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The influence of amorphization methods on the apparent solubility and dissolution rate of tadalafil

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ABSTRACT

This study for the first time investigates the solubility and dissolution rate of amorphous tadalafil (Td) – a poorly water soluble chemical compound which is commonly used for treating the erectile dysfunction. To convert the crystalline form of Td drug to its amorphous counterpart we have employed most of the commercially available amorphization techniques i.e. vitrification, cryogenic grinding, ball milling, spray drying, freeze drying and antisolvent precipitation. Among the mentioned methods only quenched cooling of the molten sample was found to be an inappropriate method of Td amorphization. This is due to the thermal decomposition of Td above 200 °C, as proved by the thermogravimetric analysis (TGA). Disordered character of all examined samples was confirmed using differential scanning calorimetry (DSC) and X-ray powder diffraction (PXRD). In the case of most amorphous powders, the largest 3-fold increase of apparent solubility was observed after 5 min, indicating their fast recrystallization in water. On the other hand, the partially amorphous precipitate of Td and hypromellose enhanced the solubility of Td approximately 14 times, as compared with a crystalline substance, which remained constant for half an hour. Finally, disk intrinsic dissolution rate (DIDR) of amorphous forms of Td was also examined.

1. Introduction

Solubility and dissolution rate are the factors considered to play a key role in the two first phases of the time course of drug distribution (LADME), i.e. liberation and absorption, significantly affecting bioavailability. The increasing number of poorly soluble drug substances in the contemporary pharmaceutical market forces to continuously search for new methods to improve these parameters (Kawabata et al., 2011). Strategies concerning the enhancement of apparent solubility and dissolution rate of drugs at the solid state present an important research area, justified by prevalence and great importance of oral solid dosage forms as means of active pharmaceutical ingredients (APIs) administration. These approaches include micro and nanosizing of API, formation of cocrystals and complexes, manufacture of solid dispersions and solutions, formation of various crystal polymorphs and amorphization (Anjana et al., 2013; Saharan et al., 2009).

The amorphization process leads to the amorphous form of a drug which, in contrast to the crystalline form, can be characterized by the disordered arrangement of molecules in the solid state. There are numerous methods and physical processes which enable formation of amorphous forms of active pharmaceutical ingredients, e.g. vitrification, grinding, freeze-drying, spray drying and rapid precipitation from a solution. The amorphous form, in comparison to the crystalline form, frequently improves the physical properties, such as solubility and dissolution rate, while maintaining the identical chemical structure and therefore the pharmacological activity of API (Nagapudi and Jona, 2008). This favorable alteration in properties is due to the higher internal energy and lower thermodynamic stability. Reported changes in solubility enhancement varied depending on chemical compounds and in respect to their lowest energy crystalline forms were, for instance, 5-fold, 50-fold and even 250-fold for caffeine, theophylline and morphine, respectively (Huang and Tong, 2004). Nevertheless, it has been documented that physicochemical properties of

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amorphous forms can be largely dependent on methods chosen for their production, as well. For instance, a study of two amorphous samples of cefditoren pivoxil obtained using spray drying at different inlet-air temperatures revealed differences in their water vapor desorption and physical stability. This diversity was present despite the same glass transition temperature of amorphous samples (Ohta and Buckton, 2005). Certain attempts to theoretically explain existence of differing amorphous forms have been made so far (Poole et al., 1995).

Tadalafil (Td), phosphodiesterase type 5 (PDE5) inhibitor used in the treatment of erectile dysfunction, is a drug substance belonging to class 2 of Biopharmaceutics Classification System (Abdel-Aziz et al., 2011). Therefore, in spite of good permeability, its bioavailability is limited by solubility and dissolution rate. However, there is little data on physicochemical properties of solid Td and inclusion in microporous silica has been the only method used for its amorphization so far (Mehanna et al., 2011). Thus, the objective of this study was to apply several different approaches in order to obtain amorphous tadalafil in a bulk state and further assess the impact of production method on the apparent solubility over time and the dissolution rate of such amorphous powders. The following methods: cryogenic grinding, ball milling, spray drying, freeze-drying and antisolvent precipitation were attempted to produce amorphous Td.

2. Materials and methods

2.1. Materials

Tadalafil (series 20211) was kindly donated by Polpharma S.A., Tween 80 was purchased from Sigma–Aldrich Chemie Company (Germany), Pharmacoat – hypromellose was bought from Shin-Etsu Chemical Company (Japan) and acetone was purchased from Corcoran Chemicals (Ireland). Ultrapure water was produced by Millipore Direct-Q 3UV-R water purification system. Sodium lauryl sulfate (SLS) and all other chemicals of analytical grade were purchased from POCH Company (Poland).

2.2. Methods

2.2.1. Preparation of amorphous tadalafil using cryogenic grinding

Cryogenic grinding of tadalafil was carried out by means of a 6770 SPEX freezer/mill. The total mass of the milled tadalafil was 1 g. The sample was placed in a stainless steel vessel and then immersed in liquid nitrogen. The stainless steel rod present in the vessel was vibrated by means of a magnetic coil. Prior to the start of grinding, the sample was subjected to 10 min of precooling. The mill was set to function at an impact frequency of 15 Hz. Ten minute grinding intervals were separated by 3 min cool-down periods. The effective grinding times were 120 min. After the cryogenic grinding, the vessel with the ground sample was equilibrated in a vacuum oven at 25 °C, until room temperature was reached.

2.2.2. Preparation of amorphous tadalafil using ball milling

The room temperature ball milling was performed using a Planetary Ball Mill (Retsch, Germany). A zirconium jar (250 ml) was filled with the examined material and 6 zirconia balls (20 mm in diameter). The rotation speed was set to 400 rpm. Three separate tests with the same amount of material (16 g) applying different grinding times were performed. Each milling cycle lasted 15 min and was followed by a 5 min break. The total milling time of tadalafil was 24 h.

2.2.3. Preparation of amorphous tadalafil using spray drying

Spray drying of Td 2% w/v solution (acetone/water 9:1, v/v) was performed using a Büchi Mini Spray Dryer B-290 (Büchi, Switzerland). The spray dryer was used in an open system with nitrogen applied as a drying and atomizing gas (open, suction mode). Spray dryer was equipped in standard atomization nozzle with a 1.5-mm cap and 0.7-mm tip. The drying gas pressure was of 6 bar at 4 cm gas flow (rotameter setting), equivalent to 473 norm liters per hour of gas flow in normal conditions (P = 1013.25 mbar and T = 0 °C). The nozzle pressure drop was measured to be 0.41 bar. The pump speed was set to 30% (9–10 ml/min) and the aspirator was operated at 100%. Inlet temperature was set to 160 °C and such setup resulted in outlet temperature of 85 °C. The additional, secondary drying was performed in an incubator with forced air flow (Gallencamp economy incubator with fan; Weiss-Gallencamp, UK) at 80 °C for 24 h.

2.2.4. Preparation of amorphous tadalafil using freeze-drying

100 mg of Td was dissolved in 50 ml of each of the following solvents or mixture of solvents (given in volume ratios): glacial acetic acid, glacial acetic acid/purified water (90/10), dioxane, dioxane/water (50/50), dioxane/methanol (90/10), dioxane/isopropanol (80/20), acetonitrile/water (45/55), acetonitrile/glacial acetic acid (50/50). The resulting solutions were obtained by stirring in a round-bottomed flask, rapidly frozen in the atmosphere of liquid nitrogen and subsequently freeze-dried for 48 h at −50 °C on the vapor capacitor, using a freeze-dryer (Alpha 1-2 LD, Germany). The sample vessel was attached externally to a manifold of the freeze dryer and the sample was subjected for 24 h to subambient temperatures due to an ongoing sublimation process. After 24 h the sample reached ambient temperature allowing for secondary drying of the residual solvents (Pikal et al., 1990). Secondary drying was continued for additional 24 h.

2.2.5. Preparation of amorphous tadalafil using antisolvent precipitation

Five various samples with composition as outlined in Table 1 were prepared. Briefly, 100 mg of Td was dissolved in the organic solvent (acetonitrile or dioxane), while antisolvent phase composed of Tween 80 or hypromellose (if used) dissolved in water. Samples 1 and 3 contained no excipient added and pure water was used an antisolvent. The organic Td solution was placed on a magnetic stirrer (1000 rpm) and the aqueous excipient solution (or water if no excipient was used) was slowly added. After the addition was complete, the formed suspension was frozen in a liquid nitrogen atmosphere and the dispersion medium was removed by freeze-drying for 48 h at −50 °C, 0.2 mbar.

2.2.6. Powder X-ray diffraction analysis (PXRD)

The X-ray diffraction measurements were carried out on the laboratory Rigaku – Denki D/MAX RAPID II-R diffractometer attached with a rotating anode Ag Kα tube (λ = 0.5608 Å), an incident beam (002) graphite monochromator and an image plate in the Debye–Scherrer geometry. The pixel size was

Table 1
The composition of samples in the antisolvent precipitation process.

Components	Sample				
	1	2	3	4	5
Tadalafil (mg)	100.0	100.0	100.0	100.0	100.0
Acetonitrile (ml)	15.0	15.0	–	15.0	15.0
Water (ml)	80.0	80.0	80.0	80.0	80.0
Dioxane (ml)	–	–	15.0	–	–
Tween 80 (mg)	–	70.0	–	70.0	–
Hypromellose (mg)	–	70.0	–	–	70.0