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Investigations on the predictability of the formation of glassy solid solutions of drugs in sugar alcohols☆

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Abstract

A prerequisite for the formation of glassy solid solutions prepared by the melting method is the miscibility of the respective drug and the carrier in the molten state. As could be shown experimentally, all investigated drug/sugar alcohol combinations miscible in the molten state form to some extent glassy solid solutions, dependent on their tendency to recrystallize during preparation. Therefore, the present study focuses on the evaluation of factors that govern the miscibility of molten drugs and sugar alcohols as carriers. In this context, solubility parameters are discussed as a means of predicting miscibility in comparison to a new approach, using calculated interaction parameters derived from molecular dynamics (MD) studies. There is evidence that a Coulomb interaction term C_{SR}, comprising short-range electrostatic interactions and hydrogen bonding energy is essential for the miscibility of drug and carrier in the molten state. To relate C_{SR} to the molecular volume, a non-dimensional parameter P_i is defined. For this parameter, a limiting value for miscibility exists. Contrary, calculated solubility parameter differences between drug and sugar alcohol in the range of 8–15 $\mathrm{MPa}^{1/2}$ are not suitable for a prediction of miscibility or immiscibility, since the mixtures deviate from regular solution behavior. In irregular mixtures of drugs and sugar alcohols, an excess entropy and the formation of hydrogen bonds between unlike molecules favor miscibility, that cannot be predicted by regular solution theory.

Keywords: Electrostatic interactions; Glassy solid solutions; Hydrogen bonding; Interaction parameter; Molecular dynamics; Poorly soluble drugs; Solubility parameters; Sugar alcohols

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1. Introduction

Solid dispersions are commonly used to increase the bioavailability of poorly water-soluble drugs by enhancing the dissolution rate of the respective drug. A specific kind of solid dispersions are glassy solid solutions, where a drug is dissolved in an amorphous carrier at the molecular level. For solid solutions, the dissolution rate of the drug in aqueous media attains its maximum and supersaturation may be obtained. The dissolution characteristics of glassy solid solutions depend on the carrier.

One common method of preparing solid solutions is the fusion process (Ford, 1986), which is applied in this investigation. In recent years, the preparation

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of solid solutions by hot melt extrusion technology has become popular and solid solutions are enjoying a renaissance (Leuner and Dressmann, 2000).

Glassy material, prepared by rapid cooling from a melt, can be regarded as supercooled liquid which is frozen in the glassy state (Craig et al., 1999). Thus, the first prerequisite for the formation of glassy solid solutions is the miscibility of the drug and the carrier in the molten form. The second one is the prevention of recrystallization during preparation and storage.

In this study, sugar alcohols are used as carriers, since it is known that glass formation is common in many polyhydroxy substances, presumably due to their strong hydrogen bonding which may prevent their crystallization (Chiou and Riegelman, 1971). Since they do not have physiological risks, the chosen sugar alcohols isomalt, maltitol, lactitol and mannitol are used in the manufacture of so-called sugar-free hard candies and dietetic food. Furthermore, they possess the advantage of high thermal stability and absence of browning reactions (Tomasik et al., 1989).

Mixtures of various drugs and sugar alcohols are investigated by hot stage microscopy to examine miscibility in the liquid state. The results are compared to predictions derived from calculated solubility parameters and from molecular modeling studies, especially molecular dynamics (MD) simulations.

In flexible molecules, it is impossible to describe accurately their “structure” as a single conformation. The “structure” can be thought of as an ensemble of individual conformations, which give rise to characteristic average molecular properties. MD simulations calculate the time dependent behavior of a molecular system, thus providing detailed information on fluctuating and conformational changes of the molecules. Model systems consisting of different drug molecules which are surrounded by an appropriate number of isomalt molecules are used. The aim is to investigate the interactions between the drugs and the carrier and to receive an explanation of observed differences in miscibility on a molecular level. In isomalt–drug mixtures hydrogen bonding interactions will dominate. However, there will be a significant contribution from the drug skeleton itself due to its polarity, its size and its conformational flexibility. Thus, it seems interesting to analyze the interaction behavior on a molecular level and to compare the results to the experimentally obtained results. Accordingly, this study concentrates on basic requirements for the miscibility of drugs with polyhydroxy carriers in the liquid state.

2. Materials and methods

2.1. Materials

Isomalt Ph.Eur. (1:1 mixture of 1-*O*-α-D-glucopyranosyl-D-mannit dihydrate and 6-*O*-α-D-glucopyranosyl-D-sorbit), type ST-F, was provided by Palatinit Süßungsmittel (Mannheim, Germany). Crystalline maltitol Ph.Eur. (4-*O*-α-D-glucopyranosyl-D-glucitol), Maltisorb®, was provided by Roquette (Lestrem, France) and lactitol monohydrate Ph.Eur. (4-*O*-β-D-galactopyranosyl-D-glucitol) by Purac biochem (Gorinchem, The Netherlands). Mannitol Ph.Eur. was purchased from Caesar & Loretz (Hilden, Germany) (Table 1). All drugs applied in this study (Fig. 1) were of analytical grade.

2.2. Methods

2.2.1. Differential scanning calorimetry (DSC) measurements

A Mettler-Toledo DSC 821e (Gießen, Germany) is used to determine melting points and glass transition temperatures of the sugar alcohols. Samples of 10 mg are investigated using a heating rate of 10 °C min^{-1} for the first ramp between 20 and 220 °C, whereas cooling of the melt and reheating are performed at 20 °C min^{-1} in the same temperature range. Crimped aluminium sample pans with a pierced lid are used with a nitrogen purge at 50 ml min^{-1}. An empty pan is used as reference and calibrations for temperature and enthalpy have been performed routinely with indium. Measurements are repeated three times and mean values with the respective standard deviation are given in the paper.

Table 1
Glass transition temperature of sugar alcohols (mean value ± S.D., $n = 3$)

Sugar alcohol (glassy carrier)	T_g (°C)
Isomalt	61.5 ± 0.7
Lactitol	59.3 ± 1.2
Maltitol	49.5 ± 0.2
Mannitol	10.7[a]

[a] Yu et al. (1998).

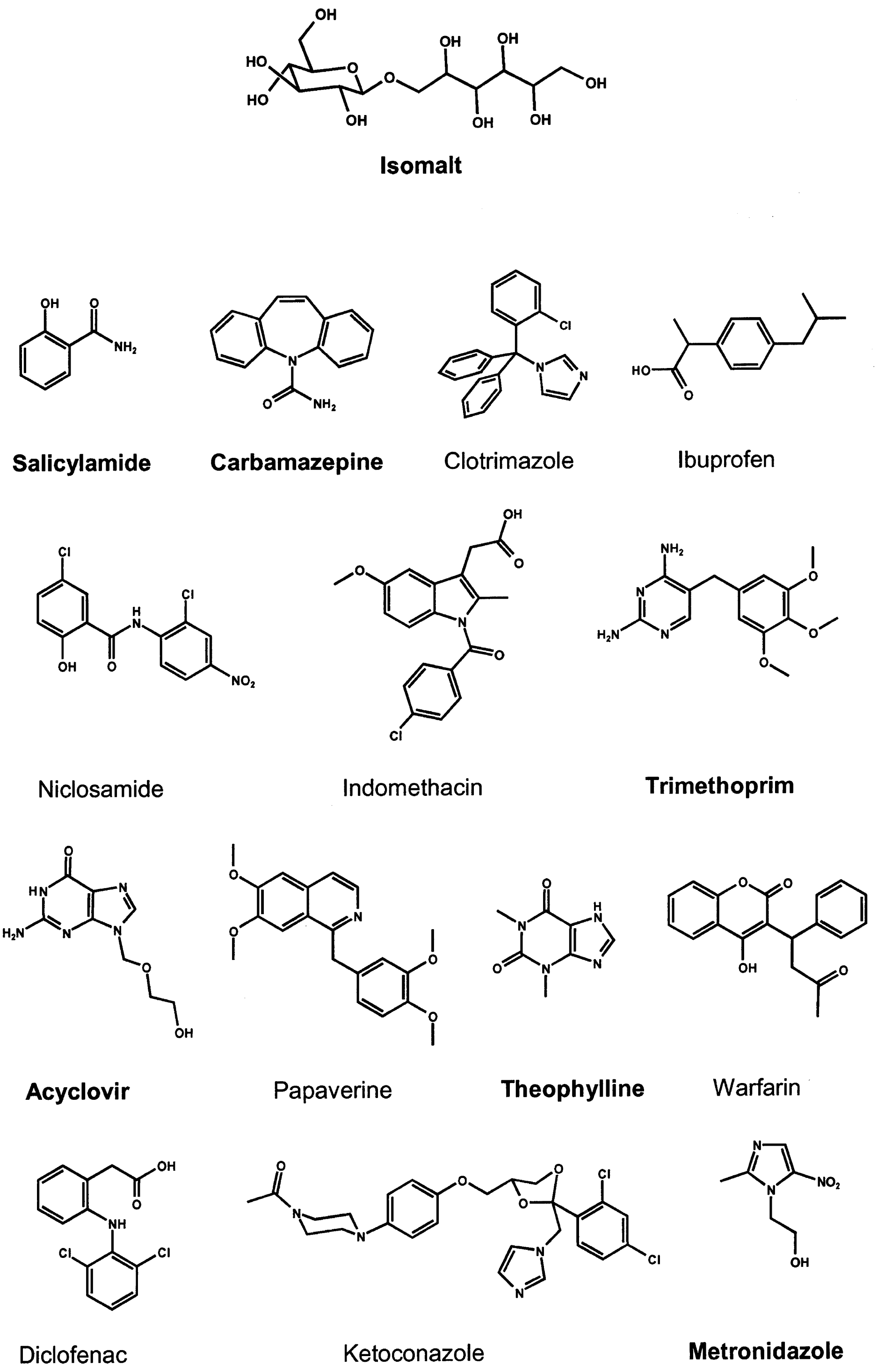

Fig. 1. Structures of isomalt and the drug molecules used in the investigation. Names of miscible drugs are shown in bold letters.

2.2.2. Miscibility in the liquid state

A Linkam THMS 600 hot stage connected with a Linkam TMS 94 temperature controller (Surrey, UK) and a Leica DMLB light microscope with a Leica DC 100 digital camera (Wetzlar, Germany) are used for the investigation of drug and carrier miscibility. Physical mixtures of the respective sugar alcohol with 5% drug are heated with 10 °C min^{-1} above their melting points, unless the drug dissolves in the molten carrier below its melting point. Melting or dissolving of crystalline drug is observed by hot stage microscopy using a total magnification of 100-fold. If the molten mixture on the slide is transparent without showing droplets, it is regarded as miscible, whereas droplets indicate phase separation. With respect to the latter, stirring by a glass rod results in a reduction of droplet size, but the amount of droplets increases.

2.2.3. Solubility in the glassy state

Molten samples containing 5 and 10% drug are cooled on slides at room temperature. Resolidified samples are immediately analyzed macroscopically and microscopically. If the dispersion appears vitreous transparent and nucleation or crystals are not detected by microscopical investigation using polarized light, the incorporated drug is assumed to be soluble in the glassy carrier. Nevertheless, solubilities given in the present paper should only be seen as approximate values, as drug molecules tend to recrystallize in the glassy carrier during storage, if supersaturated systems are obtained.

2.2.4. Solubility parameters

The Hildebrand total solubility parameter $\delta_{\mathrm{t(H)}}$ of a substance (Hildebrand and Scott, 1950) is derived from the cohesive energy density (CED) of the respective supercooled liquid at 25 °C. It is defined as square root of the CED and may be calculated from the energy of vaporization ΔE_{v} or the respective enthalpy of vaporization ΔH_{v} and the molar volume V_{m} in the liquid state (Eq. (1)).

$$\delta_{\mathrm{t(H)}} = \sqrt{\mathrm{CED}} = \sqrt{\frac{\Delta E_{\mathrm{v}}}{V_{\mathrm{m}}}} = \sqrt{\frac{\Delta H_{\mathrm{v}} - \mathrm{RT}}{V_{\mathrm{m}}}} \qquad (1)$$

As the energies of vaporization are often unknown, total solubility parameters $\delta_{\mathrm{t(H)}}$ are usually calculated using the group contribution method proposed by Fedors (1974). Throughout this paper, these calculated values are presented in the unit $\mathrm{MPa}^{1/2}$, equivalent to $\mathrm{J}^{1/2}\,\mathrm{cm}^{-3/2}$.

The partial solubility parameters δ_{d}, δ_{p} and δ_{h} are calculated according to the method of van Krevelen and Hoftyzer (1976) using group contributions for London dispersion forces, polar forces and hydrogen bonding forces. Molar volumes of the different groups are adopted from the respective group contribution proposed by Fedors. From these partial solubility parameters, the total solubility parameter δ_{t} is calculated according to Eq. (2).

$$\delta_{\mathrm{t}} = \sqrt{\delta_{\mathrm{d}}^2 + \delta_{\mathrm{p}}^2 + \delta_{\mathrm{h}}^2} \qquad (2)$$

Total solubility parameters obtained in this way are often called Hansen or three-dimensional solubility parameters.

2.2.5. Molecular modeling studies

In general, the interaction energy between drug and isomalt molecules may be subdivided in electrostatic forces, hydrogen bonds and van der Waals dispersion forces. Electrostatic interaction (or Coulomb forces or charge–charge interaction) arises from the attraction or repulsion of two charges and is inversely proportional to the distance separating the two charges. Because of their inversely proportional relation to distance, Coulomb interactions are long-range interactions. A hydrogen bond can be regarded as a short-range interaction between a positively charged hydrogen atom and a negatively charged (electronegative) acceptor atom. Due to a covalent contribution, hydrogen bonds are directive unlike electrostatic interactions which are isotropic. Despite their complex nature, the attractive interaction of hydrogen bonds, appears to be largely due to electrostatic components (Wade et al., 1993). Therefore, in the current study, hydrogen bond interactions as well as other electrostatic short-range interactions are summarized in the Coulomb short-range interaction term C_{SR}. The van der Waals forces include attractive forces arising from interactions between molecules polarizing each other and repulsive forces arising from van der Waals volume overlap. The calculation of the Lennard–Jones potential $\mathrm{LJ}_{\mathrm{in}}$ is a commonly used method to describe the attractive dispersion forces and the repulsive components of the van der Waals interaction energy.

All MD simulations are performed using the GROMACS package (Berendsen et al., 1995; Lindahl et al., 2001) and the GROMACS all-atom force-field. Atomic point charges are adopted from GROMACS building blocks or are derived by ab initio calculations. The isomalt starting ensemble is built from available crystal data (Lichtenthaler and Lindner, 1981). The model consists of 40 isomalt molecules per simulation cell. The system is heated to 450 K (177 °C) to transform the crystal to the liquid state and is equilibrated for 50 ps at 418 K (145 °C). After this procedure a cavity is formed by removing the appropriate number of isomalt molecules and one drug molecule is inserted. The drug–isomalt systems are simulated at 373 K (100 °C) for 2 ns, with a time step of 1 fs and no constraints. The presence of a hydrogen bond was determined based on a geometrical criterion. If the X···H distance was less than 0.28 nm and the Y–H···X angle greater than 120°, a hydrogen bond was considered to exist between two molecules.

The non-bonded interactions are calculated using a twin-range cut-off: 0.8 nm for the Coulomb short-range (C_{SR}) and the Lennard–Jones interactions (LJ_{in}) and 1.6 nm for the Coulomb long-range interactions. The Coulomb interaction (C) between two charged atoms (i, j) is given by

$$C(r_{ij}) = \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \tag{3}$$

where r_{ij} represents the distance between the two atoms i and j, q the charge of the atom and ε_0 the dielectric permittivity of the vacuum (Berendsen et al., 1995; Lindahl et al., 2001). The Lennard–Jones interaction LJ_{in} between two atoms i and j equals

$$LJ_{in}(r_{ij}) = \frac{C_{12}(i,j)}{r_{ij}^{12}} - \frac{C_6(i,j)}{r_{ij}^{6}} \tag{4}$$

The parameters $C_6(i, j)$ and $C_{12}(i, j)$ depend on the atom types of i and j and are taken from the GROMACS force-field parameter table.

Lennard–Jones interactions and Coulomb short-range interactions are calculated for those atom pairs i, j for which the distance r_{ij} between i and j is less than the cut-off radius (0.8 nm), Coulomb long-range forces are calculated beyond this cut-off up to 1.6 nm.

It should be noted that the resulting absolute energy values from these calculations (given in kJ/mol in Table 5) do not have any, but only the differences have physical meaning.

3. Results

3.1. Isomalt as carrier for glassy solid solutions

The four investigated sugar alcohols show similar mixing behavior with the different drugs used in this study (Fig. 1). In case of miscibility, the drug is miscible in all proportions, whereas in case of immiscibility, the drug does not mix with the melt, even at a concentration of 1%. However, mannitol as carrier is not suitable for the formation of glassy solid solutions, since immediate recrystallization of the carrier occurs during cooling at ambient temperatures, while isomalt, maltitol and lactitol remain glassy after resolidification. This may be due to higher glass transition values (T_g) in contrast to mannitol (Table 1), that has a reported T_g of 10.7 °C (Yu et al., 1998). Crystalline isomalt and maltitol have comparable melting points of about 145 and 149 °C, respectively. The melting point of lactitol is given by Yajima et al. (1997) as 99 °C for the monohydrate, but there are transformations into other modifications after the first melting. Due to the relatively high T_g of 61.5 °C and the absence of transformations after melting, isomalt seems to be best suited as carrier for glassy solid solutions. Thus, the following results refer to the miscibility of isomalt and drugs in the molten state.

3.2. Prediction of drug–isomalt miscibility by solubility parameters

As suggested by Greenhalgh et al. (1999), a general trend for miscibility in the molten state can be assumed in systems with a solubility parameter difference $\Delta\delta_{t(H)}$ below 7.5, whereas systems with a $\Delta\delta_t$ above 15.9 should reveal immiscibility over the entire composition range. Forster et al. (2001) give somewhat lower numbers as limits. Systems in between are difficult to classify. Table 2 gives a survey of the differences in calculated $\delta_{t(H)}$-values and observed miscibility in the liquid state.

It is apparent from these data, that a reliable prediction of miscibility is only possible for drugs with

Table 2
Drugs arranged according to the difference in the Hildebrand total solubility parameter $\Delta\delta_{t(H)}$ between isomalt and drug

Drug	$\delta_{t(H)}$ (MPa$^{1/2}$)	$\Delta\delta_{t(H)}$ (MPa$^{1/2}$)	Miscibility (liquid state)
Isomalt (carrier)	37.3	0	+
Acyclovir	32.6 (34.3)	4.7	+
Salicylamide	29.6 (34.0)	7.7	+
Niclosamide	28.8 (30.1)	8.5	−
Theophylline	28.8 (34.2)	8.5	+
Metronidazole	26.5	10.8	+
Warfarin	26.3	11.0	−
Diclofenac	26.0	11.3	−
Trimethoprim	26.0	11.3	+
Indomethacin	25.7 (26.9)	11.6	−
Carbamazepine	25.6 (28.1)	11.7	+
Ketoconazole	24.0 (24.8)	13.3	−
Clotrimazole	23.7	13.6	−
Papaverine	22.7	14.6	−
Ibuprofen	20.9	16.4	−

Values for $\Delta\delta_{t(H)}$ in parentheses are calculated using contributions from complete functional groups.

a solubility parameter very close to that of isomalt ($\Delta\delta_{t(H)}$ maximum 8) and of immiscibility in case that solubility parameters are very different ($\Delta\delta_{t(H)}$ above 15).

Moreover, the calculation of Hildebrand solubility parameters can yield different values, as different contributions for one structural unit can be obtained using either group contributions for the complete functional group or for the sum of its single components. This is especially true for tertiary, secondary and primary amide groups, bound or close to aromatic systems. Values for total solubility parameters are higher in the first case, as can be seen from the values in parentheses in Table 2. Since Martin et al. (1980) determined an experimental value of 28.6 MPa$^{1/2}$ for theophylline in dioxane water mixtures in accordance with the calculated $\delta_{t(H)}$ on the basis of single components, single group contributions are used to calculate ΔE_v- and V_m-values in the further study. In this way, calculated $\delta_{t(H)}$-values are also consistent with values for δ_t obtained by partial solubility parameters (Table 3), except for niclosamide. Partial solubility parameters, representing dispersion (δ_d), polar (δ_p) and hydrogen bonding interaction (δ_h) between molecules of the

Table 3
Drugs arranged according to the difference in the total solubility parameter $\Delta\delta_t$ between isomalt and drug

Drug	δ_d (MPa$^{1/2}$)	δ_p (MPa$^{1/2}$)	δ_h (MPa$^{1/2}$)	δ_t (MPa$^{1/2}$)	$\Delta\delta_t$ (MPa$^{1/2}$)	Miscibility (liquid state)
Isomalt (carrier)	21.2	8.9	32.2	39.5	0.0	+
Acyclovir	24.2	10.0	17.9	31.8	7.7	+
Niclosamide	26.3	9.3	12.5	30.6	8.9	−
Salicylamide	21.5	9.7	17.9	29.6	9.9	+
Theophylline	22.5	13.8	12.2	29.1	10.4	+
Metronidazole	19.7	11.4	14.6	27.0	12.5	+
Diclofenac	24.1	5.0	8.7	26.1	13.4	−
Trimethoprim	23.3	1.7	11.3	25.9	13.6	+
Indomethacin	23.2	5.9	9.4	25.7	13.8	−
Warfarin	21.7	5.9	11.2	25.1	14.4	−
Carbamazepine	22.0	6.6	9.6	24.9	14.6	+
Ketoconazole	22.4	5.5	8.8	24.7	14.8	−
Papaverine	22.7	3.2	6.9	23.9	15.6	−
Clotrimazole	22.0	3.9	4.6	22.8	16.7	−
Ibuprofen	17.9	2.2	7.2	19.4	20.1	−

Table 4
Drugs arranged according to the square root of the sum of squared partial solubility parameters for polar and hydrogen bonding

Drug	$\delta_p + \delta_h$ (MPa$^{1/2}$)	$(\delta_p^2 + \delta_h^2)^{1/2}$ (MPa$^{1/2}$)	Miscibility (liquid state)
Isomalt (carrier)	41.1	33.4	+
Acyclovir	27.9	20.5	+
Salicylamide	27.6	20.4	+
Metronidazole	26.0	18.5	+
Theophylline	26.0	18.4	+
Niclosamide	21.8	15.6	−
Warfarin	17.1	12.7	−
Carbamazepine	16.2	11.7	+
Trimethoprim	13.0	11.4	+
Indomethacin	15.3	11.1	−
Ketoconazole	14.3	10.4	−
Diclofenac	13.7	10.0	−
Papaverine	10.1	7.6	−
Ibuprofen	9.4	7.5	−
Clotrimazole	8.5	6.0	−

same species, have been calculated to study, whether they can give a better estimation of miscibility in the liquid state (Table 3) than total solubility parameters. Again, the values for differences in δ_t between isomalt and drug in the range of 8–15 as well as the respective partial solubility parameters do not exhibit a sharp limit between miscibility and immiscibility (Table 3). Since polar and hydrogen bonding features of drugs are thought to be decisive for the miscibility with isomalt, the sum of the partial solubility parameters for polar and hydrogen bonding interaction δ_p and δ_h as well as the square root of their square sums are calculated (Table 4). Despite a trend for immiscibility connected with low values and miscibility connected with high values, miscibility of carbamazepine and trimethoprim cannot be predicted by this approach.

Unfortunately, the miscibility of many solubility limited drugs (Löbenberg and Amidon, 2000), e.g. niclosamide, diclofenac, trimethoprim, indomethacin, carbamazepine and ketoconazole, with isomalt in the molten state cannot be derived from their solubility parameters, because the respective $\Delta\delta_t$-values are in the range of 8–15. This is also true considering only the partial solubility parameters δ_p and δ_h. Particularly for these drugs, formation of glassy solid solutions should result in an enhanced bioavailability, as a good correlation of in vitro dissolution characteristics and bioavailability exists (Amidon et al., 1995).

3.3. Prediction of drug–isomalt miscibility by molecular modeling

To investigate the miscibility of the different drugs with isomalt on a quasi atomistic level, small model mixtures consisting of one drug molecule, surrounded by 34 isomalt molecules are built in the computer. These 1:34 mixtures allow to calculate the interaction forces between the drug and isomalt molecules exclusively. The effects of drug–drug interactions are not taken into account.

Dispersion forces, respectively, the Lennard–Jones potential $\mathrm{LJ_{in}}$ between the drug and isomalt increases with a higher molecular volume of the drug, as the polarizability of the drug molecule increases, too (Atkins, 1996). With respect to this, values obtained for the Lennard–Jones potential in these studies are used to bring the Coulomb interaction energy C_{SR} in relation to the molecular volume of the drug. For this purpose the non-dimensional parameter P_i is defined as polar interaction term by Eq. (5):

$$P_i = \frac{C_{\mathrm{SR}}}{\mathrm{LJ_{in}}} \tag{5}$$

For each drug–isomalt mixture a 2 ns simulation was performed. The last 1500 ps of these simulations were used for analysis. In Fig. 2, typical examples of the drug–isomalt ensembles from such simulations are shown. C_{SR} and $\mathrm{LJ_{in}}$ were calculated according to the equations given above. The results of the

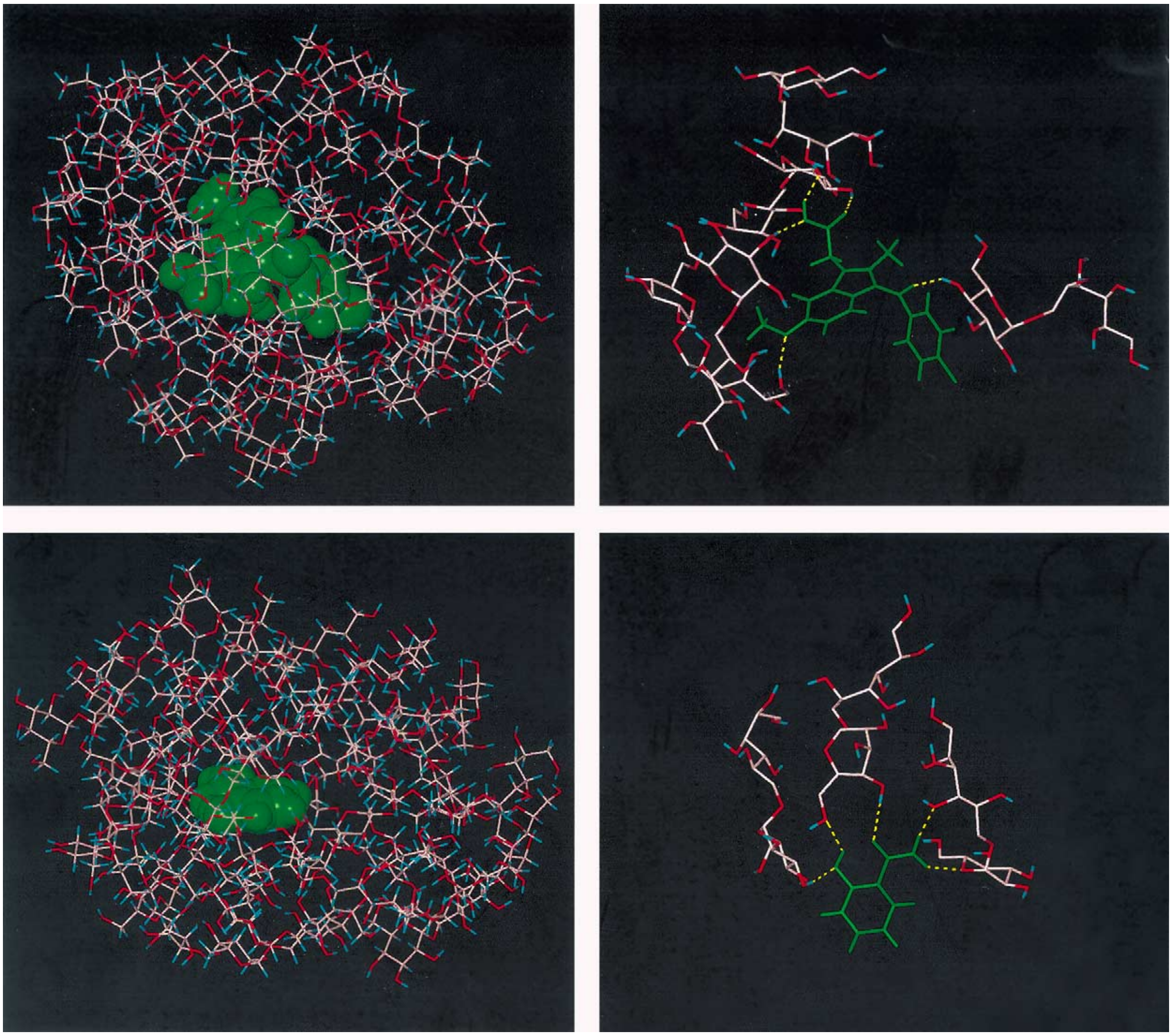

Fig. 2. Typical drug–isomalt model ensembles from the MD simulations: indomethacin (upper left) and salicylamide (lower left) in isomalt. Drug molecules are displayed in green, isomalt is displayed in sticks (carbon: white, oxygen: red, hydrogen: cyan). Detailed view of indomethacin (upper right) and salicylamide (lower right) with adjacent isomalt molecules. Both drug molecules form five hydrogen bonds (dotted yellow lines).

calculations are summarized in Table 5. In the first two columns, the contributions from C_{SR} and LJ_{in} to the interaction energies are shown. From these values no clear differences can be denoted between the miscible and the immiscible drugs. As can be seen from Fig. 2, indomethacin as well as salicylamide form the same number of hydrogen bonds with the surrounding isomalt molecules. An analysis of the total number of hydrogen bonds that are present during the simulation between both compounds and isomalt gives similar values. Indomethacin forms on the average 3.2 hydrogen bonds, slightly more than salicylamide (3.0). Due to this and its higher number of heteroatoms, indomethacin yields an energetically more favorable C_{SR} interaction energy (−81.7 kJ/mol, Table 5) than salicylamide (−75.2 kJ/mol). The contribution from the Lennard–Jones potentials LJ_{in} is also larger for indomethacin than for salicylamide. This is a result of

Table 5
P_i-values of drug–isomalt interaction arranged according to descending values, together with the respective C_{SR}-, LJ_{in}-, V_m- (Fedors) and $P_{i\,(V)}$-values

Drug	C_{SR} (kJ/mol)	LJ_{in} (kJ/mol)	P_i (Eq. (5))	V_m (cm^3/mol)	$P_{i\,(V)}$ (kJ/cm^3)	Miscibility (liquid state)	Solubility (glassy state, %)
Isomalt (carrier)	−341.6	−277.2	1.2	179.9	1.9	+	∞
Acyclovir	−155.3	−183.0	0.9	123.0	1.3	+	>10
Salicylamide	−75.2	−136.0	0.6	95.4	0.8	+	~5
Metronidazole	−79.2	−144.5	0.6	120.8	0.7	+	>10
Theophylline	−88.3	−170.6	0.5	110.2	0.8	+	>5
Carbamazepine	−116.4	−228.4	0.5	166.6	0.7	+	<5
Trimethoprim	−117.8	−238.7	0.5	197.2	0.6	+	>10
Warfarin[a]	−113.1	−303.4	0.4	213.6	0.5	−	−
Niclosamide	−79.1	−262.3	0.3	175.1	0.5	−	−
Indomethacin	−81.7	−290.7	0.3	229.8	0.4	−	−
Ibuprofen	−50.0	−206.7	0.2	195.5	0.3	−	−
Diclofenac	−49.7	−226.2	0.2	182.9	0.3	−	−
Papaverine	−63.5	−311.0	0.2	251.2	0.3	−	−
Ketoconazole	−71.8	−365.7	0.2	344.1	0.2	−	−
Clotrimazole	−52.0	−287.5	0.2	248.1	0.2	−	−

[a] RS warfarin.

the different molecular size, salicylamide has a much smaller molecular volume and thus less potential interaction points. The C_{SR}/LJ_{in} ratio P_i however, puts both values in an adequate proportionality and offers a good correlation between the calculations and the experimentally determined miscibilities. Obviously, mixing occurs at P_i-values higher than 0.4. This limiting value of P_i allows to distinguish miscible drugs from immiscible ones. In order to prove the correlation between the Lennard–Jones interaction term and the molar volume of the respective drugs, P_i-values are also calculated by using molar volumes obtained from Fedors group contribution method instead of the Lennard–Jones interaction potential (Table 5). These $P_{i\,(V)}$-values exhibit a rather similar sequence with a limiting value of around 0.5 kJ/cm^3.

3.4. Formation of glassy solid solutions

All combinations miscible in the molten state form to some extent glassy solid solutions (Table 5), dependent on their tendency to recrystallize during preparation. At a concentration of 5% drug, only carbamazepine shows immediate recrystallization during cooling at ambient temperature, resulting in a non-vitreous, white occurrence of the solid dispersion. All other miscible drugs form vitreous solid

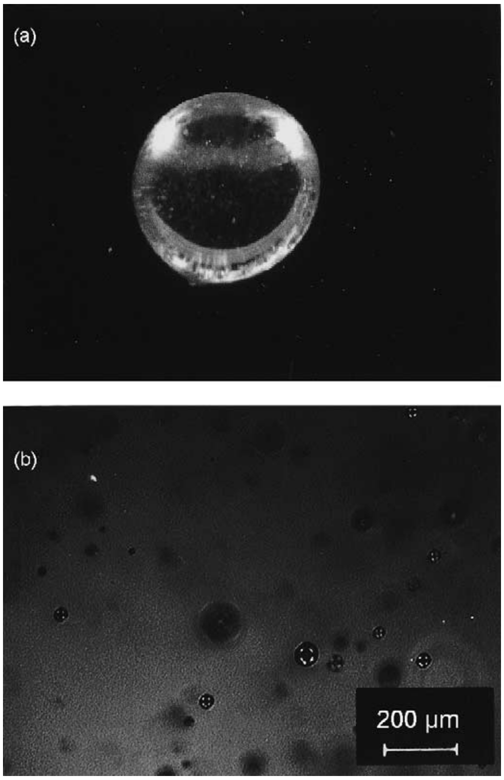

Fig. 3. Glassy solid solution of 10% acyclovir in isomalt: (a) scanned droplet; (b) microscopic picture, polarized light.

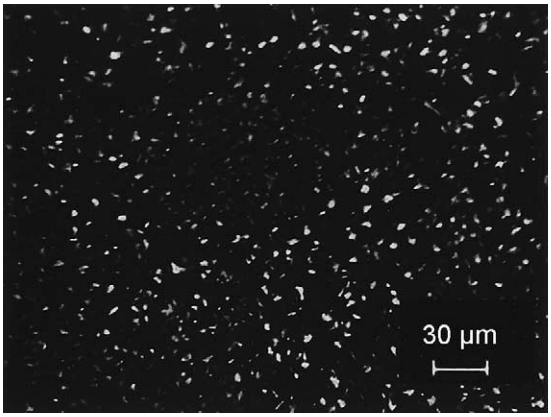

Fig. 4. Microscopic picture of 5% salicylamide in glassy isomalt, polarized light.

solutions. In the case of acyclovir, even 10% drug could be dispersed without detectable recrystallization (Fig. 3). In the case of 5% salicylamide, nucleation of drug in glassy isomalt could be observed gradually after preparation (Fig. 4). Therefore, solubility of salicylamide in glassy isomalt is assumed to be about 5%. For the manufacture of glassy solid solutions, solubilities in the glassy carrier given in Table 5 are of minor interest, since the amount of molecularly dissolved drug in the carrier isomalt can be increased by the addition of recrystallization inhibitors (Langer et al., 2000).

4. Discussion

For the miscibility of two liquids or melts, the Gibbs free energy of mixing at constant pressure ΔG_m must be negative:

$$\Delta G_m = \Delta H_m - T\,\Delta S_m \tag{6}$$

The entropy change ΔS_m of a mixing process is usually positive (Barton, 1991). In order to predict miscibility, it is necessary to evaluate the enthalpy term ΔH_m. When this term is negative, or positive but less than $T\Delta S_m$, mixing can occur. In the case of drug–isomalt mixtures we assume an endothermic heat of mixing (ΔH_m positive), as the calculated total interaction energy of −619 kJ/mol for isomalt alone is much higher than the interaction energy between isomalt and all drugs included in this study. The origin of the high interaction energy of isomalt is self-association of isomalt molecules by hydrogen bonds, resulting in the highest P_i-value of 1.23. Hence, mixing occurs due to a non-combinatorial gain in entropy upon mixing (Painter et al., 1991), because the extent of hydrogen bonded species in a mixture is lower than in the self-associated sugar alcohol. Provided that the number and enthalpy of hydrogen bond interaction in the mixture is less than in pure isomalt, the increase in entropy corresponding to the breaking of isomalt–isomalt and possible drug–drug hydrogen bonds minus the entropy loss from isomalt–drug hydrogen bonds, gives a larger negative contribution to the free energy than the positive heat of mixing, so that isomalt and drug are miscible at the respective temperature. The change of the entropy term $-T\Delta S_m$ associated with the mixing is opposite in sign and effect to the heat of mixing.

However, the formation of hydrogen bonds between isomalt and drug molecules seems to be a necessity for mixing, which is consistent with results obtained by Shamblin et al. (1998) for the miscibility of colyophilized binary sucrose mixtures. Since the key interactions between isomalt and drug molecules, i.e. hydrogen bonds besides dipole and ionic forces, are depicted in a high Coulomb interaction energy, the value of P_i is indicative for the miscibility of sugar alcohols and drugs in the molten state.

Solubility parameters refer to liquid state properties of solids regarded as supercooled liquids. The term was established to predict the miscibility of liquids from the properties of single components. According to Hildebrand and Scott (1964), the enthalpy of mixing two liquids ΔH_m is related to their solubility parameters δ_1 and δ_2 by Eq. (7), where Φ_1 and Φ_2 are the volume fractions of the components and V_m the volume of the mixture. Equal or similar δ-values lead to ΔH_m-values near zero and mutual solubility due to a negative entropy term.

$$\Delta H_m = \Phi_1\Phi_2(\delta_1 - \delta_2)^2 V_m \tag{7}$$

As Eq. (7) assumes regular mixing behavior, deviations must be expected, if specific interactions between unlike molecules exist, that cannot be predicted by the geometrical mean of interactions between like molecules. Using this approach, miscibility can be predicted rather exactly for non-polar systems, while predictions for polar systems containing hydrogen bonding molecules are less accurate. This is one reason, why miscibility for drugs with differences in their solubility parameter to isomalt ($\Delta\delta_t$) in the range of 8–15 cannot be predicted precisely. In this case the endothermic heat of mixing will be less than predicted by the solubility parameter approach.

Additionally, entropy changes are neglected for regular mixing behavior, since molecules are thought to be randomly dispersed, despite the existence of interactions which lead to a non-ideal (non-zero) enthalpy of mixing. This effectively restricts regular mixtures to those systems in which only dispersion forces are important, because the orientation effects of polar molecules cause non-random molecular distributions (Barton, 1991; James, 1986). Irregular mixtures with one self-associating component are characterized by an excess entropy (Hildebrand and Scott, 1964), that cannot be predicted by the use of solubility parameters. This is assumed as another reason for miscibility of some drugs like trimethoprim and carbamazepine with $\Delta\delta_t$-values between 8 and 15 $\mathrm{MPa}^{1/2}$.

Since dispersion forces have a negligible contribution to the excess entropy in irregular solutions, the consideration of specific interactions between unlike molecules should be more appropriate to predict miscibility for drugs with similar $\Delta\delta_t$-values. Unfortunately, the prediction of polar and hydrogen bond interactions of different structural groups is very complicated and does not obey simple rules. The partial solubility parameters δ_d, δ_p and δ_h are indicating the relative strengths of dispersion forces, polar forces and hydrogen bonding forces present in the material itself, but it is difficult to derive a relationship for the formation of specific interactions between unlike molecules. Nevertheless, high δ_p- and δ_h-values imply a hint at miscibility of drug and isomalt, except for carbamazepine and trimethoprim.

The advantage of the presented molecular modeling studies is the exact prediction of specific interactions between unlike molecules. High values of P_i indicate a high number of specific interactions between drug and carrier molecules per volume, resulting in a larger entropy ΔS_m and lower enthalpy of mixing than expected from assumptions made by solubility parameters based on regular solution theory. Thus, the first prerequisite to the formation of glassy solid solutions, namely miscibility of drug and sugar alcohol in the molten state, can be predicted by the use of P_i-values obtained by molecular dynamics studies.

Isomalt is a molecule with a very polar accessible molecular surface because it is evenly covered by hydroxyl groups. Thus, it can be anticipated that chemical species offering a high percentage of electrostatic interaction properties in proportion to their volume are miscible with isomalt. The computational method applied calculates this type of interaction very reliable. Force-field Coulomb term and Lennard–Jones potential employed in this study seem to be of sufficient accuracy to identify clearly those drugs which can mix with the carrier. However, it is important to note that in cases where electronic processes like polarization and charge transfer play the major role in interaction, force-field methods will fail. Complex types of electronic interaction only can be calculated using high level quantum chemical programs, but still limitations in system size exist and therefore the simulation of dynamic conformational changes directly is impossible. The great advantage of the force-field methods is that they give a detailed molecular picture of the conformation dependent isomalt–drug interactions, both qualitatively and quantitatively.

All investigated systems miscible in the molten state form to some extent glassy solid solutions. The extent of the formation depends on the recrystallization tendency during preparation. Recrystallization is most likely to occur during cooling, since the solubility of the drug in the supercooled carrier decreases and molecular mobility (Hancock et al., 1995) is still very high above the glass transition temperature of the carrier (Table 1). Due to practical reasons, Goldberg et al. (1965) suggested to assume the existence of a solid solution in the case, that the solubility of one component in the other exceeds 5% at the solid state. This seems not to be appropriate since the final solubility depends on the prevention of recrystallization of drug molecules from supersaturated glassy systems. Thus, stability and stabilization of metastable solid solutions by the use of recrystallization inhibitors determine the final supersaturation. This was shown by Urbanetz (2001) for interstitial crystalline solid solutions of nimodipine and PEG 2000 and by Langer et al. (2000) for glassy solid solutions of carbamazepine and isomalt.

The solubilities of drugs in glassy isomalt given in the present study are indicative of the thermodynamical solubility at ambient temperature, since the nucleation time decreases with higher degree of supersaturation for the respective drug (Raghavan et al., 2001). Hence, spontaneous crystallization is observed for drugs having a high degree of supersaturation, e.g. carbamazepine.

5. Conclusion

Glassy solid solutions of drugs in sugar alcohols can be prepared by the fusion method, if the drug is miscible with the molten carrier. MD simulations have shown that miscibility in the molten state results from electrostatic interaction forces, comprising hydrogen bonding as the key interaction of the drug molecules with the carrier molecules. Therefore, values of the non-dimensional interaction parameter P_i representing electrostatic interactions in relation to the molecular volume can be applied to distinguish immiscible drugs from miscible ones and hence to predict miscibility with the respective sugar alcohol in the molten state. Electrostatic interaction energies as well as the Lennard–Jones potential, which is used to include the molecular size, are obtained quantitatively from MD simulations. For isomalt, mixing occurs at P_i-values higher than 0.4 and glassy solid solutions are formed, if drug recrystallization can be prevented during cooling. Apart from mannitol, all sugar alcohols applied in this study resolidify in the glassy state, when cooling the melt at ambient temperatures, offering the possibility to formulate glassy solutions.

In contrast to P_i-values, solubility parameters are not suitable to evaluate electrostatic interactions between unlike molecules in irregular solutions, since they are reflecting interactions between like molecules. Therefore, they fail to predict the miscibility of drugs with the self-associated sugar alcohols, if the solubility parameter of the drug is not very close or very different to that of the carrier. Referring to the range of 8–15 $\text{MPa}^{1/2}$ for the calculated solubility parameter difference of drug and sugar alcohol this implies that the contribution of hydrogen bonding as key interaction for miscibility cannot be rated precisely by the solubility parameter method.

In conclusion, the use of P_i-values for predicting glass formation should be restricted to those systems, where self-association of the molten carrier by hydrogen bonding plays the major role for miscibility. In this context, it should be noted that P_i-values of drug–isomalt interactions seem to decrease with lower solubility of drugs in water, too.

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