Physicochemical Evaluation of Tadalafil Solid Dispersions Obtained by Antisolvent Precipitation

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ABSTRACT SUMMARY

In order to increase solubility of tadalafil (Td), its solid dispersions with different polymers were prepared using antisolvent precipitation method. After confirmation of solubility improvement, samples were subjected to physicochemical analysis to determine the mechanism of solubility growth. Preliminary research revealed partial amorphization, decrease in particles size and new hydrogen interactions between Td and polymers.

INTRODUCTION

Solubility is a key parameter influencing release and consequently gastrointestinal absorption of Td and other therapeutic substances belonging to II class of Biopharmaceutical Classification System. Since the number of these molecules is increasing dramatically and vast majority of drugs on pharmaceutical market are solid forms, searching for new physicochemical modifications in a solid phase seems to be reasonable.

Among numerous applied methods, e.g. formation of complexes and cocrystals, amorphization [1] and crystal engineering, preparation of solid dispersions with polymers is the approach utilizing the largest number of solubility enhancement mechanisms.

Thus, the aim of the study was to obtain solid dispersions of Td and further provide physicochemical characterization of samples, what can contribute to better understanding of mechanisms leading to supersaturation state.

EXPERIMENTAL METHODS

Preparation of solid dispersions

Solid dispersions of Td and different polymers, i.e. hypromellose, methylcellulose, Kollidon 25, Kollidon VA64, Soluplus and Kollicoat IR in a weight ratio of 1:1 were prepared by antisolvent precipitation. Subsequently, samples were frozen in a liquid nitrogen atmosphere and the dispersion medium was removed in a freeze-drying process for 48 h.

Solubility study

In order to determine the apparent solubility of Td, saturated solutions of solid dispersions in water were prepared and filtered at specified intervals during first two hours and after 24 h. Resulting solutions were diluted quantitatively with acetonitrile and subjected to HPLC-RP-UV analysis to determine the amount of Td dissolved.

X-ray powder diffraction analysis (XRPD)

X-ray analysis of Td solid dispersions was made with a powder diffractometer D/max Rapid II R.

Differential scanning calorimetry (DSC)

Calorimetric measurements were carried out by Mettler-Toledo DSC apparatus at the heating rate of 10 K/min under nitrogen atmosphere (60ml/min).

Infrared spectroscopy (FTIR)

FTIR spectra were obtained using Jasco FR/IR-410 spectrometer. In order to carry out an analysis, a small amount of each material was used and compressed in KBr tablets. The spectra were obtained in the region of 400–4000 cm⁻¹.

Scanning electron microscopy (SEM)

Microstructural observations of the examined solid dispersions were conducted using the JEOL-7600F scanning electron microscope equipped with an Oxford Instruments X-ray Energy Dispersive Spectroscope (EDS).

RESULTS AND DISCUSSION

Solubility studies performed for all solid dispersions revealed the enhancement of apparent solubility of Td in comparison to its crystalline form, especially within the first hour of investigation. However, the growth differed significantly depending on the polymer used and was the highest (tenfold) for hypromellose and the lowest (double) for Kollicoat IR (Figure 1). Kollicoat IR was the only polymer with highly hydrophilic structure and inability to be dissolved in acetonitrile that was used as organic solvent in the precipitation process. This might have resulted in its undesirable precipitation while mixing its water solution with acetonitrile and further prevented from its adsorption on the surface of forming Td crystals.

What is important, mechanism of solubilization in the case of hypromellose dispersion was excluded on the...
basis of research into physical mixture of the same composition, which did not change Td solubility.

Diffraction patterns obtained for all dispersions revealed partial amorphization and no differences in crystallinity among them (Figure 2). Thus, crystallinity variations cannot be justification for different dissolution profiles. This result is in agreement with our previous research which indicated lack of significant influence of amorphization on apparent solubility of Td.

Figure 2. Diffraction patterns of selected Td solid dispersions.

FTIR study conducted for hypromellose and Td solid dispersion allowed to demonstrate the existence of chemical interactions between Td and polymer, contrary to the physical mixture. IR spectrum reveals the increase in absorbance of hypromellose hydroxyl groups in this dispersion at a wavelength of 3500-3250 cm\(^{-1}\). As well, this is confirmed by the change in the fingerprint region above 1000 cm\(^{-1}\) and the distortion of dual signal of Td lactame group at 1690 cm\(^{-1}\) (Figure 3, 4). Changes observed prove hydrogen interactions between hydroxide groups of hypromellose and Td, pointing the participation of the lactame group in this interaction.

Figure 3. IR spectra of tadalafil, hypromellose, their solid dispersion and physical mixture.

SEM analysis conducted for hypromellose solid dispersion revealed micronization of particles and, in comparison to crystalline Td, confirmed chaotic structure of powder. However, contrary to nanosized particles that according to some authors can increase apparent solubility [2], micronization is capable of improving only dissolution rate.

Figure 4. Chemical structure of tadalafil.

CONCLUSION

All obtained solid dispersions increased Td apparent solubility, however, unequally. Since the highest increase was observed after dispersal in hypromellose, this sample has been analyzed most accurately so far. Kollicoat IR with typical hydrophilic structure had the lowest ability to improve Td solubility. Since all samples were partially amorphous differences in apparent solubility of Td did not result from variations in crystallinity. FTIR study indicated the existence of hydrogen bonds between hydroxyl groups of hypromellose and lactame group of Td in solid dispersion. Such interactions were not present in a physical mixture of the same composition. Additionally, research confirmed micronization of powder in hypromellose solid dispersion.

REFERENCES

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