Journal of Thermal Analysis and Calorimetry, Vol. 95 (2009) 3, 885–890

INVESTIGATION OF THE THERMAL AND STRUCTURAL BEHAVIOUR OF DICLOFENAC SODIUM–SUGAR ESTER SURFACTANT SYSTEMS

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Sugar esters (SEs) have a wide range of hydrophilic–lipophilic balance (HLB) values (1–16) and hence can be applied as surfactants or as solubility or penetration enhancers. They can be used for hot melt technology and solvent method which are frequently applied techniques to preparation of solid dispersions. In this study drug-SE products were prepared by physical mixing, melt technology and solvent methods. The products were investigated by DSC, X-ray powder diffraction and dissolution tests. Diclofenac sodium (DS) as model drug and two SEs, P1670 (HLB=16) and S970 (HLB=9) were used for the preparation of the products.

DSC curves revealed considerable melting range and enthalpy decreases for the DS–SE products. The dissolved drug molecules broke down the structures of the SEs but were not built into the crystalline phase of the carrier. The melt technology led to a solid dispersion while in the case of the solvent methods the DS was in molecularly dispersed form which resulted in faster dissolution. The drug release was influenced by the structures resulting from the various treatments, by the HLB and by the gel-forming behaviour of the SEs.

Keywords: *drug release, DSC, solid dispersion, sugar ester, X-ray*

Introduction

Sugar esters (SEs) are widely used in the pharmaceutical and food industries. They are non-ionic surface-active agents consisting of sucrose as hydrophilic group and fatty acids as lipophilic groups. Through variation of the type or number of the fatty acid groups a wide range of HLB values can be obtained [1]. Depending on their HLB values the SEs are available with a broad range of properties: O/W and W/O emulsifying properties, solubilizing and foaming properties [2, 3], enhancement or inhibition of crystal growth in fat [4], lubrication [5] and releasing properties [6–8].

SEs are commonly used in hot-melt technology [9–11], because their melting points are low and they decompose only above 220°C. The thermal properties of SEs were previously studied and demonstrated differences between SEs with various HLB values [12]. The results of our MTDSC measurements revealed that SEs with high (e.g. P1670) or moderate (S970) HLB values undergo a glass transition, which coincides with the melting points of the materials. Investigations with hot-stage microscopy showed that hydrophilic SEs were only softened whereas lipophilic SEs were melted by heating.

It was found that only SEs with low HLB values can be used well in hot-melt technology, while the distribution of drugs is more difficult in SEs with high or moderate HLB values. Because of their polarity, the latter SEs can be used in the solvent method too. They dissolve in polar solvents such as ethanol or chloroform. In spite of their HLB values, they do not dissolve well in water, with which they form a gel, and water evaporation from the products is then very difficult in consequence of their hygroscopicity. Thus, only organic solvents such as ethanol are applicable in the case of these SEs.

The literature data indicate that the effects of hydrophilic SEs on the dissolution of drugs are very different: SEs with high HLB values are used to increase or sometimes to sustain drug release. For example, S1670 (HLB=16) has been used to improve the rate of dissolution of glybuzole [9] and S1670, L1695 and M1695 (HLB=16) to increase the rate of dissolution of spironolactone [10]. Although S1670 is hydrophilic, Seiler *et al.* used this SE to prepare controlled release matrix formulations of theophylline [11]. S1570 and P1570 with a HLB of 15 were also used as matrix-forming agents for ibuprofen and theophylline [8].

In preformulation studies it is very important to know the thermal and structural properties of the materials [13–15]. The aim of the present study was to compare the thermal behaviour and structures of hydrophilic SEs without and with active agent and to examine the effects of the SEs on drug release. The ap-

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1388–6150/$20.00

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plicability of SEs with a high or medium HLB value in the melt and in the solvent method was also investigated. For comparison, drug-SE physical mixtures were used. In the selection of the model drug, the solubility of the active agent was an important factor. Diclofenac sodium (DS) was chosen for the investigations because, like the SEs it dissolves well in ethanol. DS belongs in the BCS II class: it is slightly soluble in water its solubility increasing as the pH rises.

Experimental

Materials

The Ryoto SEs (Mitsubishi-Kagaku Foods Corporation, Japan) are a family of vehicles consisting of sucrose and mixtures of mono- to octaesters of fatty acids. Two SEs were applied in this study: one with an HLB value of 16 (P1670) and one with an HLB value of 9 (S970). The longer the fatty acid chains in the SEs and the higher the degree of esterification, the lower the HLB value (Table 1).

DS was from Sigma Co. (Hungary). Its particle size was $d(0.9)$=6 μm.

Sample preparation

In the preparation of the physical mixtures, DS and SE (in a ratio of 1:1) were homogenized in a mortar.

For the melted products the DS–SE physical mixtures were melted in a porcelain dish in an oven (Factory for Laboratory Equipment, Budapest, Hungary, Labor type 123) by heating from 25 to 100°C and then cooled back to room temperature.

Solvent products were made as follows: DS and SE (in a ratio of 1:1) were dissolved in absolute ethanol with use of a magnetic stirrer and the solvent was evaporated off in a microwave apparatus (ETHOS Touch Control, Microwave Laboratory System, Milestone).

After the preparations the samples were in all cases pulverized in a mortar and sieved to 200 μm.

For comparison of the results the two commercial SEs were used, the melted and solidified SEs without active agent, and the dissolved and recrystallized SEs without drug. The notations applied: for the physical mixtures: 'phys. mixt.'; for the melted and solidified samples: 'melt'; and for the dissolved and recrystallized samples: 'solvent'.

Methods

Differential scanning calorimetry

DSC studies were performed with a DSC 821^e (Mettler-Toledo GmbH, Switzerland). The instrument was calibrated by using indium. Samples of 10 mg were heated in a sealed aluminium pan. Measurements were made in a N_2 atmosphere at a flow rate of 50 mL min^{-1}. The samples were heated from 25 to 300°C at a heating rate of 10°C min^{-1}.

X-ray powder diffraction

XRPD profiles were taken with a Philips X-ray diffractometer (PW 1930 generator, PW 1820 goniometer). The measurement conditions were as follows: CuK_α radiation (λ=0.15418 nm), 40 kV, 35 mA. The basal spacing (d_L) was calculated from the diffraction peaks by using the Bragg equation.

In vitro drug release study

For the dissolution tests the DS–SE products were filled into hard gelatine capsules. The capsules contained 50 mg of DS (and 50 mg of SE). The release of the model drug was studied by using Pharmatest equipment (Hainburg, Germany) at a paddle speed of 100 rpm. 900 mL gastric juice (pH=1.1±0.05) at 37°C (±0.5°C) was used. The drug contents of the samples were measured spectrophotometrically (λ_{DS}=272 nm) (Unicam UV/VIS spectrophotometer).

Results and discussion

Thermal properties

Table 2 shows the results obtained by DSC. After melting and solidification (melt technology) or after the solvent evaporation (solvent method) the structures of the SEs without drug broke down and were then rebuilt to varying extents. In the cases of the P1670(melt) and P1670(solvent), the breaking-down of the structure shifted the melting range and both the onset and endset values were lower than those of the initial SE and enthalpy decreases. In the case of S970 the melting range was slightly changed after treatment but the total enthalpy of the SE was less after the solidification than after the solvent evaporation.

Table 1 Data on SEs from Mitsubishi-Kagaku Foods Co.

SE	Fatty acid	HLB	*Mp*/°C	Decomposition temperature/°C	Degree of esterification
P1670	palmitate (C16)	16	48	235	mono-, di- and triester
S970	stearate (C18)	9	56	234	mono-, di-, tri- and tetraester

Table 2 DSC data on SEs, DS-SE products and DS

	Melting range onset-endset/°C	Total enthalpy/ J g^{-1}
P1670	41–62	–52.2
P1670(melt)	36–53	–42.5
P1670(solvent)	37–53	–42.6
DS-P1670(phys. mixt.)	37–53	–23.2
DS-P1670(melt)	36–48	–5.7
DS-P1670(solvent)	37–53	–3.4
S970	46–67	–58.7
S970(melt)	43–65	–31.2
S970(solvent)	42–65	–52.6
DS-S970(phys. mixt.)	39–67	–26.5
DS-S970(melt)	36–58	–17.9
DS-S970(solvent)	45–57	–1.2
DS	280–294	–93.9
DS(solvent)	279–292	–76.0

The thermal behaviour of DS was investigated with DSC, too. The melting of the drug (at 291°C) was followed by an exothermic peak caused by decomposition of the drug. For this drug, therefore, the melt technology can be used only with carriers at lower temperature. After DS dissolves in ethanol it recrystallizes quickly and without structural change; only the enthalpy is a little decreased (Table 2).

The comparisons revealed that the drug brought about considerable structural changes in the SEs. The melting ranges for the DS-P1670 products were similar but the total enthalpies of P1670 were different. The enthalpies decreased in all the cases but especially for the DS-P1670(melt), and DS-P1670(solvent) (Table 2). The melting ranges likewise changed considerably for the DS-S970 products and the enthalpy decreased too, especially after solvent evaporation.

The behaviour of the SEs in the presence of drug was examined in a wider temperature interval. The melting point of DS is at 291°C, and the measurements were therefore performed in the 25-300°C range. However, the SEs decompose over 200°C, so the curves were not plotted above this temperature (Figs 1 and 2). For the drug-containing products the melting point of DS could not be seen after the decomposition of the SEs; this melting probably took place simultaneously with the decomposition of the SE and part of the drug could have been dissolved in the melted SE.

For the DS-P1670 products a new endothermic peak appeared at 171°C for the DS-P1670(phys. mixt.), at 171°C for the DS-P1670(melt) and at 166°C for the DS-P1670(solvent) (Fig. 1). The part of DS which did not dissolve into the SE must have melted before the decomposition of P1670. The DSC curves

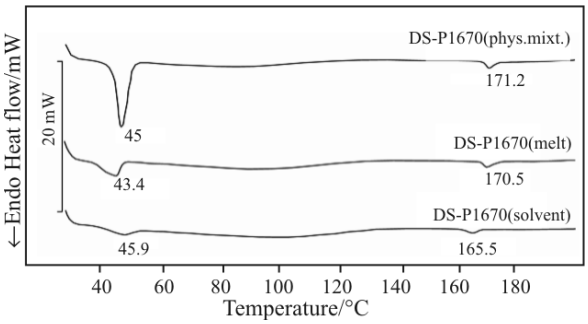

Fig. 1 DSC curves of DS-P1670 products

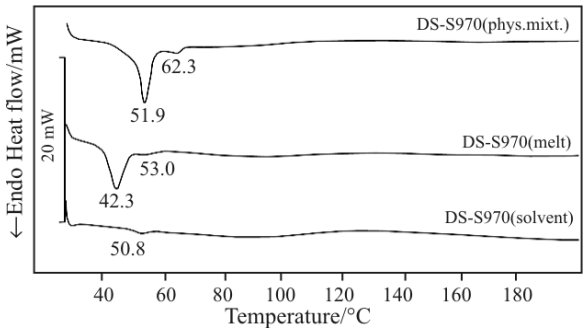

Fig. 2 DSC curves of DS-S970 products

showed that the physical mixing caused a lower change but the solvent method a major change. The enthalpy of the DS-P1670(solvent) was lower and the second peak appeared by 6°C lower temperature than in the case of the DS-P1670(phys. mixt.). The enthalpy of the DS-P1670(melt) was also considerably less than that of the DS-P1670(phys. mixt.). For the DS-S970 products only the peak characteristic of S970 appeared in the DSC curve up to 200°C; there was no new endothermic peak. The differences in thermal behaviour of the products can be explained by the various HLB values of the SEs. P1670 has a high HLB value of 16, so more of the drug can dissolve in the SE in the DS-P1670 products, while in the DS-S970 products the amount of the dissolved drug in the SE is less because of the lower HLB value of 9. For the DS-S970 products, the total enthalpy of S970 after solvent evaporation was very low (Fig. 2), while the simple mixing and the melting did not cause such a great change (Table 2).

The DSC results demonstrated that the drug brought about great structural changes in the SEs. Simple mixing was sufficient to break down the structures of the SEs but the degree of recrystallization differs in the various methods; it was least after solvent evaporation.

X-ray powder diffraction

The SEs have only 2 or 3 characteristic peaks in their X-ray diffractograms the majority of them appear at

Table 3 X-ray data on SEs and DS-SE products

	2θ/°	Basal spacing/nm	Counts
P1670	2.2	4.14	18605
P1670(melt)	2.2	4.14	9101
P1670(solvent)	2.2	4.14	19404
DS-P1670(phys. mixt.)	2.2	3.99	2725
DS-P1670(melt)	2.2	4	2190
DS-P1670(solvent)	2.7	3.31	1584
S970	1.6 and 2.1	5.78 and 4.14	4597 and 3648
S970(melt)	1.6	5.51	6939
S970(solvent)	2.3	3.86	7225
DS-S970(phys. mixt.)	1.6 and 2.3	5.51 and 3.86	930 and 992
DS-S970(melt)	2.2	4.14	1640
DS-S970(solvent)	2.6	3.38	1560

small angles where DS gives no signal. After melting and solidification or solvent evaporation the position and basal spacing of the characteristic peak of P1670 at 2.2° 2θ were the same; only the counts were changed (Table 3). The initial S970 has two characteristic peaks (at 1.6 and 2.1° 2θ), whereas the S970(melt) gave only the first (at 1.6° 2θ) and S970(solvent) only the second (at 2.3° 2θ). The X-ray examinations demonstrated that the structures of the SEs were rearranged after melting or dissolution, and then rebuilt to varying extents.

The building-in or intercalation of the drug can be inferred from the changes in the basal spacing of the SEs. If the basal spacing increases, it can be presumed that the drug has been built into the crystalline phase of the carrier. During our investigations the basal spacings of the SEs did not increase in any of the cases (Table 3), which leads to the conclusion that DS was not built into the crystalline phase of the SEs.

DS is a crystalline drug whose X-ray diffraction pattern contains 40 peaks, the most characteristics are at 6.6, 8.5, 15.2, 17.1, 19.8, 23.4, 27 and 27.9° 2θ; these were unchanged after solvent evaporation and recrystallization.

Figures 3 and 4 show the X-ray diffractograms of the DS-SE products. The characteristic peaks of both P1670 and the drug appeared for the DS-P1670(phys. mixt.); only the counts were decreased; new peaks did not appear anywhere. The X-ray diffractogram of the DS-P1670(melt) was very similar to that of the DS-P1670(phys. mixt.); the number of peaks was the same but the counts were slightly less for the DS-P1670(melt). Fewer than half of the peaks characteristic of DS appeared (17 peaks) in the X-ray diffraction pattern of the DS-P1670(solvent) and the count was decreased considerably, while the back-intensity was increased, so the DS was not in a

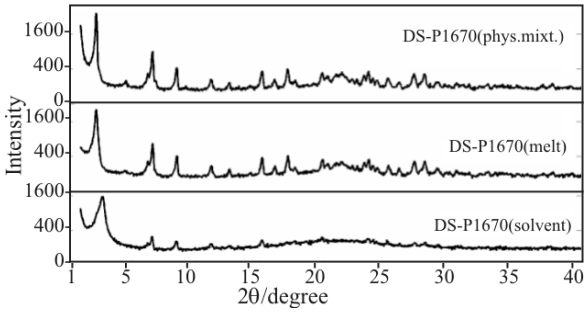

Fig. 3 X-ray diffractograms of DS-P1670 products

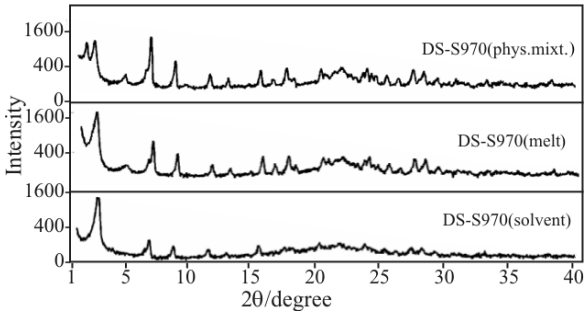

Fig. 4 X-ray diffractograms of DS-S970 products

crystalline state in this case (Fig. 3). The diffractograms of the DS-S970(phys. mixt.) and DS-S970(melt) were very similar to each other; only the counts were decreased somewhat after melting and solidification (Fig. 4). Similarly as for the DS-P1670(solvent), the counts and number of peaks characteristic of DS were decreased considerably for the DS-S970(solvent) (20 peaks appeared), but there were more crystalline phases in the diffractograms than in the case of the DS-P1670(solvent).

It can be stated that the X-ray measurements confirmed the DSC findings: the drug broke down the structures of the SEs and the degree of rebuilding then

differend. After the drug mixing (DS-SE(phys. mixt.)) or melting and solidification (DS-SE(melt)), the degree of recrystallization was considerable, while in the case of the DS-SE(solvent) products there was less crystalline phase. After dissolution and solvent evaporation, the bulk of the drug was in molecularly dispersed form in the SE matrix (solid solution).

Dissolution results

The effect of the treatment on the drug release was investigated, too. DS dissolves only slightly in water at pH 1.2; merely 8% of the drug is dissolved in 2 h. The solubility from the DS-P1670(phys. mixt.) (13%) was somewhat higher than that of the pure drug, and it was the same as for the DS-P1670(melt) (12%). The amount of drug dissolved from the DS-P1670(solvent) was 23% (Fig. 5). In spite of the molecularly dispersed state of the DS, the drug release did not reach 100%, which can be explained partly by the low equilibrium solubility of DS (0.005 mg mL^{-1} at pH=1.2; 37°C) and partly by the gel-forming behaviour of P1670. Due to an interaction between the DS and P1670 the swelling of the SE decreased with amount of dissolved DS, so this property had a role only in the first few min during the dissolution process. The change in the drug release was not significant in the cases of the DS-S970(phys. mixt.) (6%) and DS-S970(melt) (7%), but the dissolution was better from the DS-S970(solvent) (16%) (Fig. 6), which can be explained by the different drug distribution.

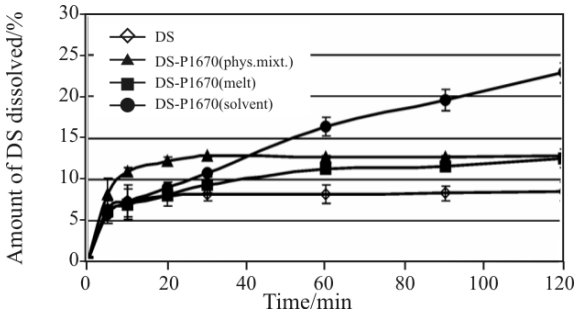

Fig. 5 Dissolution of DS and DS-P1670 products

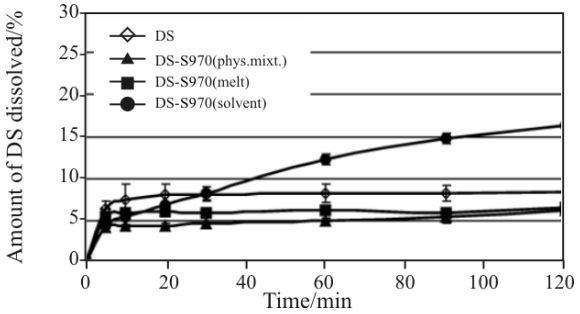

Fig. 6 Dissolution of DS and DS-S970 products

Conclusions

Our results have demonstrated that SEs with high or medium HLB values are applicable carriers in melt technology and in the solvent method. They are semicrystalline materials and the distribution of the drug in their melts is more difficult than in their solutions. DSC curves indicate a lower degree of reconstruction of the structures of the SEs after solvent evaporation than after simple drug mixing or after melting and solidification. SEs with high or medium HLB values soften during heating; for the melted products, therefore, only a small proportion of the DS can dissolve in the melted SE, after which it quickly recrystallizes. DS and the hydrophilic SEs dissolve well in ethanol; thus, the drug may dissolve completely in the solvent and is in a molecularly dispersed form after the fast solvent evaporation. DSC measurements and the X-ray diffractograms showed more considerable structural changes for the DS-SE(solvent) products where DS was not in a crystalline state. It must also be said that the solvent method is not always applicable, but only when the drug and SE have a common solvent. The fastest drug release can be reached with the DS-P1670(solvent), because this SE has the highest HLB value, and the part of the drug was in molecularly dispersed state in this SE.

Acknowledgements

The authors are grateful to Mitsubishi-Kagaku Foods Corporation (Japan) and Syntapharm GmbH (Germany) for providing sugar esters. We would like to thank Prof. Róbert Rajkó for his assistance in the construction of the Figures. This work was supported by the ERASMUS scholarship.

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Received: February 5, 2008
Accepted: April 21, 1008
OnlineFirst: September 20, 2008

DOI: 10.1007/s10973-008-9051-x