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

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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).

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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).