PO C 2

Glassy Solid Solutions of Poorly Soluble Drugs in Isomalt for a Rapid Bioavailability

M. Langer, N. A. Urbanetz, B. C. Lippold

Institut für Pharmazeutische Technologie
Heinrich-Heine-Universität Düsseldorf, D-40225 Düsseldorf

Commonly, the term solid dispersion means the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting, solvent, or melting-solvent method. Four types of solid suspensions and two types of solid solutions exist, considering the crystalline or amorphous state of the respective drug and carrier as well as the level of dispersion [1]. Glassy solid solutions are a specific kind of solid dispersions, wherein a drug is dissolved in an amorphous carrier at the molecular level. In order to distinguish between solid suspensions and solid solutions in the case of isomalt as carrier, hot stage microscopy (HSM), dissolution testing and differential scanning calorimetry (DSC) are used.

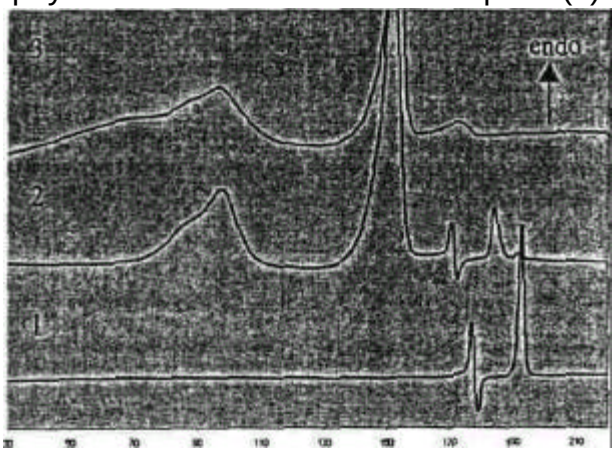
The carrier isomalt (1-O-α-D-glucopyranosyl-D-mannit dihydrate/6-O-α-D-glucopyranosyl-D-sorbit) is registered as sugar substitute and is mainly used for the production of sugar free hard candies. Isomalt can be heated above its melting point without decomposition. By cooling the melt to room temperature, it solidifies amorphously with a glass transition at 60°C. Other sugar polyols exhibit lower Tg values, e.g. mannitol and sorbitol have reported values of 10.7°C and 0°C. Thus, glassy systems of isomalt should be more stable than glassy systems of other polyols. Carbamazepine is chosen as model drug, since it is well known that the poor solubility and polymorphism can limitate its bioavailability. Solid dispersions of carbamazepine in isomalt are prepared either by melting the ingredients up to 205°C in a melting pot or by DSC heating scans.

By HSM, 5 % carbamazepine are found to be miscible with isomalt in the liquid or molten state at 190 to 200°C. Nevertheless, when cooling the melt to room temperature, molecular dissolved carbamazepine recrystallizes immediately as can be observed macroscopically: The transparent system changes into an opaque solid suspension. Only the addition of a special excipient leads to a glassy solid solution of carbamazepine in isomalt as can be proved by DSC scans and dissolution profiles of solid dispersions with different compositions. According to the dissolution studies, only 2 % carbamazepine are soluble in glassy isomalt at room temperature whereas 10 to 15 % carbamazepine are dissolvable in the isomalt system containing 25 % of the special excipient. By pouring the ternary melt into 2 g tablet moulds, highly transparent glassy tablets with a light yellow appearance are obtained. All tablets show a significantly enhanced dissolution rate of carbamazepine up to 10 % active ingredient compared with the respective physical mixture.

DSC studies identify the commercially available carbamazepine (scan 1) as polymorph I referring to Kobayashi [2], which is thermodynamically stable at room temperature and melts at 176°C. Polymorph III is preferred above 71 °C and melts at 190°C. In contrast to isomalt alone as carrier (scan 2), form I gradually dissolves in the liquid isomalt/excipient mixture (scan 3).

The solid solution of isomalt and the excipient exhibits a 6°C higher Tg as isomalt and no enthalpy relaxation peak after 15 minutes of storage. Thus, the excipient prevents the system from recrystallization by specific interactions on the molecular level, hereby improving the solubility of carbamazepine in isomalt. With respect to these findings, it seems necessary to use special excipients in order to dissolve reasonable amounts of carbamazepine in glassy isomalt.

DSC scans: Carbamazepine alone (1), physical mixture with isomalt (2) and physical mixture with isomalt/excipient (3).



Temperature [°C]

[1] Urbanetz, N. A., 1999. Thesis, in press
[2] Kobayashi, Y., International Journal of Pharmaceutics, 193 (2000) 137-146