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SOLID DISPERSIONS OF NIMODIPINE AND POLYOXYETHYLENE -AN ADDITIVE PREVENTS THE DRUG FROM RECRYSTALLIZATION

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Introduction: The insufficient solubility of many new drug substances in water as well as in the aqueous gastric fluids cause problems in bioavailability. The development of solid dispersions is an appropriate means to overcome these problems and to guarantee a reasonable bioavailability. Several methods exist to prepare solid dispersions, the melting method being the most convenient. The melting procedure includes the melting of the carrier, the subsequent dissolution of the drug within the melt and finally, the cooling of the obtained solution. During the cooling process the molecular dispersion of the drug within the carrier may be maintained or the drug may recrystallize as a result of the increasing supersaturation due to the lowering of temperature. Moreover, recrystallization can take place during storage as well. The precipitation usually leads to a decrease in the dissolution rate of the drug in the dissolution medium as amorphous materials dissolve faster because of their higher solubility. Therefore an attempt has been made to prevent the drug from recrystallization.

Materials and methods: For the preparation of solid dispersions by the melting method, polyoxyethylene 2000 has been chosen as a carrier due to its low melting point. Nimodipine, a poorly soluble calcium channel antagonist was used as model drug. The characterization of the products was performed by dissolution testing, differential scanning calorimetry (DSC) and hot stage microscopy (HSM).

Results and discussion: Solid dispersions of nimodipine in polyoxyethylene 2000 exhibit a low dissolution rate and lack the capability to supersaturate the dissolution medium. The high tendency of polyoxyethylene 2000 to crystallize during the cooling process or during storage probably leads to an expulsion of the drug from the crystal lattice of the carrier. As a result, the drug first concentrates in areas of lower crystallinity where it subsequently recrystallizes itself when the concentration exceeds the solubility within the carrier. Unexpectedly, investigations by DSC can not prove the existence of crystalline nimodipine in these products. Thermograms only exhibit the melting of polyoxyethylene 2000. In contrast, examinations by HSM reliably allow the detection of fine nimodipine crystals after the melting of polyoxyethylene 2000. Subsequently, as the heating program continues, the gradual dissolution of these crystals can be observed.

The aim of further investigations was to avoid the recrystallization of the drug within the carrier in order to obtain solid dispersions with more favourable dissolution profiles. In contrast to most binary mixtures of polymers where the two components are immiscible, it has been found one polymeric substance to be soluble in polyoxyethylene 2000. The two polymers together form a new homogeneous carrier material. The dispersion of nimodipine in the composed carrier leads to a product with an enhanced dissolution rate and a pronounced supersaturation in the dissolution medium. Investigations by DSC as well as by HSM indicate the absence of nimodipine crystals in these systems. Thus, the new carrier material proves to be suitable for the preparation of solid dispersions with favourable dissolution properties.

Summary: The reasonable development of solid dispersions containing nimodipine and polyoxyethylene 2000 with favourable dissolution profiles is based on the proper characterization of the obtained products by thermal analysis. In this context, HSM proves to be an essential tool for the correct interpretation of DSC thermograms. By these means, it is possible to ascribe insufficient dissolution properties of solid dispersions containing only nimodipine and polyoxyethylene 2000 to the presence of crystalline nimodipine within the carrier. Thus, the addition of a substance which prevents the drug from recrystallization successfully leads to products with a high dissolution rate and a pronounced supersaturation in the dissolution medium.