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Research Paper

Physicochemical properties of tadalafil solid dispersions – Impact of polymer on the apparent solubility and dissolution rate of tadalafil

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ABSTRACT

To improve solubility of tadalafil (Td), a Biopharmaceutics Classification System class II drug with thermodynamic solubility in water of 3 μg/ml, six different solid dispersions (1:1, w/w) using the following polymers: HPMC, MC, PVP, PVP-VA, Kollicoat IR and Soluplus were successfully produced by freeze-drying. Scanning electron microscopy showed a morphological structure of solid dispersions typical of lyophilisates. Apparent solubility and intrinsic dissolution rate studies revealed the greatest, a 16-fold, increase in drug solubility (50 μg/ml) and a significant, 20-fold, dissolution rate enhancement for the Td/PVP-VA solid dispersion in comparison with crystalline Td. However, the longest duration of the supersaturation state in water (27 μg/ml) over 24 h was observed for the Td solid dispersion in HPMC. The improved dissolution of Td from Td/PVP-VA was confirmed in the standard dissolution test of capsules filled with solid dispersions. Powder X-ray diffraction and thermal analysis showed the amorphous nature of these binary systems and indicated the existence of dispersion at the molecular level and its supersaturated character, respectively. Nevertheless, as evidenced by film casting, the greatest ability to dissolve Td in polymer was determined for PVP-VA. The crystallization tendency of Td dispersed in Kollicoat IR could be explained by the low T_g (113 °C) of the solid dispersion and the highest difference in Hansen solubility parameters (6.8 $MPa^{0.5}$) between Td and the polymer, although this relationship was not satisfied for the partially crystalline dispersion in PVP. Similarly, no correlation was found between the strength of hydrogen bonds investigated using infrared spectroscopy and the physical stability of solid dispersions or the level of supersaturation in aqueous solution.

1. Introduction

Searching for new drug substances is a complex process that needs to consider many pharmacodynamic and pharmacokinetic properties, resulting from the chemical structure of a molecule. As there is no perfect therapeutic substance, its design is a compromise between individual pharmacological parameters [19]. Biological activity and lack of systemic toxicity are the fundamental criteria in the design of a new chemical entity and some of the unfavorable pharmacokinetic parameters can be improved by means of pharmaceutical technology as well as applied and clinical pharmacy in the later stage of development.

One of the most distinctive problems related to the complexity of the drug development is a considerable growth in the number of poorly soluble drug substances resulting in limited and variable bioavailability after oral administration. It has been estimated that approximately 40% of currently marketed drugs and 75% of substances under development can be characterized as practically insoluble in water [3]. Therefore, significant efforts have been made to find and develop efficient methods of solubility and dissolution rate improvement. Since solubility in water results from intermolecular solute interactions and solute–solvent affinity, these approaches can be divided into two main groups based on the nature of changes either in the Gibbs free energy of solid molecules or in drug–solvent interactions. The first group utilizes the

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phenomenon of polymorphism, amorphizm and cocrystals, while solubility improvement by surfactants, cosolvents and cyclodextrins is an example of the latter group. However, this classification is not always unambiguous as e.g. size reduction or salt formation may lead to both, change in crystal molecules interaction energy and enhanced affinity for water [24].

Tadalafil (Td) is commonly used in the treatment of erectile dysfunction and belongs to the Biopharmaceutical Classification System class II. Poor solubility in water is a limiting factor for its absorption leading to significant differences in the pharmacological response. Several methods have been already investigated for Td solubility enhancement including cyclodextrin complexation [1], preparation of nanoparticles [16] and self-nanoemulsifying drug delivery systems [4]. In our previous study the amorphous form of Td was obtained using several commercially available amorphization techniques [25]. As a result of its relatively high glass transition point (T_g), which is 147 °C, Td can be considered as a good glass former in conjunction with its melting point (T_m) at 302 °C, with the T_g/T_m ratio equal to 0.73 [22]. However, Td on its own showed poor physical stability upon contact with water and crystallized immediately, resulting in a quick return to thermodynamic solubility. Therefore, the utilization of the apparent solubility improvement of Td from the amorphous form requires its physical stabilization, which can be achieved using e.g. incorporation in microporous silica [12] or the preparation of solid dispersions.

In general, the solid dispersion approach applied in this work is hoped to improve apparent solubility of a drug substance by different mechanism i.e. aforementioned amorphization, size reduction or enhanced wettability of drug molecules. However, the detailed impact of these factors on the apparent solubility of drug has not been clearly defined and requires further study. Td solid dispersions have been described several times to date but they were based on block polyethylene and polypropylene glycol copolymer (Pluronic, Poloxamer) as a polymeric matrix [23,11]. Since this substance is known to be capable of forming micelles in a solution, an increase in apparent solubility in this case is a result of an additional solubilizing effect visible even for physical mixtures.

Thus, the objective of this study was to investigate the impact of six different polymers i.e. hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), polyvinylpyrrolidone (PVP), vinylpyrrolidone – vinyl acetate copolymer (PVP-VA), macrogol – polyvinyl alcohol copolymer (Kollicoat IR) and vinylcaprolactam – macrogol – vinyl acetate copolymer (Soluplus) on apparent solubility and dissolution rate of Td as well as the ability to maintain a supersaturated state of the drug in water. The use of a few different, in terms of the physicochemical properties, polymers should provide a greater insight into the importance of the various mechanisms of the dissolution process. To correlate the solubility results with the solid state properties, a comprehensive analysis of Td solid dispersions including X-ray diffraction, thermal, microscopic and spectroscopic methods was carried out with a particular emphasis on two selected samples i.e. Td solid dispersions in HPMC and PVP-VA, which yielded the greatest apparent solubility and dissolution rate improvement. Solid dispersions of Td and polymers were obtained using solvent evaporation approach i.e. freeze-drying, which has been already used in the preparation of two-component solid systems [2,18].

2. Materials and methods

2.1. Materials

Tadalafil (series 20211) was kindly donated by Polpharma S.A. (Poland). Hydroxypropyl methylcellulose (Pharmacoat grade 606, HPMC) was bought from Shin-Etsu Chemical Company (Japan), methylcellulose (Methocel grade 100, MC) from The Dow Chemical Company (USA) while the other polymers i.e. polyvinylpyrrolidone (Kollidon 25, PVP), vinylpyrrolidone – vinyl acetate copolymer (Kollidon VA 64, PVP-VA), macrogol – polyvinyl alcohol copolymer (Kollicoat IR) and vinylcaprolactam – macrogol – vinyl acetate copolymer (Soluplus) were donated by BASF SE (Germany). Ultrapure water was produced by Millipore Direct-Q 3UV-R water purification system. Acetonitrile and all other chemicals of analytical grade were purchased from POCH Company (Poland).

2.2. Methods

2.2.1. Preparation of samples

2.2.1.1. Preparation of tadalafil solid dispersions using freeze drying. Six different polymers presented in Table 1, i.e. HPMC, MC, PVP, PVP-VA, Kollicoat IR and Soluplus, were used to produce Td solid dispersions (1:1, w/w). Briefly, two separate solutions: 100 mg of polymer in 27.5 ml of purified water and 100 mg of Td in 22.5 ml of acetonitrile were prepared using a magnetic stirrer. The resulting solutions were mixed in a round-bottomed flask and after visually confirming that no precipitation occurred the mix was rapidly frozen in liquid nitrogen. The samples were subsequently freeze-dried for 72 h in a vacuum of 0.2 mbar at 50 °C on the vapor capacitor, using an Alpha 1–2 LD freeze-dryer (Germany). The sample flasks were attached externally to manifolds 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 which was continued for another 48 h. Solid dispersions were stored in sealed containers at 8 °C and slightly pulverized in a mortar before further experiments.

Td solid dispersions in PVP-VA and HPMC were additionally prepared in different weight ratios (1:1.5, 1:2, 1:4 for PVP-VA and 1:1.5, 1:2, 1:4, 1:6, 1:8 for HPMC) proportionally increasing the amount of polymer dissolved in 27.5 ml of purified water and following the above procedure. Neat amorphous Td used in DSC and FTIR analysis was obtained by freeze-drying as described by Wlodarski et al. [25].

2.2.1.2. Preparation of tadalafil physical mixtures. Physical mixtures, as reference materials, were prepared by grinding Td and polymer

Table 1
Physicochemical properties of polymers. T_gs of Kollicoat IR and Soluplus (*) were taken from literature [8]. Dynamic viscosity of 10% polymer solutions (**5%) was measured at 25 °C. Hansen solubility parameters of polymers and tadalafil (25.7 $MPa^{0.5}$) were calculated based on the Van Krevelen method [21].

Trade name	Chemical name	T_g (°C)	Dynamic viscosity (mPa s)	Total solubility parameter ($MPa^{0.5}$)
Pharmacoat	Hydroxypropyl methylcellulose (HPMC)	172 ± 0.72	300	27.8
Methocel	Methylcellulose (MC)	124 ± 0.43	330**	30.0
Kollidon 25	Polyvinylpyrrolidone (PVP)	155 ± 0.40	4.9	22.5
Kollidon VA 64	Vinylpyrrolidone – vinyl acetate copolymer (PVP-VA)	101 ± 0.21	5.1	21.6
Kollicoat IR	Macrogol – polyvinyl alcohol copolymer	45*	9.8	32.5
Soluplus	Vinylcaprolactam – macrogol – vinyl acetate copolymer	70*	5.9	20.7

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