of Td and PVP-VA blends upon spray drying and ball milling.

3.2. Solubility studies

The ability to create a supersaturated aqueous solution is one of the most valuable features of amorphous solid dispersions desirable when developing formulations of poorly soluble drug substances. A decrease in the drug particle size to molecular dimensions, breaking the strong crystal lattice and wetting activity of polymers are thought to be responsible for this phenomenon [26]. Both Td/PVP-VA solid dispersions yielded a significant but different improvement in Td apparent solubility in comparison with thermodynamic solubility of the crystalline drug (3 μg/ml) as well as the Td and PVP-VA (1:1, w/w) physical mixture (Fig. 5). The concentrations of Td in water after 1 h of solubility studies were 82 μg/ml and 54 μg/ml for the spray dried and ball milled solid dispersion, respectively. The supersaturation levels of both samples were roughly stable throughout the first 2 h of the study. However, for the spray dried solid dispersion a substantial decrease in the concentration of Td to 14 μg/ml was observed after 24 h, while for the ball milled system a slight increase to 63 μg/ml occurred after this time.

As both Td/PVP-VA solid dispersions had the same solid state characteristics, which have been confirmed by diffractometric, thermal and spectroscopic studies, differences in the apparent solubility profiles might have resulted from the different size and shapes of Td/PVP-VA particles (Fig. 2). Spray drying led to the formation of round and small (approximately 10 μm) particles, which facilitated the dissolution process and allowed to obtain higher water supersaturation in the initial phase of the study in comparison with the ball milled system (approximately 20 μg/ml difference at the 2 h time point). However, this greater level of supersaturation resulted in more rapid de-supersaturation due to extensive spontaneous nucleation, crystallization and thereby a decrease of drug concentration in the solution [18,24]. The particles of the ball milled Td/PVP-VA were approximately 50 μm in size and yielded lower supersaturation, which was constantly growing throughout 24 h.

Results of the next investigation, i.e. the intrinsic dissolution rate study, depicted as concentration and dissolution rate changes over time are shown on the upper (A) and lower (B) part of Fig. 6, respectively. This experiment allowed to compare the flux rates of Td molecules from solid dispersions to water having eliminated the influence of surface area of powders by their compression. The spray dried and ball milled Td/PVP-VA solid dispersions showed a significant improvement in the Td dissolution rate when compared to crystalline Td. Concentrations of Td obtained after 2 h of study were 0.06 μg/ml, 0.46 μg/ml and 0.6 μg/ml for crystalline Td, spray dried and ball milled Td/PVP-VA solid dispersion, respectively (Fig. 6A). A 10-fold (0.15 μg cm^{-2} s^{-1}) and an 8-fold

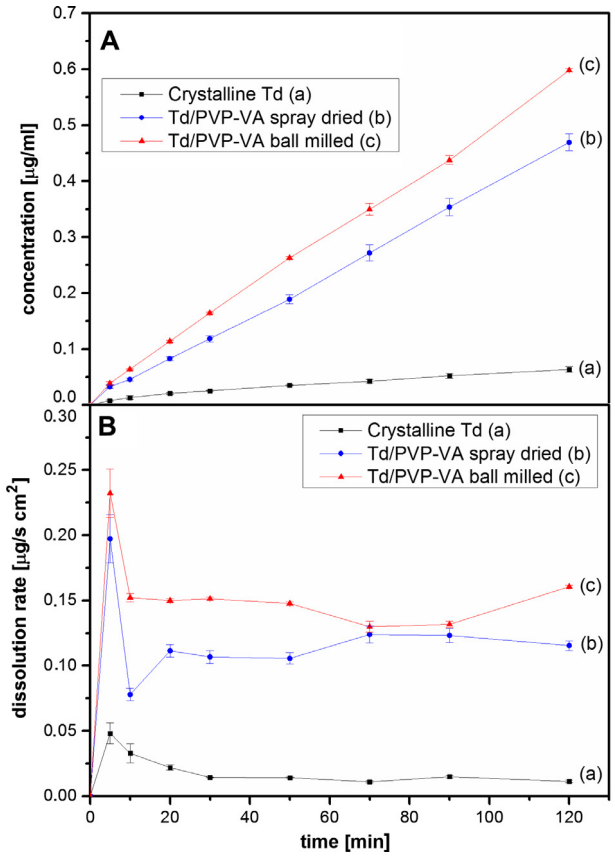

Fig. 6. Disk intrinsic dissolution rate study of crystalline Td, spray dried Td/PVP-VA solid dispersion and ball milled Td/PVP-VA solid dispersion depicted as Td concentration (A) and dissolution rate (B) changes.

(0.12 µg cm^{-2} s^{-1}) increase in the Td dissolution rate was achieved in comparison with crystalline Td (0.015 µg cm^{-2} s^{-1}) with the ball milled and spray dried Td/PVP-VA solid dispersion, respectively. The relatively unchanging flux of Td molecules throughout the entire study period indicated a probable lack of PVP-VA swelling and no inhibitory effect of this polymeric matrix on Td dissolution.

Nevertheless, these results were inconsistent with the above results study on Td apparent solubility presenting a higher concentration of Td achieved after a shorter time in the case of the spray dried solid dispersion. It is possible that under the influence of pressure and possible plastic deformation, the previously seen effect of yielding a higher supersaturation in comparison with the ball milled equivalent sample has become secondary. This effect might be especially important with respect to IRSDTs prepared by direct compression.

3.3. Tablets with Td/PVP-VA solid dispersion

3.3.1. Tableting process and physicochemical properties of tablets

After the preformulation studies both Td/PVP-VA solid dispersions and crystalline Td were used to formulate directly compressible tablets. Tablettose 80 and Avicel PH 101 were selected as bulking and binding agents due to their good wettability. It has been demonstrated that water-soluble fillers, like mannitol and lactose, in combination with microcrystalline cellulose of preferably small particle size can hinder the formation of gelling polymer network, which is especially important for instant release formulations with amorphous drugs [7,13]. To ensure quick disintegration of tablets, seven formulations (A-G) with crystalline Td and different disintegrant agents were additionally produced (Table 1). All of the tablet batches were comparable in respect to the average diameter, thickness, mass, hardness and friability (data not presented), which enabled to assess the impact of different excipients. There were only small differences in disintegration of tablets which occurred always within the first minute (Table 1) and hence PVP CL was chosen for further research. This polymer used in small quantities in tablet formulations may additionally enhance dissolution of poorly soluble drug substances, as stated by the manufacturer.

The final composition of formulations with amorphous solid dispersions subjected to detailed physicochemical analysis is presented in Table 2. A combination of three different doses of Td, i.e. 2.5 mg, 10 mg and 20 mg, with the three different forms of Td: spray dried Td/PVP-VA, ball milled Td/PVP-VA and crystalline Td resulted in nine different tablet formulations (D_1–D_9). The doses contained in tablets corresponded to those available on the market so that dissolution profiles could be compared. This design gave the opportunity to assess the possible appearance of supersaturated concentrations of Td in release media. Considering thermodynamic solubility of Td in water (3 µg/ml), the entire dose of 2.5 mg tablets could be theoretically dissolved, however without the maintenance of sink conditions, in the volume of water used for dissolution studies (900 ml), while the release of Td from 10 mg and 20 mg tablets might be inhibited by the drug reaching saturation in 900 ml of water.

Direct compression of the Td/PVP-VA solid dispersion regardless of its preparation method, i.e. spray drying and ball milling, turned out to be a simple and effective method to produce IRSDTs. Both amorphous solid dispersions could be easily mixed with excipients and the final blends were characterized by good flowability. Sieving through a sieve before mixing was especially important for the ball milled solid dispersion since its relatively large particles could not be homogenously combined with other powders. The tableting process proceeded equally efficiently for all blends regardless of the physical form and dose of Td, which was confirmed by repetitive pouring into the die, no capping and adhesion of blends to the punches and acceptable appearance of tablets. It should be highlighted that 20 mg tablets contained 40 mg of Td/PVP-VA solid dispersion, which constituted almost 30% content of the total tablet weight.

All tablet formulations fulfilled requirements set by the Ph.Eur. and were comparable with respect to one another regarding the physical properties. The diameters and thicknesses of tablets were around 7 mm and 3 mm, respectively. The weight was set to around 140 mg which, applying the compression force of 5 kN, resulted in hardness of around 100 N and acceptable friability below 1%. Disintegration of tablets occurred practically immediately upon contact with water except for the formulation D6 with 20 mg of spray dried Td/PVP-VA solid dispersion, which disintegrated after 4 min. Relative standard deviation of the content of Td in tablets was never greater than 15% (Ph.Eur. 2.9.6), regarding the nominal content of Td (Table 3). The adequate content uniformity was additionally confirmed by applying the Ph.Eur. 2.9.40 protocol and none of the acceptance values (AV) calculated for all formulations was higher than 15.0.

3.3.2. Release studies

In general, all tablets with Td/PVP-VA solid dispersions subjected to dissolution study in the paddle apparatus successfully revealed a significant enhancement in Td release when compared to tablets containing crystalline Td (Fig. 7).

In the case of 2.5 mg Td dose (Fig. 7A), where theoretically the entire amount of Td could be dissolved, tablets with the spray dried Td/PVP-VA solid dispersion were the only formulation, which released more than 85% of Td after 45 min. The tablets with the ball milled Td/PVP-VA solid dispersion and crystalline Td released only

Table 3
Physicochemical properties of tablet D formulations.

D formulations	Tablet parameters						
	Diameter (mm)	Thickness (mm)	Mass (mg)	Hardness (N)	Friability (%)	Disintegration time (s)	Td content (%)
D1	6.98 ± 0.06	3.11 ± 0.03	139.3 ± 3.0	104.7 ± 10.1	0.07	11	89.5 ± 1.4
D2	6.98 ± 0.01	3.12 ± 0.04	140.7 ± 2.4	108.8 ± 13.4	0.14	14	92.2 ± 0.6
D3	6.98 ± 0.00	3.11 ± 0.02	139.3 ± 2.3	121.5 ± 6.5	0.14	14	92.7 ± 4.3
D4	6.97 ± 0.01	3.11 ± 0.06	140.1 ± 3.5	126.1 ± 9.8	0.07	18	93.0 ± 1.3
D5	6.97 ± 0.00	3.30 ± 0.05	140.2 ± 2.1	103.0 ± 17.1	0.07	21	93.0 ± 3.9
D6	6.96 ± 0.00	3.45 ± 0.01	140.2 ± 1.6	105.1 ± 6.15	0.14	255	100.9 ± 11.5
D7	6.97 ± 0.00	3.14 ± 0.01	140.3 ± 1.8	114.8 ± 4.87	0.21	9	90.0 ± 4.0
D8	6.98 ± 0.02	3.19 ± 0.02	138.3 ± 1.5	105.3 ± 12.58	0.07	11	86.4 ± 1.7
D9	6.96 ± 0.00	3.36 ± 0.01	140.2 ± 1.5	109.4 ± 6.0	0.14	13	89.8 ± 6.7

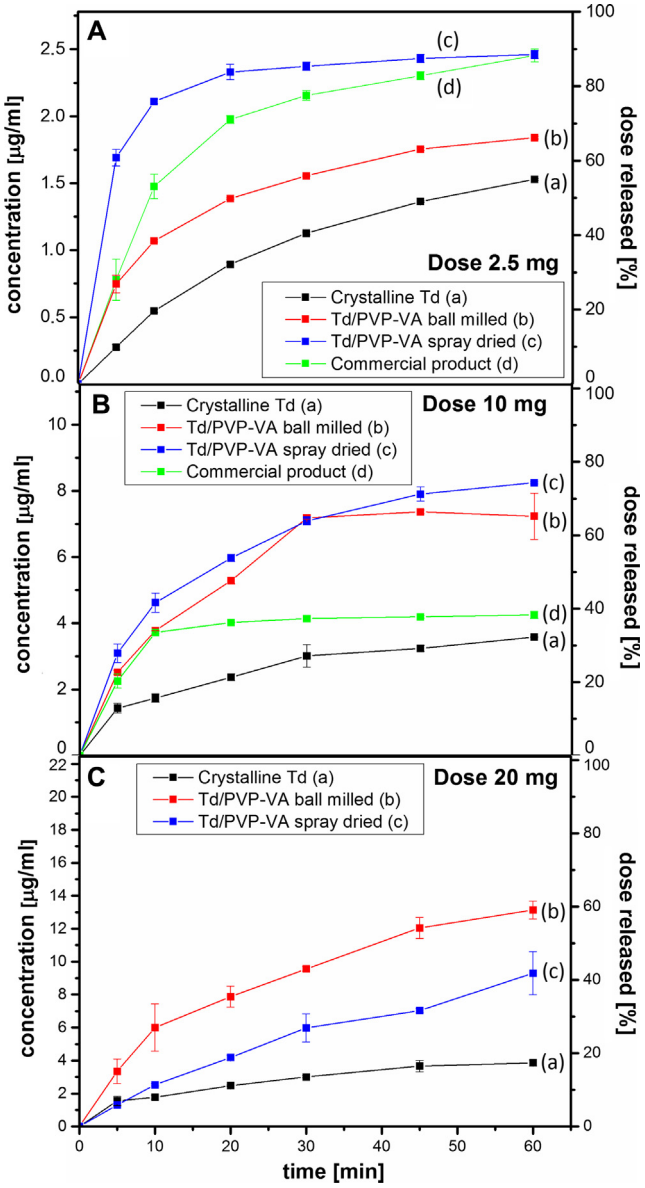

Fig. 7. Release profiles of tablets comprising crystalline Td, spray dried and ball milled Td/PVP-VA solid dispersions and marketed drugs at Td doses of 2.5 mg (A), 10 mg (B) and 20 mg (C) obtained in distilled water.

64% and 49% of Td at the same time, respectively. The dissolution properties of formulation D_4 were better when compared to dissolution of the drug from the marketed product, which contains sodium lauryl sulfate acting as a solubilizing agent.

In the case of 10 mg Td dose (Fig. 7B), the dissolution profile of Td from the commercial product was similar to the IRSDTs profiles for the first 10 min of the study. After this time dissolution of Td from Cialis was finished as a result of reaching intrinsic solubility of Td. However, dissolution of Td from formulations D_5 and D_8 was continued leading to 74% and 65% of Td released after 1 h, respectively. These amounts corresponded to Td water concentrations of 8.3 μg/ml and 7.2 μg/ml confirming the manufacture of supersaturable oral solid dosage forms. Dissolution studies carried out on the 20 mg Td tablets (Fig. 7C) revealed even higher Td water supersaturation provided by IRSDTs and inhibition in Td dissolution from formulation D_3 once the Td concentration reached 3.6 μg/ml.

The general conclusion arising from the dissolution studies (Fig. 7) is that the higher the drug content in a tablet the higher the Td concentration dissolved and the lower the percentage of the drug released. This relationship was especially apparent for formulations with the spray dried Td/PVP-VA solid dispersion and crystalline Td while the percentage of dose released from tablets with ball milled Td/PVP-VA solid dispersion was virtually constant (60–65%). It can be observed that for tablets comprising 2.5 mg Td the drug release from the formulation with the spray dried Td/PVP-VA solid dispersion was improved when compared to Td release from tablets containing the ball milled Td/PVP-VA solid dispersion. For tablets with 20 mg Td this trend was reversed, while for the formulations containing 10 mg Td the dissolution profiles of tablets comprising the solid dispersions were very similar. The unexpected relative retardation in dissolution characteristics of tablets D_6 (Fig. 7C) is in agreement with their delayed disintegration time (Table 3) and might be related to the formation of gelling polymer network, which does not occur at lower Td doses. However, such delay was not visible for the tablets comprising the ball milled solid dispersion at the same dose of 20 mg Td, which indicates the importance of particle morphology. Another observation is that, based on apparent solubility and dissolution rate studies (Figs. 5 and 6), one cannot predict the release profiles of IRSDTs with an amorphous binary system that was obtained in different processes.

The standard dissolution test on non-encapsulated and encapsulated Td/PVP-VA solid dispersions under the same dissolution conditions (900 ml of distilled water at 37 °C in dissolution apparatus) was carried out as a comparative research for release of Td from tablets. Two doses of Td corresponding to those contained in tablet formulations, i.e. 2.5 mg and 10 mg, were selected for this investigation and their dissolution profiles are depicted in Figs. 8 and 9, respectively. A comparison of the amounts of Td dissolved from tablets, encapsulated powders and non-encapsulated powders after 1 h dissolution studies is presented in Table 4.

Regardless of the solid dispersion preparation methods and doses of Td the dissolution of the drug from non-encapsulated Td/PVP-VA solid dispersion powders was the greatest, followed

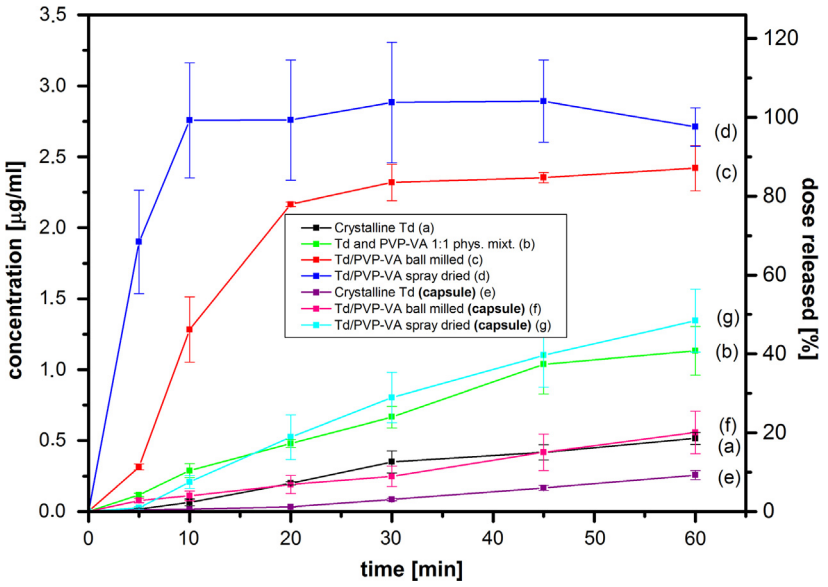

Fig. 8. Standard dissolution test of non-encapsulated and capsulated crystalline Td, spray dried and ball milled Td/PVP-VA solid dispersions as well as non-encapsulated Td and PVP-VA (1:1, w/w) physical mixture at Td dose of 2.5 mg.

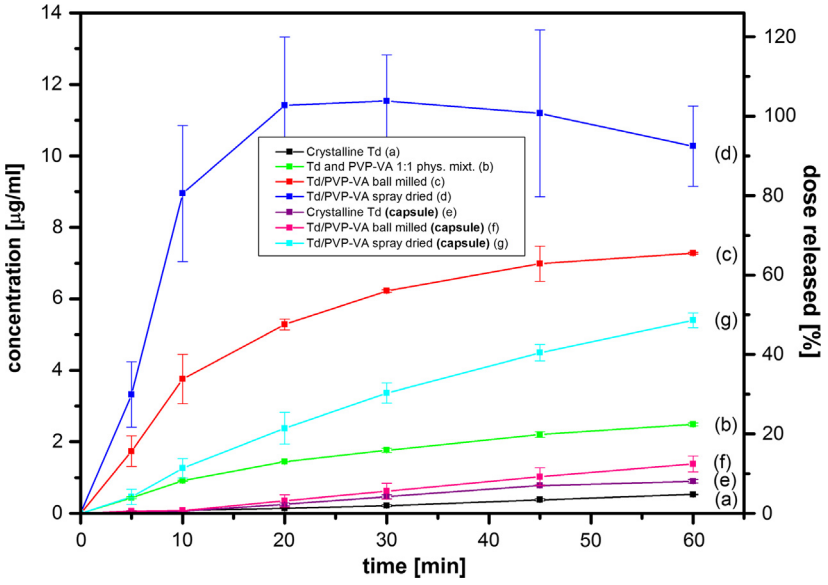

Fig. 9. Standard dissolution test of non-encapsulated and capsulated crystalline Td, spray dried and ball milled Td/PVP-VA solid dispersions as well as non-encapsulated Td and PVP-VA (1:1, w/w) physical mixture at Td dose of 10 mg.

Table 4
The percentage of dose released in dissolution studies (after 1 h) from crystalline Td, spray dried and ball milled Td/PVP-VA solid dispersions at two Td doses of 2.5 mg and 10 mg in the form of powders, capsules and tablets.

	Dose released in 900 ml of water after 1 h in dissolution apparatus (%)		
	Powders	Capsules	Tablets
2.5 mg			
Tadalafil	18.5 ± 1.6	9.2 ± 1.1	55.0 ± 0.3
Spray dried Td/PVP-VA	97.6 ± 4.8	48.4 ± 7.9	88.5 ± 1.1
Ball milled Td/PVP-VA	87.1 ± 5.7	20.1 ± 5.4	66.2 ± 0.4
10 mg			
Tadalafil	4.7 ± 0.1	8.1 ± 0.4	32.3 ± 0.1
Spray dried Td/PVP-VA	92.5 ± 10.1	48.6 ± 1.8	74.3 ± 0.3
Ball milled Td/PVP	65.5 ± 0.2	12.4 ± 2.0	65.1 ± 6.3

by the amounts released from the tablets and lastly, from the capsules. A significant reduction in the dose dissolved from capsules containing no additional excipients might have been caused by the formation of undispersed plugs, which were observed in this study and have been already mentioned in previous research [21]. Therefore, this investigation confirms the important role of excipients used to prepare tablets, which should prevent the formation of particle aggregates in release media. It should be also highlighted that release of crystalline Td from tablets was noticeably improved when compared to the neat powder, from 18.5% to 55% and from 4.7% to 32.3% for doses of 2.5 mg and 10 mg Td, respectively (Table 4). This phenomenon can be explained by improved wettability of lipophilic drug particles when surrounded by hydrophilic excipients in the tablet core.

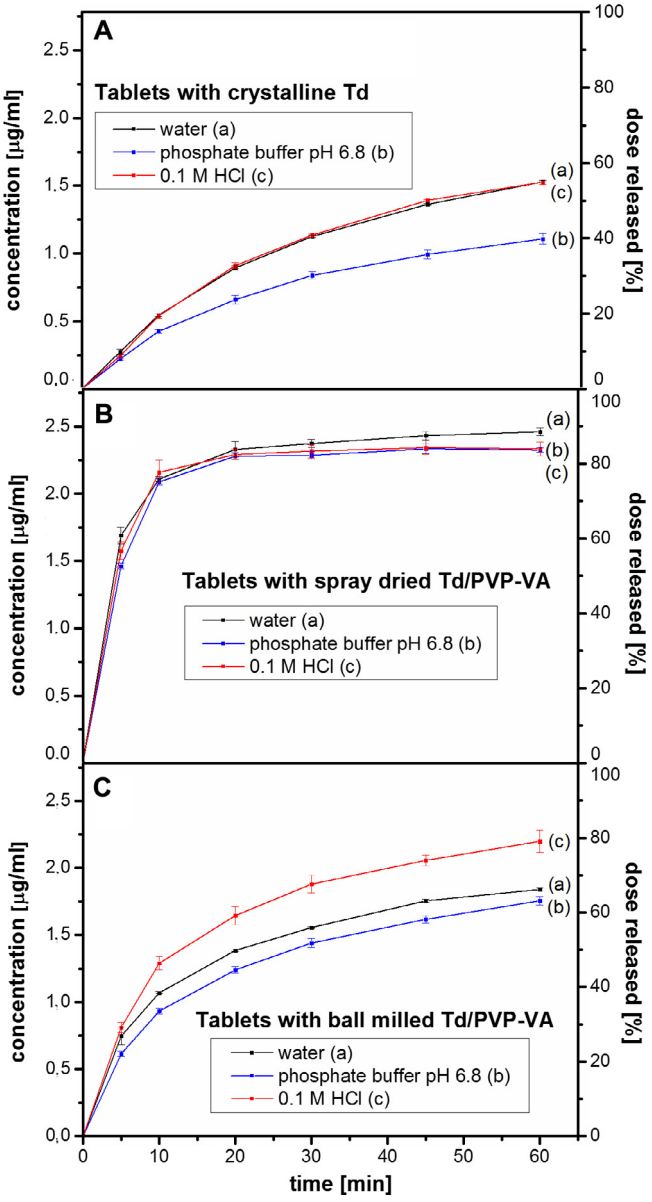

Fig. 10. Release profiles of tablets comprising crystalline Td (A), spray dried (B) and ball milled (C) Td/PVP-VA solid dispersions at Td dose of 2.5 mg obtained in distilled water, 0.1 M hydrochloric acid and phosphate buffer 6.8.

Distilled water was chosen as the solvent in preformulation studies and dissolution of tablets since solubility of Td as well as all excipients used to prepare IRSDTs is pH-independent [26]. However, to attain a more complete characteristic of the dosage forms, dissolution profiles of three formulations containing 2.5 mg of Td (D_1, D_4, D_7) were additionally investigated in different release media, i.e. 0.1 M hydrochloric acid and phosphate buffer pH 6.8 (Fig. 10). This study confirmed a negligible effect of pH on Td release for tablets with the spray dried Td/PVP-VA solid dispersion (Fig. 10B), while percentages of dose released for formulations with crystalline Td and ball milled solid dispersion were considerably decreased in the phosphate buffer (Fig. 10A and C).

4. Conclusions

The 1:1 (w/w) Td/PVP-VA solid dispersions obtained using two different technologies, i.e. spray drying and ball milling, were characterized as amorphous molecularly dispersed binary systems, i.e. solid solutions. This is the confirmation that mechanical activation as well as a solvent-evaporation method may lead to an intimate mixture of molecules of two substances. Despite this, the different size and shape of the spray dried and milled Td/PVP-VA particles had a significant impact on Td apparent solubility, stabilization of supersaturation as well as intrinsic dissolution rate in water.

Direct compression of both solid dispersions appeared to be a simple and efficient method to develop IRSDTs. It should be highlighted that spray drying has been well established in the formulation of IRSDTs, while ball milling has not been exploited in the formulation of these systems to the same degree. Along with crystalline Td, preparation of tablets at three Td doses i.e. 2.5 mg, 10 mg and 20 mg resulted in nine different formulations (D_1-D_9), which successfully fulfilled requirements set by the Ph.Eur.

IRSDTs were considered supersaturable formulations and had significantly improved Td aqueous dissolution profiles in comparison with tablets comprising crystalline Td or the marketed products. Tablets containing either the spray dried or the ball milled Td/PVP-VA solid dispersion achieved a different improvement in dissolution depending on the investigated doses, i.e. 2.5 mg and 20 mg. Dissolution of Td from the Td/PVP-VA solid dispersion delivered in different dosage forms occurred in the following order: powders > tablets > capsules. This result shows the crucial influence of excipients included in the formulations with solid dispersions, e.g. disintegrants and fillers, which are responsible for preventing the formation of particle aggregates in release media. Their formation, observed in dissolution studies on capsules, might abolish the favorable effect of amorphous solid dispersions on aqueous solubility and dissolution rate of poorly soluble drug substances.

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