Solid state characterization of glyburide-cyclodextrin coground products

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Glyburide is an oral hypoglycemic agent whose poor aqueous solubility can give rise to variations in its dissolution rate and incomplete and/or unpredictable bioavailability. Different approaches to enhance drug dissolution properties have been experimented [1,2], including amorphization by spray drying [3]. However the activated amorphous form was highly instable and rapidly reverted to the crystalline form [3].

Co-grinding with suitable adjuvants is a technique often employed to improve dissolution of poorly water-soluble drugs by reducing particle size and leading to drug amorphization [4,5]. Moreover, the adjuvant can sometimes act as a stabilizing agent of the obtained amorphous state, by preventing or at least slowing down drug recrystallization.

In the present work cyclodextrins were selected as potential carriers for improving glyburide dissolution and Differential Scanning Calorimetry (DSC) was used to investigate the drug solid state modifications induced by co-grinding in a high energy vibrational micromill. X-Ray Powder Diffraction (XRD) and Fourier Transform Infrared Spectroscopy (FT-IR) were also used as additional techniques, to support DSC results. Drug:cyclodextrin physical mixtures at 1:1 mol/mol ratio were prepared using both natural crystalline cyclodextrins (α-, β- and γ-Cd) and amorphous derivatives (hydroxyproylβ-Cd and methylβ-Cd). The blends were then coground for different times (up to 1 h) at constant vibration frequency (24 Hz). DSC analysis enabled monitoring of the drug solid state modifications which occurred as a function of grinding time.

Solid state studies of the binary systems not only showed progressive drug amorphization with increasing the grinding time but also revealed different behaviour depending on the type of cyclodextrin used.

Furthermore, stability studies allowed exclusion of any drug recrystallization process in the selected coground binary systems stored for up to four months at room temperature, thus accounting for the suitability of cyclodextrin co-grinding technique to obtain and stabilize glyburide in the activated amorphous form.

References

[1] Betageri, G.V., Makarla, K.R., Int. J. Pharm., 126 (1995) 155-160

[2] Iwata, M., Ueda, H., Drug Dev. Ind. Pharm., 22 (1996) 1161-1165

[3] Cordes, D., Müller, B.W. Eur. J. Pharm. Sci., 4 (1996) 187

[4] Rubinstein, M. H., Gould, P. Drug Dev. Ind. Pharm., 13 (1987) 81-87

[5] Yonemochi E., Kitahara S., Maeda S., Yamamura S., Oguchi T. and Yamamoto K. Eur. J. Pharm. Sci., 7 (1999) 331-338