Obtaining of amorphous drug – polyvinylpyrrolidone mixtures by cryogenic grinding

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Co-grinding is one of the efficient methods to prepare solid dispersions of the drugs in order to enhance the rate of dissolution and bioavailability of poorly water-soluble drugs [1]. Usually a nanocrystalline material is formed after the mechanical treatment in a mill, but sometimes, it is possible to obtain amorphous mixtures.

The formation of amorphous pharmaceutical mixtures is more attractive in the context of enhancing the rate of dissolution of the drugs [2]. Recently, the advantages of ball milling for obtaining amorphous molecular alloys was demonstrated [3]. Cryogenic grinding was also efficiently used for preparation of amorphous states of the drugs [4, 5]. It allows to obtain amorphous state avoiding melting and degradation of the samples.

The objective of the present work was to obtain the amorphous mixtures of piroxicam and indomethacin with polyvinylpyrrolidone (PVP) by cryogrinding and study their physical-chemical properties. The regions of miscibility of small molecules of drugs under consideration and PVP were identified. The results obtained were compared with the results for room temperature grinding and the properties of drug - PVP compositions synthesized by other methods [6, 7].

Milling was performed using a cryogenic mill (6750 Freezer/Mill, SPEX CertiPrep, Inc., USA) consisting of a stainless steel vessel immersed in liquid nitrogen within which a stainless steel rod is vibrated. The effect of cryogenic grinding on the mixtures of drugs with PVP was studied by powder X-ray diffraction, differential scanning calorimetry (DSC) as well as modulated temperature DSC (MDSC), and Raman spectroscopy.

It has been shown that the X-ray amorphous samples of drug – PVP mixtures can be obtained by cryogrinding depending on the PVP content and time of milling. In the case of piroxicam, the mixtures containing low contents of PVP, 10-25 %, need more time of grinding to obtain amorphous samples than the mixtures with more content of PVP.

Comparing with the results obtained under milling at room temperatures, cryogrinding allowed to prepare amorphous samples at a low content of the polymer. An increase in the crystallization temperature was observed with increasing PVP content. For the piroxicam mixtures containing 10-50 % PVP, crystallization was observed in the glass transition temperature region. No crystallization exotherms were observed at PVP concentration above 40 % and 60 % for indomethacin and piroxicam containing systems, respectively.

Though the T_g practically didn't depend on PVP content in the region of 10-50 % PVP, the shift of crystallization temperature was observed. This suggests that increasing T_g is not the only determining factor in controlling crystallization rate.

There are some factors which might contribute to the inhibitory effect of PVP on the crystallization of the drug from the amorphous state. PVP might inhibit the association of the

drug molecules to form the crystal nucleus and inhibit the crystal growth [8]. It is possible that PVP is able to complex with a drug causing a change in molecular motions at T_g for the mixed systems and in this way cause inhibition of crystallization [7].

Raman spectroscopy studies did not reveal the interaction of the components during cryogrinding PVP-indomethacin mixtures. The inhibitory effect of PVP on crystallization may be due to its accumulation at the interface and acting as a steric barrier for nucleation and growth of a crystalline phase.

It was assumed that at low contents of PVP the samples are not amorphous alloys but the mixtures of amorphous components. Formation of amorphous alloys is possible for large quantities of polymer; a single glass transition event is characteristic for such systems.

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