Journal of Pharmaceutical and Biomedical Analysis 48 (2008) 1136–1142

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Study of the effects of drugs on the structures of sucrose esters and the effects of solid-state interactions on drug release

Angéla Szűts[a], Zsolt Makai[a], Róbert Rajkó[b], Piroska Szabó-Révész[a,*]

[a] Department of Pharmaceutical Technology, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary
[b] Department of Unit Operations and Environmental Engineering, University of Szeged, H-6725 Szeged, Moszkvai krt. 5-7, Hungary

ARTICLE INFO

Article history:
Received 20 May 2008
Received in revised form 20 July 2008
Accepted 26 August 2008
Available online 2 September 2008

Keywords:
Sucrose ester
Differential scanning calorimetry
X-ray powder diffraction
Rheological measurement
Polarity
Solid-state interaction

ABSTRACT

Sucrose 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. In general, SEs are used in hot-melt technology, because of their low melting points, but literature data are not available on the effects of active agents on the structures of SEs and the possible solid-state interactions. In this study, drug–SE products were prepared by melt technology and investigated by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), rheological measurements and dissolution tests. The model drugs meloxicam and diclofenac sodium and three SEs with different polarities (P1670, S970 and B370) were chosen for the preparation of the products.

The DSC and XRPD results revealed that the structures of the SEs were rearranged, with a decrease in the degree of crystallinity. The dissolved drug molecules broke down the structures of the SEs, but were not built into the crystalline phase of the carrier. The dissolution of the drugs was influenced by the different HLB values and gel-forming behaviour of the SEs, and also by the polarity of the drug and the interactions between the drug and the SEs.

1. Introduction

Hot-melt technology is frequently used to influence the dissolution rate and bioavailability of drugs [1–3]. Many carriers are used in melt technology, such as PEGs, PVP, glycerides or mannitol, and their physicochemical properties are well known [4–8]. Sucrose esters (SEs) too, are applied in hot-melt technology, but the information available on these carriers is not sufficient and further investigations are needed. SEs are non-ionic surface-active agents consisting of sucrose as hydrophilic moiety 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 [9]. SEs can be applied in pharmaceutical technology as emulsifiers, solubilizing agents [10,11], liberation and absorption enhancers [12] or lubricants [13]. In most cases, SEs are used in melt technology to improve the bioavailability of poorly water-soluble materials. For example, S1670 (HLB = 16) has been utilized to improve the rate of dissolution of glybuzole [14]. Marton et al. used three SEs with HLB = 16 (S1670, L1695 and M1695) to increase the rate of dissolution of spironolactone [15]. They found a linear relationship between the amount of drug dissolved and the SE concentration. Csóka et al. influenced the dissolution of ibuprofen with SEs with different HLB values [16]. Seiler et al. examined the possibility of preparing CR matrix formulations of theophylline with the use of S1670 by hot-melt extrusion. Although S1670 is hydrophilic, its formulations underwent controlled drug release [17]. The results can differ considerably: SEs with high HLB values are used to increase or sometimes to slow down drug release. To be able to predict the drug release, it is necessary first to understand the material properties. The cause of different and unanticipated behaviour can be an interaction between the drug and the excipient. Hence, it is important to evaluate not only the character of the individual materials, but also the possible interactions. This is a crucial part of normal studies up to the final formulation setting of a solid dosage form [18–24]. We earlier studied the influence of thermal treatment of SEs on the structure without active agents [25]. The aim of the present work was to examine the effects of active agents on the thermal behaviour and structures of SEs and the effects of the drug–SE solid-state interactions on the drug release. In this respect, examinations of SEs have not been published in the literature so far.

2. Materials and methods

2.1. Materials

The following SEs were kindly provided by Syntapharm GmbH (Germany): P1670 (HLB = 16), S970 (HLB = 9) and B370 (HLB = 3).

* Corresponding author. Tel.: +36 62 545572; fax: +36 62 545571.
E-mail address: revesz@pharm.u-szeged.hu (P. Szabó-Révész).

0731-7085/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2008.08.028

Meloxicam (ME) was supplied by EGIS Ltd. (Hungary). Diclofenac sodium (DS) was from Sigma Co. (Hungary).

The particle sizes of the drugs: $d(0.9) = 65\ \mu m$ for ME, and $d(0.9) = 6\ \mu m$ for DS.

2.2. Sample preparation

Drug–SE physical mixtures (in a ratio of 1:1) were melted in a porcelain dish in an oven (Factory for Laboratory Equipment, Budapest, Hungary, Labor type 123), with heating from 25 to 100 °C, and then cooled back to room temperature. After melting and solidification, the freshly solidified samples were pulverized in a mortar and sieved to 200 μm.

For comparison of the results, we used the commercial SEs and the melted and solidified SEs without active agent. The notations applied: for the melted and solidified samples (for the SEs and drug–SE products): "melt" (e.g. ME–P1670(melt)).

2.3. 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 an 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}.

2.4. 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: Cu Kα radiation ($\lambda = 0.15418$ nm), 40 kV, 35 mA. The basal spacing (d_L) was calculated from the diffraction peaks by using the Bragg equation.

2.5. Contact angle measurements

The contact angle (θ) of the solids was determined by means of the sessile drop technique, using the OCA 20 Optical Contact Angle Measuring System (Dataphysics, Filderstadt, Germany). Contact angles must be measured with several liquids in order to assess the surface free energy of a powder. In the method of Wu, two liquids with known polar (γ_l^p) and dispersion (γ_l^d) components are used for measurement [26]. The solid surface free energy is the sum of the polar (γ^p) and non-polar (γ^d) components, and is calculated according to Eq. (1):

$$(1 + \cos\ \theta)\gamma_l = \frac{4(\gamma_s^d \gamma_l^d)}{\gamma_s^d + \gamma_l^d} + \frac{4(\gamma_s^p \gamma_l^p)}{\gamma_s^p + \gamma_l^p} \quad (1)$$

where θ is the contact angle, γ_s is the solid surface free energy and γ_l is the liquid surface tension.

For two components (Wu's method), a combination of water and diiodomethane, polar and non-polar liquids with the highest possible surface tension, exerts the minimum influence on the result. The liquids used for contact angle measurement were bidistilled water ($\gamma^p = 50.2$ mN m^{-1} and $\gamma^d = 22.6$ mN m^{-1}) and diiodomethane ($\gamma^p = 1.8$ mN m^{-1} and $\gamma^d = 49$ mN m^{-1}). The polarity percentage was calculated from the γ^p and γ values: $(\gamma^p/\gamma)100$.

2.6. Temperature sweep tests

For these measurements, a PaarPhysica MCR101 type rheometer (Anton Paar GmbH, Graz, Austria) was used (in controlled rate mode), equipped with a cone-and-plate measuring system (cone diameter, 50 mm; cone angle, 1°; truncation, 49 μm). During the measurements, the temperature of the samples was modulated from 25 to 40 °C with a heating rate of 1 °C min^{-1} while the resulting viscosity changes were recorded. The tested liquid contained 5% SE and 5% drug in water.

Table 1
DSC data on SEs, SE melts and drug–SE melted products

	Melting range (°C) onset–endset	Total enthalpy (J g^{-1})
P1670	41–62	−52.2
P1670(melt)	36–53	−42.5
ME–P1670(melt)	36–55	−19.4
DS–P1670(melt)	36–48	−5.7
S970	46–67	−58.7
S970(melt)	43–65	−31.2
ME–S970(melt)	43–65	−15.1
DS–S970(melt)	36–58	−17.9
B370	50–88	−89.6
B370(melt)	53–90	−65.9
ME–B370(melt)	54–91	−28.4
DS–B370(melt)	40–86	−44.1

2.7. Dissolution studies

For the dissolution tests, the ME–SE or DS–SE melted products were filled into hard gelatine capsules. The capsules contained 15 mg of ME and 15 mg of SE, or 50 mg of DS and 50 mg of SE.

The release of the model drugs was studied by using Pharmatest equipment (Hainburg, Germany), at a paddle speed of 100 rpm. 900 ml artificial enteric juice (Ph.Eur. 5) with a pH of 7.5 (±0.05) at 37 °C (±0.5 °C) was used. The drug contents of the samples were measured spectrophotometrically ($\lambda_{ME} = 362$ nm; $\lambda_{DS} = 276$ nm) (Unicam UV/Vis spectrophotometer). The dissolution experiments were conducted in triplicate.

2.8. Statistical calculations

The standard deviation (S.D.) and the two-sample analysis were carried out with the Microsoft Statistical Program; the confidence limit was 95%.

3. Results and discussion

3.1. Differential scanning calorimetry

Table 1 shows the results obtained with DSC. After melting and solidification, the structures of all three SEs without drug broke down, and were then rebuilt to varying extents. In the case of P1670, 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; the enthalpy decreased. In the cases of S970 and B370, the melting range was slightly changed after treatment, but the enthalpy exhibited a major decrease here too.

The comparisons revealed that the drug brought about considerable structural changes in the SEs, to different extents with the three SEs. For ME–P1670(melt), the melting range was not changed significantly as compared with P1670(melt), while the enthalpy decreased to half. An even greater change occurred for DS–P1670(melt): here the melting finished 5 °C sooner than for P1670(melt), and the enthalpy decreased considerably (Table 1). The change in ME–S970(melt) in comparison with S970(melt) was similar to that for P1670: the melting range did not change, but the enthalpy was reduced to half. The melting of DS–S970(melt) started and finished 7 °C sooner than that of S970(melt), but the enthalpy decreased only to half, as in the case of ME–S970(melt).

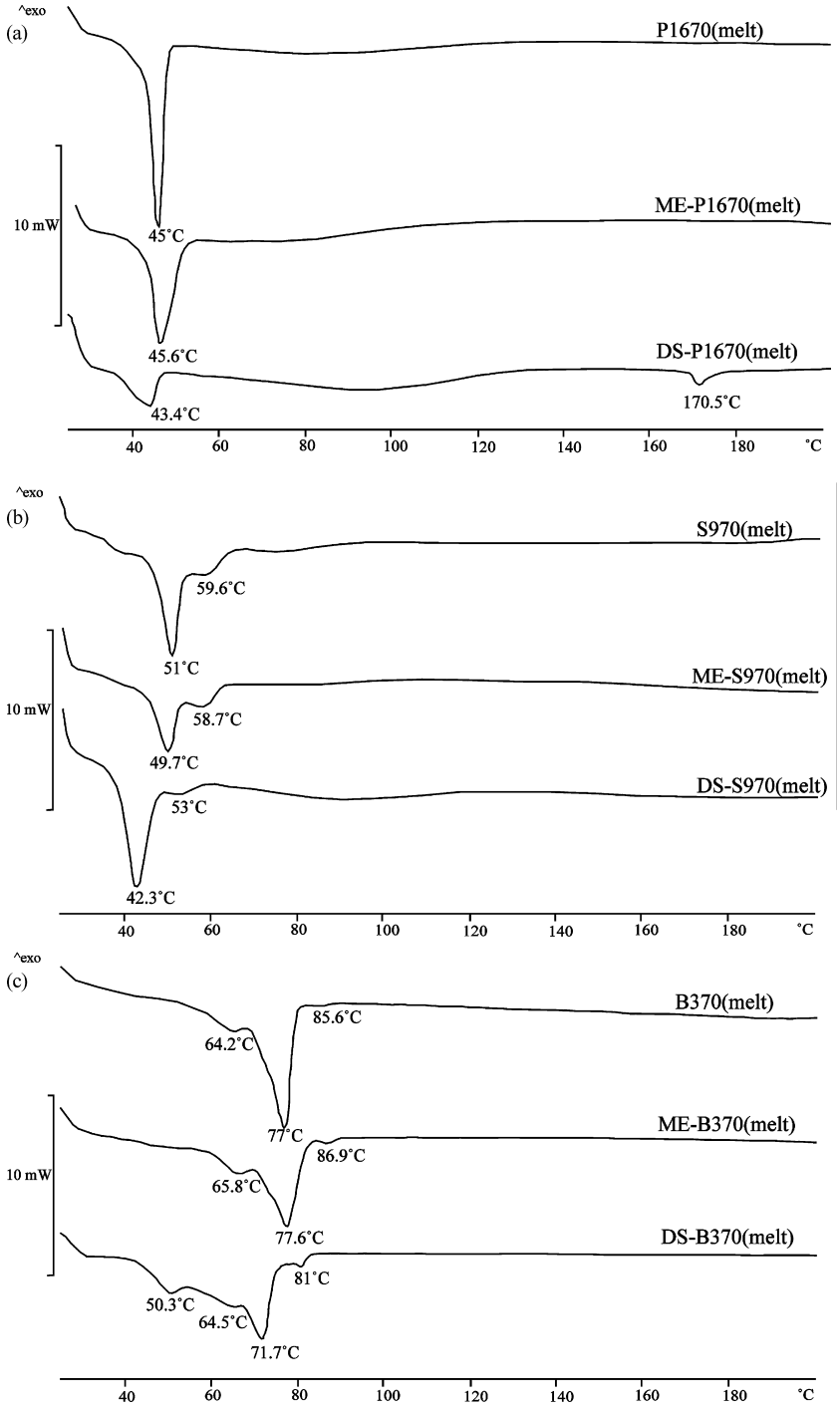

Fig. 1. DSC curves of SE melts and drug–SE melted products. (a) P1670(melt) and drug–P1670(melt), (b) S970(melt) and drug–S970(melt) and (c) B370(melt) and drug–B370(melt).

The melting range of ME–B370(melt) was not changed relative to that of B370(melt), though the enthalpy was decreased, while the melting of DS–B370(melt) started more than 10 °C earlier than that of B370(melt) (Table 1).

The behaviour of each SE in the presence of these drugs was examined in a wider temperature interval, too. The melting point of ME is at 263 °C, and that of DS is at 291 °C, and the measurements were therefore performed in the range 25–300 °C. However, the SEs can be pyrolysed above 200 °C [27], so the curves were not plotted above this temperature (Fig. 1). For the drug-containing products, the melting points of ME and DS could not be seen after the pyrolysis of the SEs; this melting probably took place simultaneously with the pyrolysis of the SE, and part of the drug could have dissolved in the melted SE. For the DS–P1670 product, a new endothermic peak appeared at 170.5 °C (Fig. 1a). The DS, which did not dissolve in the SE must have melted before the pyrolysis of P1670.

3.2. X-ray powder diffractometry

The X-ray diffractograms demonstrated that the peaks characteristic of SEs and of the drug appeared for each drug–SE product; only the numbers of counts decreased, new peaks not appearing

Table 2
X-ray data on SEs, SE melts and drug–SE melted products

	2θ (°)	Counts
P1670	2.2	10,692
P1670(melt)	2.2	9,101
ME–P1670(melt)	2.2	2,852
DS–P1670(melt)	2.2	2,190
S970	1.6 and 2.1	4,597 and 3,648
S970(melt)	1.6	6,939
ME–S970(melt)	1.6	1,739
DS–S970(melt)	2.2	1,640
B370	1.3 and 1.9	5,184 and 2,841
B370(melt)	1.4	6,352
ME–B370(melt)	1.3	1,303
DS–B370(melt)	2	955

anywhere. Only 2 or 3 peaks can be seen in the X-ray pictures of the SEs, the majority of them at small angles where the drugs give no sign. 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. The positions of the peaks of the SEs at small angles and their intensities are listed in Table 2, and plotted in Figs. 2–4, where the basal spacings are also indicated. For P1670, neither the position of the characteristic peak of SE nor the basal spacing changes considerably; only the degree of crystallinity decreases to a third as compared with P1670(melt), both for ME–P1670(melt) and for DS–P1670(melt) (Fig. 2). For ME–S970(melt), the degree of crystallinity decreases to a quarter relative to S970(melt), just as in the case of the DS–S970(melt). It is clear from Fig. 3 that only one characteristic peak of the SEs appears for the products, at different positions for the two drugs. The greatest decrease in crystallinity is

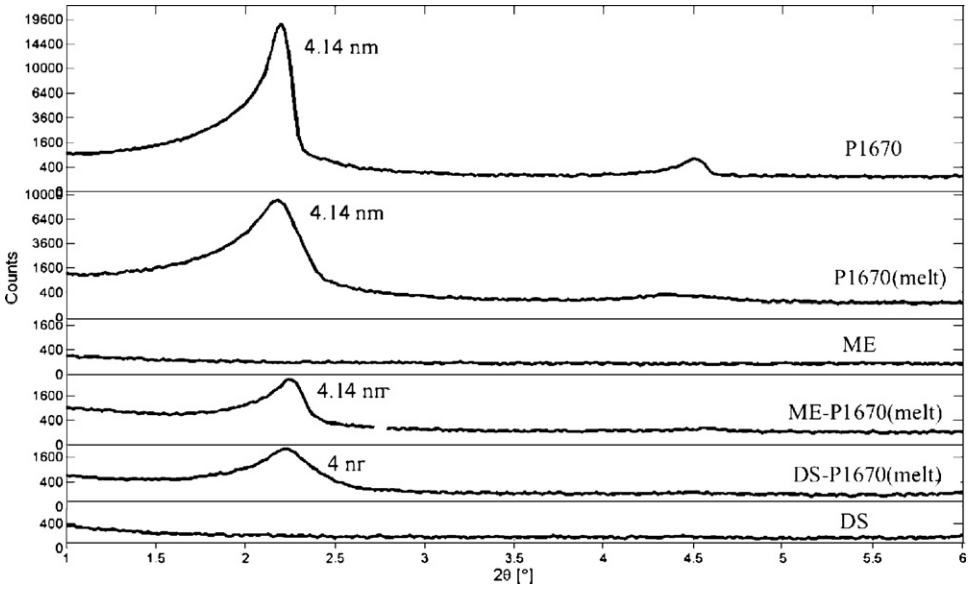

Fig. 2. X-ray diffractograms of drugs, P1670 and drug–P1670 melted products.

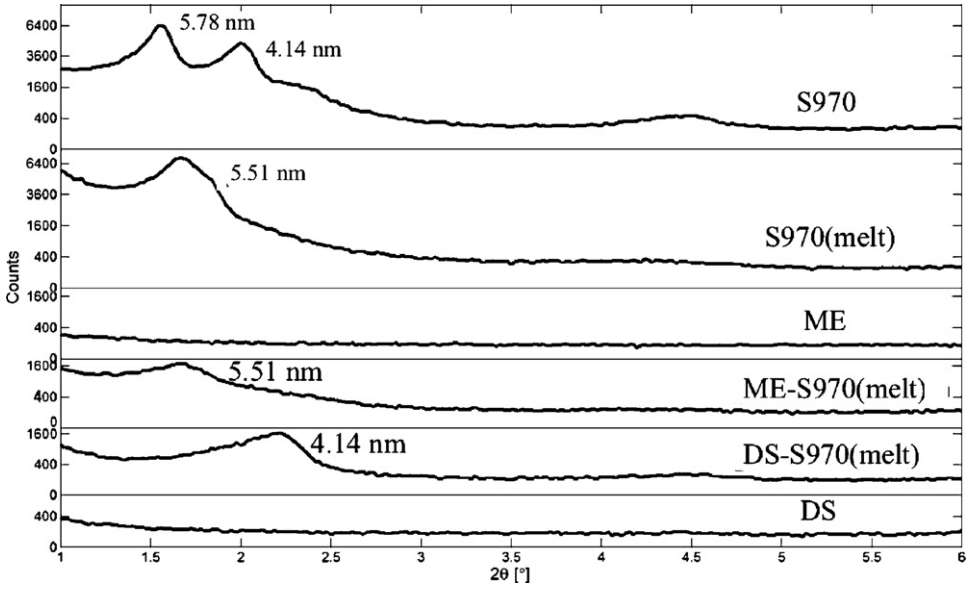

Fig. 3. X-ray diffractograms of drugs, S970 and drug–S970 melted products.

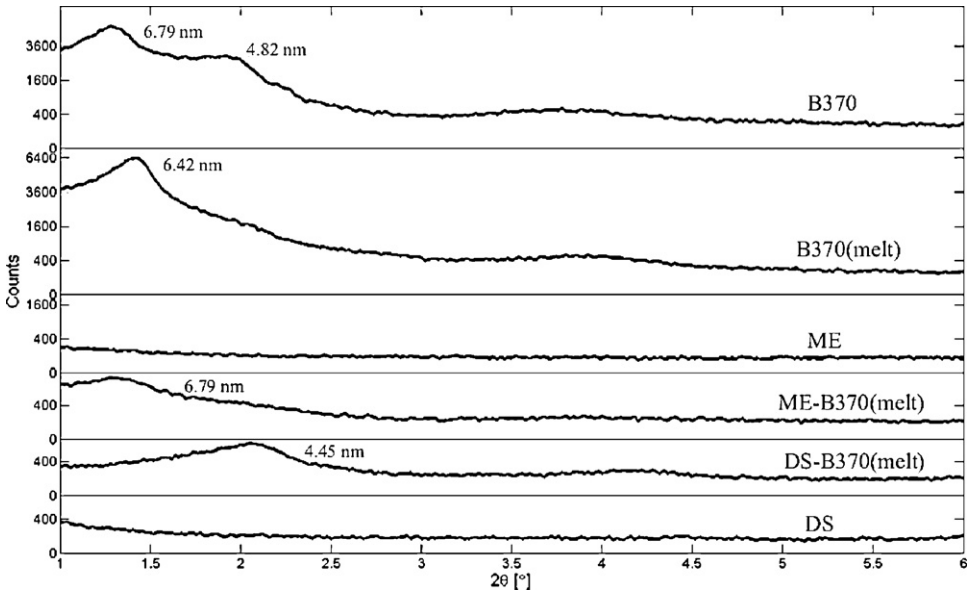

Fig. 4. X-ray diffractograms of drugs, B370 and drug–B370 melted products.

that for drug–B370(melt) as compared with B370(melt); the drugs are best distributed in this SE. The characteristic peak of B370 appears in different positions, as a result of the effects of the two drugs (Fig. 4). The basal spacings of the SEs did not change considerably in any of the cases, which leads to the conclusion that neither drug was built into the crystalline phase of the SEs.

In agreement with the DSC examinations, the X-ray examinations revealed that the structures of the SEs were rearranged after melting, to the accompaniment of a decrease in the degree of crystallinity. The change was greater when a drug was present, especially in the case of lipophilic B370, where the degree of crystallinity of the SE was reduced to a fifth by the drug. The crystallinity decreased to only a smaller extent in the case of SE with a high HLB value (P1670) or a medium HLB value (S970). Comparison of the changes caused by the two drugs indicates that, in accord with the results of the DSC examinations, the X-ray sign of SE appears at the same position for ME–SE(melt) as for SE(melt), while in the case of DS–SE(melt) the characteristic peak typical of the SEs appears at a different position. Thus, DS brings about a greater structural rearrangement in the SE than ME does.

3.3. Contact angle measurement

The distribution of the drugs in the SE melt is influenced by the polarities of the initial materials. The results of contact angle measurements, which provide information about the surface free energies and polarities of the drugs and the SEs, are presented in Table 3. The different HLB values are manifested in the various polarity values of the SEs, while the different wetting properties of the two drugs point to possible drug–SE interactions.

ME is a lipophilic material (polarity: 25.90%), so it can be assumed that it does not dissolve in the melt of the more polar P1670 (polarity: 60.96%) or S970 (polarity: 53.85%); the ME crystals are only wetted by these SEs, and thus the drug will be present in the solidified product in a suspended form. As the polarity of B370 (16.60%) is closer to that of ME, it can be presumed that ME dissolves and may be build into the crystal structure of SE. The polarity of DS (45.10%) is closer to those of the SEs with high HLB values, and it can dissolve in their melts, while it will probably not do so in the lipophilic B370. By virtue of the size of their molecules, both ME [28] and DS [29] would fit in among the lamellas of the SE, and thus it could reasonably be expected that the drug molecules with polarities similar to that of the SE would be built into the crystalline phase of the SEs, thereby increasing their basal spacing. However, the X-ray examinations revealed that, as compared with the SE without drug, the basal spacing typical of the characteristic peaks of SEs appearing at small 2θ was not changed greatly in any of the cases. The signs typical of the drugs and the SEs invariably appeared in the X-ray diffractograms, which proves that neither of the drugs was built into the crystalline phase of the SEs.

The contact angle, surface free energy and polarity of different mixtures were also determined and the results are summarized in

Table 3
Contact angles, surface free energies and polarities of the materials

Materials	θ_{water} (°)	$\theta_{diiodomethane}$ (°)	γ^d (mN m^{-1})	γ^p (mN m^{-1})	γ (mN m^{-1})	Polarity (%)
P1670	18.49 ± 0.85	58.76 ± 0.72	27.37	42.73	70.10	60.96
S970	46.79 ± 1.76	62.99 ± 1.10	25.50	29.75	55.25	53.85
B370	89.81 ± 1.03	54.77 ± 1.01	30.09	5.99	36.08	16.60
ME	61.56 ± 1.71	15.44 ± 0.83	44.53	15.56	60.08	25.90
DS	16.8 ± 1.5	19.53 ± 1.78	43.19	35.48	78.67	45.10
ME–P1670	22.4 ± 1.34	45.4 ± 1.99	33.51	37.70	71.21	52.94
ME–S970	45 ± 1.71	57.3 ± 1.59	28.12	29.40	57.51	51.12
ME–B370	85.32 ± 1.9	54.82 ± 1.79	29.85	7.9	37.75	20.93
DS–P1670	24.4 ± 1.68	43 ± 1.38	34.58	36.42	71.00	51.29
DS–S970	20.28 ± 2.51	50.09 ± 1.95	31.37	39.59	70.97	55.78
DS–B370	65.58 ± 1.99	50.55 ± 1.39	31.42	16.79	48.2	34.83

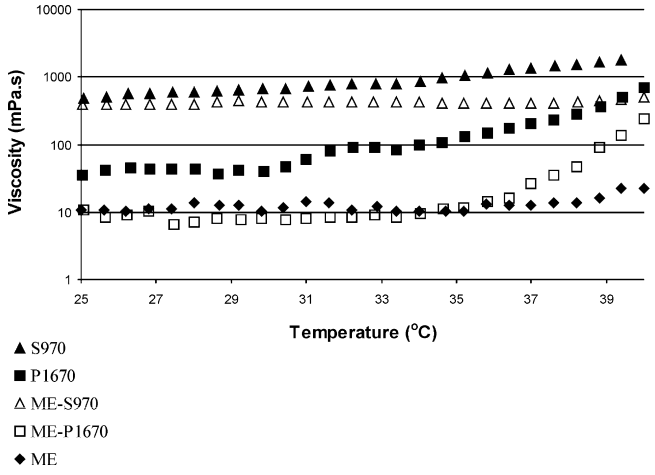

Fig. 5. Viscosity of ME, SEs and ME–SEs in water.

Table 3. It can be seen, that SEs influenced the wetting behaviour of the drugs according to their HLB values, from which is predictable how SEs can change the dissolution of the drugs.

3.4. Temperature sweep test

On the basis of the different swelling properties observed through the SE contact angle measurements, the viscosities of the SEs were examined in water as a function of temperature. It was found that P1670 (with a high HLB) gelled over 35 °C, while S970 (with a medium HLB value) displayed high viscosity even at room temperature. Lipophilic B370 has poor wetting properties in water, and its viscosity does not increase with increase of temperature. The viscosities of the two gel-forming SEs (P1670 and S970) are depicted in Figs. 5 and 6, without and with drugs. Drug materials alone were tested also as a control. It is clear from Fig. 5 that in the presence of ME the viscosities of both P1670 and S970 were lower than without ME but the swelling behaviour is observable in this case too. On the other hand, the viscosities of both SEs decreased considerably in the presence of DS (Fig. 6). This interaction can be influenced to a large extent by the dissolution of DS. The measurements also revealed that the viscosities of the products containing S970 were always higher than those of the products with P1670.

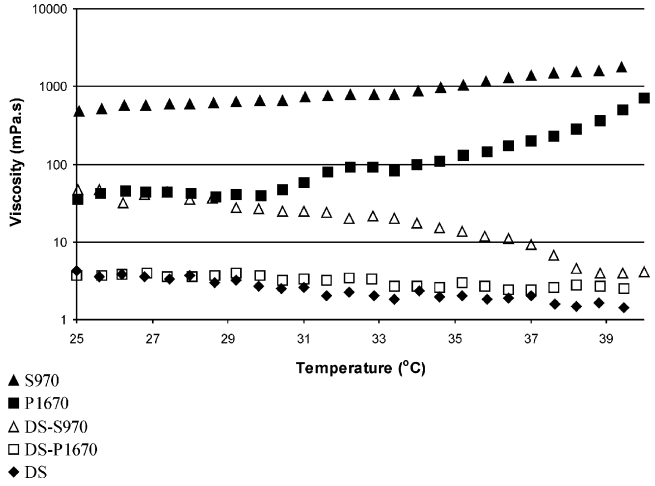

Fig. 6. Viscosity of DS, SEs and DS–SEs in water.

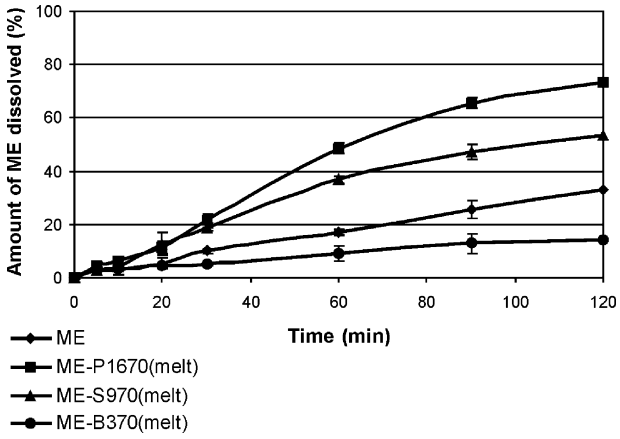

Fig. 7. Dissolution of ME and ME–SE melted products.

3.5. Dissolution studies

The drug release is influenced not only by the different HLB values, but also by the gel-forming behaviour of the SEs, the polarities of the drugs and the interactions between the drugs and the SEs.

ME is a poorly water-soluble drug; it is absorbed mostly from the intestine. Its release was increased by the presence of a SE with a high HLB value (P1670), when 70% of the ME was dissolved in 2 h as compared with only 30% from pure ME. The SE with a medium HLB value (S970) slightly increased the release of ME, but the quantity dissolved in 2 h hardly exceeded 50%. Although the drug release did change as a function of the HLB value, 100% dissolution could not be achieved even with P1670, which has a HLB of 16, and a gel-like residue could be seen in the capsule holder at the end of the examinations. The drug release was greatly slowed down by the lipophilic B370: only 15% of the ME was dissolved in 2 h, instead of 30% (Fig. 7). DS dissolved well at pH 7.5, 100% of the pure drug passing into solution in artificial intestinal juice in a few minutes. P1670 did not bring about appreciable changes; the dissolution was similar to that of DS without a carrier. The dissolution of DS was delayed by S970, but the drug was completely dissolved in 1 h. The release of DS was greatly decreased by the lipophilic B370: the quantity of drug dissolved was in 2 h less than 50% (Fig. 8).

The dissolution studies indicate that the release of the different drugs were influenced differently by the SEs. The hydrophilic P1670 increased the dissolution of ME considerably, but 100% drug release could not be achieved. In spite of their high HLB values, it can occur

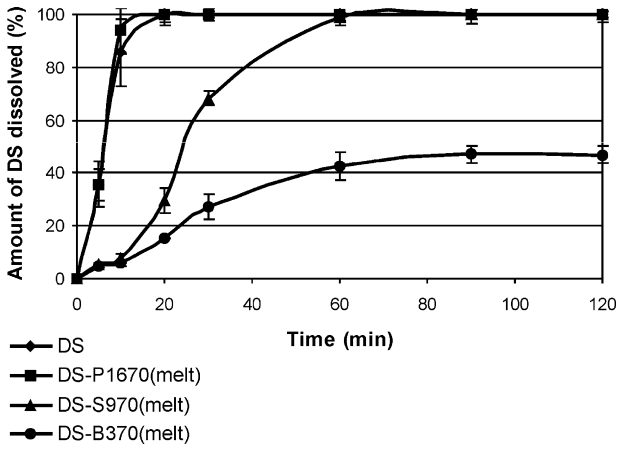

Fig. 8. Dissolution of DS and DS–SE melted products.

that hydrophilic SEs do not accelerate, but rather delay the dissolution of certain drugs: there have been reports of the use of SEs with high HLB values as matrix-forming agents in CR dosage forms, for example, S1670 with a HLB of 16 in the case of theophylline [17], or S1570 and P1570 with a HLB of 15 in the cases of ibuprofen and theophylline [30]. The latter authors attributed the matrix-forming property to the H-bonding formed between the SE and the cellulose molecule present in the formulated product. As there was no carrier other than SE in our composition, the viscosity of the carrier was examined. It was found that P1670 gelled at 37 °C, which explains why 100% release could not be achieved in the case of ME despite the high HLB value. S970, with a medium HLB value, slightly increases the release of ME due to its polarity and wetting effect, but in higher concentrations its gel-forming property may come to the forefront and it may slow down the dissolution of the drug. The lipophilic B370 has a low viscosity in aqueous medium; in this case, only the HLB value plays a role, and it decreases the release of ME. DS was dissolved in the intestinal juice within a few minutes, and the effect of the hydrophilic P1670 was not manifested here. As the viscosity of P1670 was decreased considerably by the drug in aqueous medium, the dissolution of DS could not be delayed with this SE. In this case, the interaction between the drug and the SE plays a role, which is related partly to the different pH (pH of DS aqueous solution: 7.8; pH of P1670 aqueous solution: 5.5) and partly to the salting-out effect of DS. Although its polarity is almost the same as that of the drug, S970 slows down the dissolution of DS because of its gel-forming property. Here again, the viscosity of the SE is largely reduced by the action of the drug in aqueous medium, but to a smaller extent than in the case of P1670. B370 has the lowest HLB value among the SEs examined; it decreases the release of DS because of its polarity.

4. Conclusions

The present results allow the conclusion that, when SEs are used in melt technology, not only the HLB value, but also their gel-forming properties and the features of the drugs have to be considered. With respect to HLB, P1670 can be a suitable carrier for enhancing the release of drugs with poor water-solubility, while the lipophilic B370 can be used for retardation. S970, with a medium HLB value, can promote the dissolution of drugs with poor wettability (such as ME), but it can slow down the release of a soluble drug (such as DS). On account of their gel-forming properties, P1670 and S970 can be suitable for delaying the release of certain drugs. However, during formulation it is also important to consider the properties of the drug, because they can influence the structure of the SE or the gel structure formed.

Acknowledgement

The authors are grateful to Syntapharm GmbH (Germany) for providing the sucrose esters.

References

[1] W.L. Chiou, S. Riegelman, J. Pharm. Sci. 60 (1971) 1281–1302.
[2] A.T.M. Serajuddin, J. Pharm. Sci. 88 (1999) 1058–1066.
[3] J. Breitenbach, Eur. J. Pharm. Biopharm. 54 (2002) 107–117.
[4] D.Q.M. Craig, J.M. Newton, Int. J. Pharm. 74 (1991) 33–41.
[5] D.Q.M. Craig, in: D.R. Karsa, R.A. Stephenson (Eds.), Excipients and delivery systems for pharmaceutical formulations, The Royal Society of Chemistry, Cambridge, 1994, pp. 148–170.
[6] C. Leuner, J. Dressman, Eur. J. Pharm. Biopharm. 50 (2000) 47–60.
[7] A. Forster, J. Hempenstall, T. Rades, J. Pharm. Pharmacol. 53 (2001) 303–315.
[8] J. Hamdani, A.J. Moës, K. Amighi, Int. J. Pharm. 260 (2003) 47–57.
[9] Mitsubishi-Kagaku Foods Corporation, Ryoto Sugar Ester Technical Information, 1982.
[10] L. Hahn, H. Sucker, Pharm. Res. 6 (1989) 958–960.
[11] L. Lehmann, S. Keipert, M. Gloor, Eur. J. Pharm. Biopharm. 52 (2001) 129–136.
[12] G. Csóka, S. Marton, R. Zelko, N. Otomo, I. Antal, Eur. J. Pharm. Biopharm. 65 (2007) 233–237.
[13] D. Shibata, Y. Shimada, Y. Yonezawa, H. Sunada, N. Otomo, K. Kasahara, J. Pharm. Sci. Technol. 62 (2002) 133–145.
[14] M. Otsuka, T. Ofusa, Y. Matsuda, Colloids Surf. B 10 (1998) 217–226.
[15] S. Marton, A. Auner, G. Csóka, Eur. J. Pharm. Sci. 25S1 (2005) S155–S157.
[16] G. Csóka, S. Marton, I. Klebovich, Proceedings of the 1st BBBB Conference on Pharmaceutical Sciences, Programme Book, 2005, pp. 119–122.
[17] F. Seiler, J.S. Burton, J.B. Dressman, J. Pharm. Pharmacol. 57 (Suppl.) (2005) S28–S29.
[18] M. Tomassetti, A. Catalani, V. Rossi, S. Vecchio, J. Pharm. Biomed. Anal. 37 (2005) 949–955.
[19] R.K. Verma, S. Garg, J. Pharm. Biomed. Anal. 38 (2005) 633–644.
[20] P. Reisi Nassab, R. Rajkó, P. Szabó-Révész, J. Pharm. Biomed. Anal. 41 (2006) 1191–1197.
[21] M.S.S. Cunha-Filho, R. Martínez-Pacheco, M. Landín, J. Pharm. Biomed. Anal. 45 (2007) 590–598.
[22] P. Sipos, M. Szűcs, A. Szabó, I. Erős, P. Szabó-Révész, J. Pharm. Biomed. Anal. 46 (2008) 288–294.
[23] A. Flemming, K.M. Picker-Freyer, Eur. J. Pharm. Biopharm. 68 (2008) 802–810.
[24] I. Pasquali, J.-M. Andanson, S.G. Kazarian, R. Bettini, J. Supercrit. Fluids 45 (2008) 384–390.
[25] A. Szűts, E. Pallagi, G. Regdon jr., Z. Aigner, P. Szabó-Révész, Int. J. Pharm. 336 (2007) 199–207.
[26] S. Wu, J. Polym. Sci. 34 (1971) 19–30.
[27] T. Ushikusa, T. Maruyama, I. Niiya, M. Okada, Yukagaku 39 (1990) 38–41.
[28] P. Luger, K. Daneck, W. Engel, G. Trummlitz, K. Wagner, Eur. J. Pharm. Sci. 4 (1996) 175–187.
[29] V. Ambrogi, G. Fardella, G. Grandolini, L. Perioli, M.C. Tiralti, AAPS PharmSciTech 3 (2002) article 26 (http://www.aapspharmsci.org).
[30] J.D. Ntawukulilyayo, C. Demuynck, J.P. Remon, Int. J. Pharm. 121 (1995) 205–210.