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PhD Thesis

STUDY OF THE APPLICABILITY OF SUCROSE ESTERS IN HOT-MELT TECHNOLOGY

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LIST OF ORIGINAL PUBLICATIONS

I. **Szűts, A.,** Pallagi, E., Regdon jr., G., Aigner, Z., Szabó-Révész, P., Study of thermal behaviour of sugar esters, Int. J. Pharm., 336 (2007) 199-207

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II. **Szűts, A.,** Laczkovich, O., Reisi Nassab, P., Aigner, Z., Szabó-Révész, P., Cukorészterek alkalmazhatósága az olvadéktechnológiában, Acta Pharm. Hung., 77 (2007) 97-101

III. **Szűts, A.,** Makai, Zs., Rajkó, R., Szabó-Révész, P., Study of the effects of drugs on the structures of sucrose esters, the effects of solid-state interactions on drug release, J. Pharm. Biomed. Anal., 48 (2008) 1136-1142

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IV. **Szűts, A.,** Sorrenti, M., Catenacci, L., Bettinetti, G., Szabó-Révész, P., Investigation of the thermal and structural behaviour of diclofenac sodium-sugar ester surfactant systems, J. Therm. Anal. Cal., 95 (2009) 885-890

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ABSTRACTS

V. **Szűts, A.,** Pallagi, E., Szabó-Révész, P., Cukorészterek termoanalitikai vizsgálata, Congressus Pharmaceuticus Hungaricus XIII, Budapest, 2006., pp 85-86., P-74

VI. Reisi Nassab, P., **Szűts, A.**, Szabó-Révész, P.**,** Meloxicam oldódási sebességének növelése szilárd gyógyszerformák előállítása céljából, Gyógyszerkutatási Szimpózium, Debrecen, 2006., pp 53., P-18

VII. **Szűts A**: Cukorészterek termoanalitikai vizsgálata, Magyar Tudomány Napja, Szeged, SZAB Székház, 2006. november 9.

VIII. **Szűts A:** Cukorészterek termikus viselkedésének és szerkezeti változásának hatása a hatóanyag-felszabadulásra, II. Szent-Györgyi Albert Konferencia, Budapest, 2008. március 8.

IX. **Szűts, A.,** Sorrenti, M., Catenacci, L., Bettinetti, G., Szabó-Révész, P., Sugar esters in melt technology. Influence of thermal behaviour and solid-state interactions on drug release, 6^{th} World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Barcelona, Spain, 2008., P-133

X. Szabó-Révész, P., **Szűts, A.**, Study of the effects of drugs on the structures of sucrose esters and the effects of solid-state interactions on drug release, 7th Central European Symposium on Pharmaceutical Technology and Biodelivery Systems, Ljubljana, Slovenia, 2008, OP022

ABBREVIATIONS

CI	[%]	crystallinity index
D(0.9)	[μm]	particle size where 90% of the particles are finer
d_L	[nm]	basal spacing
DS		diclofenac sodium
DSC		differential scanning calorimetry
DS-SE(melt)		melted and solidified diclofenac sodium-sucrose ester
HLB		hydrophilic-lipophilic balance
HSM		hot-stage microscopy
ME		meloxicam
ME-SE(melt)		melted and solidified meloxicam-sucrose ester
Mp	[ºC]	melting point
MTDSC		modulated-temperature differential scanning calorimetry
SE		sucrose ester
SE(A1week)		melted and solidified sucrose ester stored for 1 week
SE(A4weeks)		melted and solidified sucrose ester stored for 4 weeks
SE(melt)		melted and solidified sucrose ester
T_g	[ºC]	glass-transition temperature
TG		thermogravimetry
XRPD		X-ray powder diffraction
γ	[mN m^{-1}]	surface tension
γ^d	[mN m^{-1}]	disperse part of surface free energy
γ^p	[mN m^{-1}]	polar part of surface free energy
ΔH	[J g^{-1}]	normalized enthalpy
θ	[˚]	contact angle

1. INTRODUCTION

One of the most important tasks in pharmaceutical technology is to optimize the drug release. The hot-melt technology is a method of modifying the bioavailibility. Sekiguchi and Obi [1] introduced the melting method comprising melting of the drug within the carrier, followed by cooling and pulverization of the product. They used urea as a highly water-soluble carrier to enhance the rate of dissolution of sulphathiazole. Since then, many other carriers have been applied in melt technology to modify the release of different drugs. At first, crystalline materials were used, such as urea and sugars, which form crystalline solid dispersions. Later, carriers with an amorphous region were used in melt technology, *e.g.* polyethylene glycols (PEGs) or polyvinyl pyrrolidone (PVP). With these polymers, it is possible to form an amorphous solid dispersion, where the drugs are molecularly dispersed in the carrier, and the drug release from the product is accelerated. Recently, there has been great interest in the surface-active carriers, such as inulin or Gelucire®. With these surfactants, the highest degree of bioavailability can be achieved for poorly-soluble drugs [2].

For the substances utilized in melt technology, investigation of their thermal behaviour is necessary. There are many methods with which to study the thermal properties of materials, *e.g.* standard and modulated differential scanning calorimetry (DSC and MTDSC), thermogravimetry (TG) or hot-stage microscopy (HSM). If the thermal behaviour of the materials is known, it can help in the prediction of the changes in substances during various technological processes. The other important way to characterize the initial materials is structural investigation. In the characterization of structure, X-ray powder diffraction (XRPD) is the most common procedure.

Sucrose esters (SEs) are often used in the melt method, but the information available about these carriers is not sufficient. The aim of authors who used SEs with active agents was to increase or decrease the dissolution of drugs. To be able to predict the drug release, it is necessary first to understand the material properties. SEs are promising carriers for the hot-melt technology, because of their low melting points and their surfactant properties, so it is useful to evaluate their structural and thermal properties.

2. AIMS

SEs are often applied in hot-melt technology, but the information available on these carriers is not sufficient and further investigations are needed. Hence, the aim of my PhD work was to investigate the thermal behaviour and structure of SEs in order to ascertain the applicability of these carriers in melt technology.

A. The primary objective was to study the structure and the thermal properties of some commercial SEs (P1670, S1670, S970, S370 and B370), to evaluate and analyse the time-dependent solid-state changes (crystalline-amorphous phases and polymorphism) in these SEs, to study their swelling behaviour and to demonstrate differences between the properties of SEs with various hydrophilic-lipophilic balance (HLB) values.

B. After the characterization of the SEs, the next purpose of my work was to study the effects of active agents on the structure and thermal behaviour of SEs. Meloxicam (ME) and diclofenac sodium (DS) as model drugs and three SEs with different polarities (P1670, S970 and B370) were chosen for these investigations. Drug-SE products were prepared by melt technology, and the effects of the SEs and the drug-SE solid-state interactions on the drug release were examined. The factors affecting the drug release from the SE-containing products were studied.

C. Finally, conclusions were drawn concerning the applicability of SEs in practical work.

3. LITERATURE

3.1. Compositions of sucrose esters of fatty acids

SEs are non-ionic surface-active agents consisting of sucrose as hydrophilic group and fatty acids as lipophilic groups. Sucrose contains 8 hydroxy groups, and it is therefore possible to produce sucrose esters containing from 1 to 8 fatty acid moieties (Fig. 1).

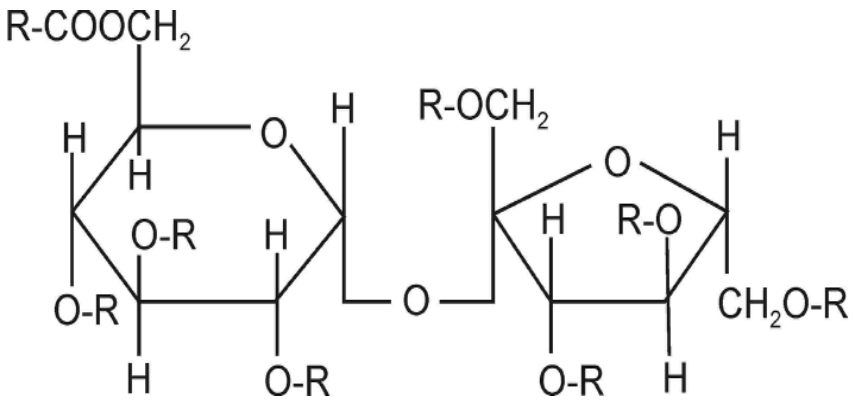

Fig. 1 Chemical structure of sucrose ester

The most common fatty acids used in SEs are lauric (C12), myristic (C14), palmitic (C16), stearic (C18), oleic (C18) and behenic acids (C22). By changing the nature or number of the fatty acid groups, a wide range of HLB values can be obtained (Fig. 2).

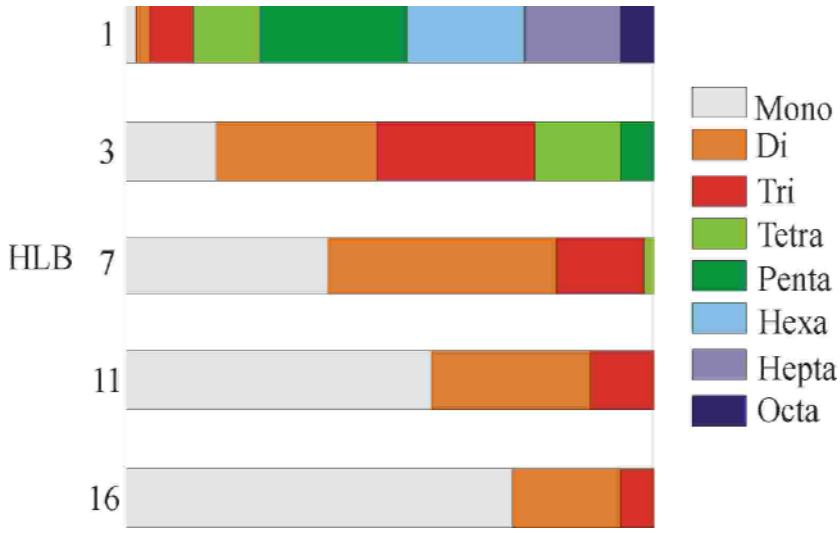

Fig. 2 Relation between the degree of esterification and the HLB value of SEs [3]

3.2. Chemical and physical properties of fatty acid products

For a better understanding of the behaviour of SEs, it is helpful to consider first the properties of the well-known fatty acid products.

There are various natural and artificial products, which consist of fatty acids and long have been used in pharmaceutical technology, *e.g.* the fatty acid esters of glycerol, sorbitan fatty acid esters, propylene glycol fatty acid esters or polysorbates.

Among the least complex fatty acid products are the esters produced from one molecule of glycerol and one, two or three fatty acids. Glycerol is a trihydroxy alcohol that can combine with up to three fatty acids to form monoglycerides, diglycerides and triglycerides. The hydrocarbon chain can be saturated (*e.g.* capric, lauric, myristic, palmitic and stearic acids) or unsaturated (*e.g.* oleic, linoleic and palmitoleic acids). There are abundant literature data on the chemical and physical properties of the glycerides, and it is well known that these materials display very complex behaviour. For example, they have different crystal forms (α, β, and β' polymorphs), which have been extensively reviewed, and correspondingly complex melting and crystallization behaviour [4-15].

Other products have more complex structures and hence similarly complex properties.

In the SEs, the fatty acids are attached to sucrose, a disaccharide consisting of two monosaccharides, glucose and fructose. The commercial SEs are mixtures of SEs with various esterification degrees; due to their complexicity, they exhibit very diverse behaviour, like the glycerides.

As compared with other fatty acid products, SEs have high HLB value range (Fig. 3), and thus very diverse properties.

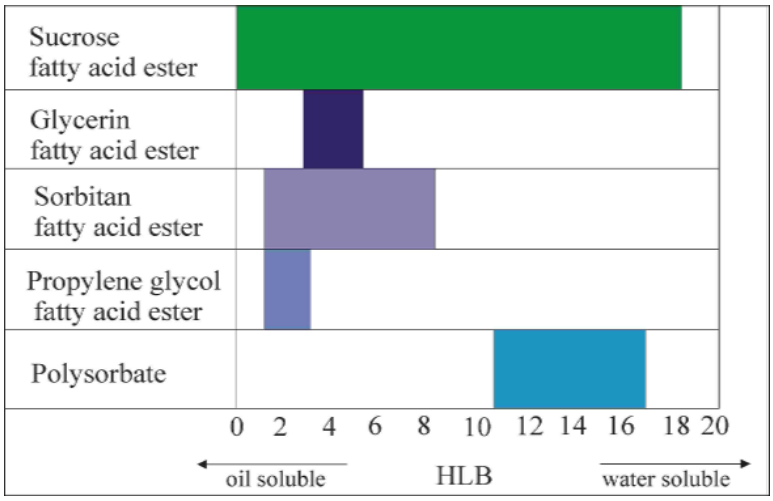

Fig. 3 HLB values of some fatty acid products [3]

3.3. Nomenclature of the sucrose esters

A number of manufacturers supply SEs, *e.g.* Dai-Ichi-Kogyo Seiyaku and Mitsubishi in Japan, Croda in the USA, or Sisterna and Goldschmidt in Germany [16, 17].

The major manufacturer of SEs in Japan is the Mitsubishi-Kagaku Foods Corporation, which produces SEs under the name Ryoto Sugar Esters. They sell SEs for food (Ryoto Sugar Ester), cosmetic (Surfhope SE Cosme) and pharmaceutical (Surfhope SE Pharma) applications.

The nomenclature of the SEs in different grades varies (Table 1).

Table 1 Nomenclature of SEs

	Food grade	Cosmetic grade	Pharma grade
Leading letter	Initial of fatty acid	C	D
Last two numbers	% of named fatty acid	HLB	HLB
First 1/2 numbers	HLB	Fatty acid chain length*	Fatty acid chain length*

* For unsaturated acids, the chain length is reduced by 1

SEs with the same composition therefore have different grade names, depending on their application (some examples are given in Table 2).

Table 2 Examples of the different grade names of SEs

Fatty acid chain length	Degree of unsaturation	Fatty acid	% of named fatty acid	HLB	Food grade	Cosmetic grade	Pharma grade
12	0	Lauric	95	16	L-1695	C-1216	D-1216
16	0	Palmitic	70	16	P-1670	C-1616	D-1616
18	0	Stearic	70	3	S-370	C-1803	D-1803
18	1	Oleic	70	1	O-170	C-1701	

It must be said that in the literature the food grade names of SEs are generally used, for the pharmaceutical applications too. This procedure will be followed in this thesis.

3.4. The use of sucrose esters in pharmaceutical dosage forms

SEs are commonly used in food industry as emulsifiers, antibacterial agents or crystallization inhibitors [3, 18-23], and recently there is a great interest to use them also in the field of pharmacy. They have attracted considerable interest as pharmaceutical excipients for a number of reasons. The wide range of HLB values of SEs results in a similarly wide range of properties. They can be applied in pharmaceutical technology as O/W or W/O emulsifiers, wetting and solubilizing agents, liberation and absorption modifying agents or lubricants [24-44].

The most common pharmaceutical application of SEs is for the modification of bioavailability. Due to the wide range of their HLB values, they can increase or decrease drug liberation or absorption. There are some literature data about the applicability of SEs as permeation enhancers through the skin or mucosa. For example, L-595 and L-1695 have been used in microemulsions to improve the penetration of hydrocortisone through the stratum corneum [30]. Ganem-Quintanar *et al*. [31] studied four SEs (S-1670, O-1570, P-1670 and L-1695) as absorption enhancers for the oral mucosal permeation of lidocaine hydrochloride. They observed an increase in the passage of lidocaine through the mucosa only for L-1695;

the other SEs did not display any promoting effect. Ayala-Bravo *et al.* [32] investigated the effect of sucrose oleate (O-1570) and sucrose laurate (L-1695) in water or in Transcutol® on the stratum corneum barrier properties *in vivo*. They examined the impact of these SEs on the *in vivo* percutaneous penetration of the model penetrant 4-hydroxy-benzonitrile. Their results showed that the combination of SEs with Transcutol® is able to temporally alter the stratum corneum barrier properties, thereby promoting 4-hydroxy-benzonitrile penetration. Okamoto *et al*. [33] examined the effects of SEs on the transdermal permeation of lidocaine and ketoprofen. They suggested the combination of J-1205 and propylene glycol as a potent vehicle for transdermal formulations. Csóka *et al*. [34] also examined the applicability of different SEs (S-370, S-970, S-1670, O-1570, P-1670, L-1695 and M-1695) as drug-delivery agents in transdermal therapeutic systems. They demonstrated that all SEs increased the drug (metoprolol tartrate) release, but this effect depended on the HLB value and the C atom number of the fatty acid chain in the SE.

Drug release has also been investigated from physical mixtures, solid dispersions, coprecipitates and tablets. For example, Ntawukulilyayo *et al*. [35] evaluated the dissolution rate-enhancement properties of nifedipine-SE-containing coprecipitates. The use of sucrose palmitate of high HLB value dramatically improved the dissolution rate, especially when a drug:ester ratio of 1:14 was used. Otsuka *et al*. [36, 37] also examined the dissolution-enhancement properties of SEs. They used S-1670 (HLB=16) to improve the rate of dissolution of phenytoin and glybuzole. Marton *et al*. [38] utilized three SEs with an HLB value of 16 (S-1670, L-1695 and M-1695) to increase the rate of dissolution of spironolactone. They found a linear relationship between the amount of drug dissolved and the SE concentration. Csóka *et al*. [39] applied SEs with different HLB values (S-370, S-970, S-1170, S-1670, L-1695, M-1695 and O-1570) to influence the dissolution of ibuprofen. Seiler *et al*. [40] examined the possibility of preparing controlled-release matrix formulations of theophylline by using S-1670 with hot-melt extrusion. Although S-1670 is hydrophilic, the formulations exhibited controlled drug release. Ntawukulilyayo *et al*. [41] also used SEs with high HLB values (S-1570 and P-1570) as tablet matrix-forming agents, in the cases of ibuprofen and theophylline. The latter authors attributed the matrix-forming property to the H-bond formed between the SE and the cellulose molecule present in the formulated product.

Ullrich *et al.* [42] recently investigated the rheological behaviour of aqueous SE (S-1170F) dispersions, and concluded that SEs are applicable as alternative new matrices in

lipid-based drug-delivery systems. Abd-Elbary *et al.* [43] developed controlled release proniosome-derived niosomes, using sucrose stearates as non-ionic surfactants for the nebulisable delivery of cromolyn sodium. They used S-1170 and S-1670 and found that SEs are promising carriers for the preparation of niosomal dispersion.

There are some products, especially on the German market, in which SEs are utilized as controlled-release agents (*e.g.* Ibu KD retard, Esprenit retard and Cronasma retard) [44].

3.5. Melt technology

Melt technology has been commonly used since the early 1960s, when Sekiguchi and Obi [1] prepared a eutectic mixture with the hot-melt method. With this technology, they attained faster release of the poorly water-soluble sulphathiazole and chloramphenicol. Since then, much research has been performed in efforts to influence the bioavailability of drugs with hot-melt technology, and numerous reviews have appeared in the literature on this method [45-62]. Much research work has likewise been performed to characterize the physicochemical properties of the applicable carriers [63-80].

In the melt method, the drug and the excipient are usually melted together and, after solidification, a eutectic mixture, solid dispersion, or solid solution is obtained. The carrier may be crystalline (with an ordered structure), amorphous (with a disordered structure) or semicrystalline (with ordered and disordered regions), and the drug can be present in a fully crystalline state, a semicrystalline state, or an amorphous state [81]. When the drug is distributed in a crystalline carrier, a crystalline solid dispersion is formed. When the active substance is dispersed in an amorphous carrier or in the amorphous region of a semicrystalline material, an amorphous solid dispersion is obtained. Depending on their molecular distribution, three different types of amorphous solid dispersions can be distinguished:

1. An amorphous solid solution consists of an amorphous carrier in which the drug is molecularly distributed. This type of solid dispersion is homogeneous at a molecular level. Only one phase is present.
2. In an amorphous solid suspension, the drug is dispersed as amorphous clusters in the amorphous carrier. This system is not homogeneous at a molecular level and consists of two phases.

3. One part of the drug is sometimes molecularly dispersed, while the remainder is suspended in the amorphous carrier. This is the third type of amorphous solid dispersions [82].

Figure 4 shows the classification of solid dispersions according to Vasconcelos *et al* [2]:

- The first-generation solid dispersions were prepared by using crystalline carriers, such as urea and sugars, which were the first carriers to be employed in solid dispersions. They have the disadvantage of forming crystalline solid dispersions, which are more thermodynamically stable and do not release the drug as quickly as amorphous ones.

- The second-generation solid dispersions contained amorphous or semi-crystalline carriers instead of crystalline ones. In these systems, the drugs are molecularly dispersed in an irregular form within the amorphous region of the carriers, which are usually polymers such as PVP, PEGs or cellulose derivatives.

- The third-generation solid dispersions contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. The surfactants commonly used in solid dispersion systems are inulin, Inutec SP1®, Compritol 888 ATO®, Gelucire 44/14 and Poloxamer 407® [2]. Surface-active carriers have an important biopharmaceutical role. They can influence the bioavailability by increasing the thermodynamic activity of the active substance and by changing the permeability of cellular membranes [83]. The third-generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly-soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization.

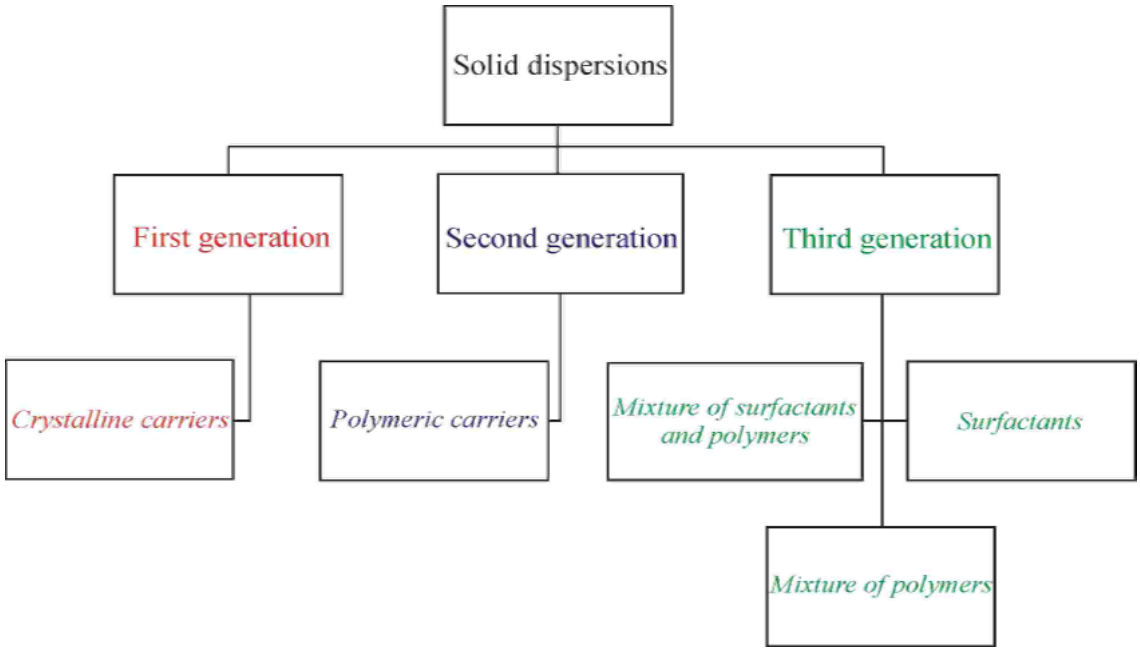

Fig. 4 Classification of solid dispersions [2]

Recently, there has been great interest in solid dispersion systems, and it is useful to characterize new carriers which can be used in melt technology, especially substances with lower melting points such as the SEs. If the active substance decomposes at high temperature, only carriers with low melting points can be used in the hot-melt method, and the drug (without melting) should be mixed into the melted carrier. Due to their surfactant properties, low melting points and wide range of HLB values, SEs are promising carriers for the preparation of solid dispersions by melt technology.

4. MATERIALS AND METHODS

4.1. Materials

SEs (Mitsubishi-Kagaku Foods Corporation, Japan) with high (P1670 and S1670), medium (S970) or low HLB values (S370 and B370) were studied in my PhD work. The longer the fatty acid chains in the SEs and the higher the degree of esterification, the lower the HLB value (Table 3).

Table 3 Data on SEs by Mitsubishi-Kagaku Foods Corporation

Name of SE	Fatty acid	HLB	Mp [°C]	Decomposition temperature [°C]	Degree of Esterification
P1670	palmitate (C16)	16	48	235	mono-, di- and triester
S1670	stearate (C18)	16	56	237	mono-, di- and triester
S970	stearate (C18)	9	56	234	mono-, di-, tri- and tetraester
S370	stearate (C18)	3	58 and 69	238	mono-, di-, tri-, tetra- and pentaester
B370	behenate (C22)	3	63 and 79	241	mono-, di-, tri-, tetra- and pentaester

They have many favourable properties, *e.g.* they are tasteless, odourless, non-toxic, non-irritant to the skin, and biodegradable.

As model drugs, two NSAIDs, ME (EGIS Ltd, Hungary) and DS (Sigma Co., Hungary) were used. They belong in BCS class II: ME is a poorly water-soluble material, while DS is slightly soluble in water, but its solubility increases as the pH rises. The particle sizes of the drugs: $D(0.9)$ = 65 μm for ME, and $D(0.9)$ = 6 μm for DS.

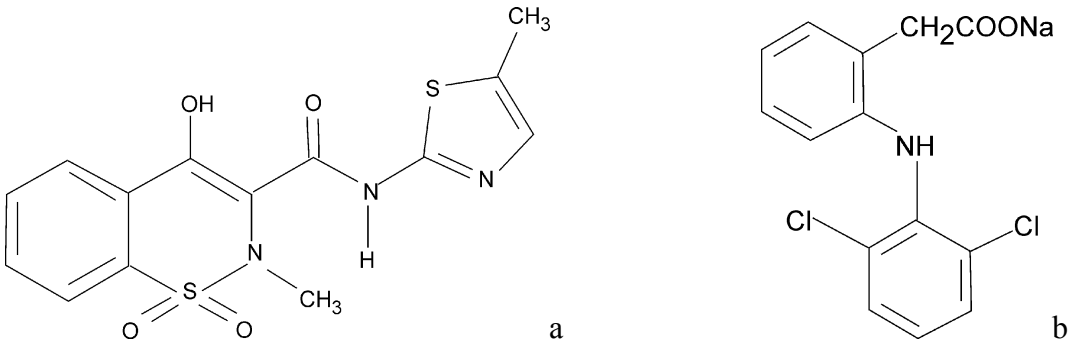

Fig. 5 Chemical structures of ME (a) and DS (b)

4.2. Sample preparation

For the physical evaluation of SEs, three types of samples were used:

- Untreated samples (SE): SEs without any special treatment (commercial).
- Freshly solidified samples (SE(melt)): SEs were melted in a porcelain dish in an oven (Factory for Laboratory Equipment, Budapest, Hungary, Labor type 123) from 25 °C to 100 °C, and then allowed to recrystallize at room temperature.
- Aged samples: The freshly solidified samples were stored for up to 4 weeks at room temperature (20±2 °C) to detect any physical aging effect:
    - SE(A1week): samples stored for 1 week
    - SE(A4weeks): samples stored for 4 weeks

The drug-containing melted products were prepared as follows: The drug-SE physical mixtures (1:1) were melted in a porcelain dish in an oven (Factory for Laboratory Equipment, Budapest, Hungary, Labor type 123), with heating from 25 °C to 100 °C, and then cooled back to room temperature. The notation applied for the melted and solidified samples is "drug-SE(melt)" (*e.g.* ME-P1670(melt)). After the preparations, the samples were in all cases pulverized in a mortar and sieved to 200 μm.

4.3. Methods

4.3.1. Hot-stage microscopy

HSM is a powerful tool that is widely used for the visual characterization of all kinds of thermal transitions. It is an analytical technique, which combines the best properties of microscopy and thermal analysis to enable the characterization of the physical properties of materials as a function of temperature [84]. HSM observations of morphological features and changes during heating were carried out with a Leica MZ6 microscope (Wetzlar GmbH, Germany) equipped with a Leica 350 heating stage and a JVC TK-128OE (Japan) colour video camera. The structural changes in the SEs during heating were observed under the

microscope by using a scanning speed of 1 °C min^{-1}. Data were imported into a computer and captured images were analysed by using the Leica Q500MC program.

4.3.2. Thermogravimetry

TG is a method commonly used in the identification of drugs and excipients. It can be employed to study any physical (such as evaporation) or chemical process (such as thermal degradation) that causes a material to lose volatile gases [85]. In TG studies, 50 mg of SE and 50 mg of inert Al_2O_3 were placed into the platinum container of a Derivatograph-C apparatus (MOM, Hungary). The instrument was calibrated by using $CuSO_4 \cdot 5H_2O$. The samples were heated from 25 to 100 °C at a heating rate of 5 °C min^{-1}.

4.3.3. Differential scanning calorimetry

DSC is the most highly regarded thermoanalytical method and is an essential tool for materials research and development [85-87]. 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 Ar atmosphere at a flow rate of 100 ml min^{-1}. The samples were heated from 25 to 100 °C at a heating rate of 1 °C min^{-1}. For analysis of the recrystallization process, samples were heated up to 100 °C as described above, then cooled down to 25 °C at a rate of 2 °C min^{-1}, and reheated to 100 °C at a heating rate of 1 °C min^{-1}.

The crystallinity indices for the freshly solidified sample ($CI_{SE(melt)}$) and the aged sample ($CI_{SE(aged)}$) were calculated from the heats of fusion:

$$CI_{SE(melt)}(\%) = \frac{\Delta H_{SE(melt)}}{\Delta H_{SE}} \times 100 \quad (1)$$

$$CI_{SE(aged)}(\%) = \frac{\Delta H_{SE(aged)}}{\Delta H_{SE}} \times 100 \quad (2)$$

where

$\Delta H_{SE\,(melt)}$ = the normalized enthalpy (J g^{-1}) of the freshly solidified sample,

ΔH_{SE} = the normalized enthalpy (J g^{-1}) of the untreated sample, and

$\Delta H_{SE\,(aged)}$ = the normalized enthalpy (J g^{-1}) of the aged sample.

Drugs may influence the structure and thermal behaviour of carriers [88]; hence, it is important to study the characteristics of the drug-carrier systems. For analysis of the drug-containing SEs, samples of 10 mg were heated from 25 ^{o}C to 300 °C at a heating rate of 10 °C min^{-1}.

4.3.4. Modulated-temperature differential scanning calorimetry

MTDSC is nowadays a widely recognized technique; as compared with standard DSC, it offers particular advantages, including the enhancement of both sensitivity and resolution in the same experiment, the analysis of complex overlapping transitions, and the detection of weak glass transitions [89, 90]. MTDSC studies were performed with a DSC 821^{e} instrument (Mettler-Toledo GmbH, Switzerland). The measurement conditions were as follows: start temperature: 25 °C, heating rate: 1 °C min^{-1}, amplitude: 1 °C, period: 60 s, and end temperature: 75 °C.

4.3.5. X-ray powder diffraction

The method most commonly used to complement thermal analysis is XRPD. It is one of the most powerful methods for the study of crystalline and partially crystalline solid-state materials [91-95]. 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 (λ = 0.15418 nm), 40 kV, 35 mA. The basal spacing (d_L) was calculated from the diffraction peaks by using the Bragg equation.

Bragg's Law is: $n\lambda = 2d \sin\theta$ (3)

where the integer n is the order of the diffracted beam, λ is the wavelength of the incident X-ray beam, d is the distance between adjacent planes of atoms (the d-spacing), and θ is the angle of incidence of the X-ray beam. Since we know λ and we can measure θ, we can calculate the d-spacings [95].

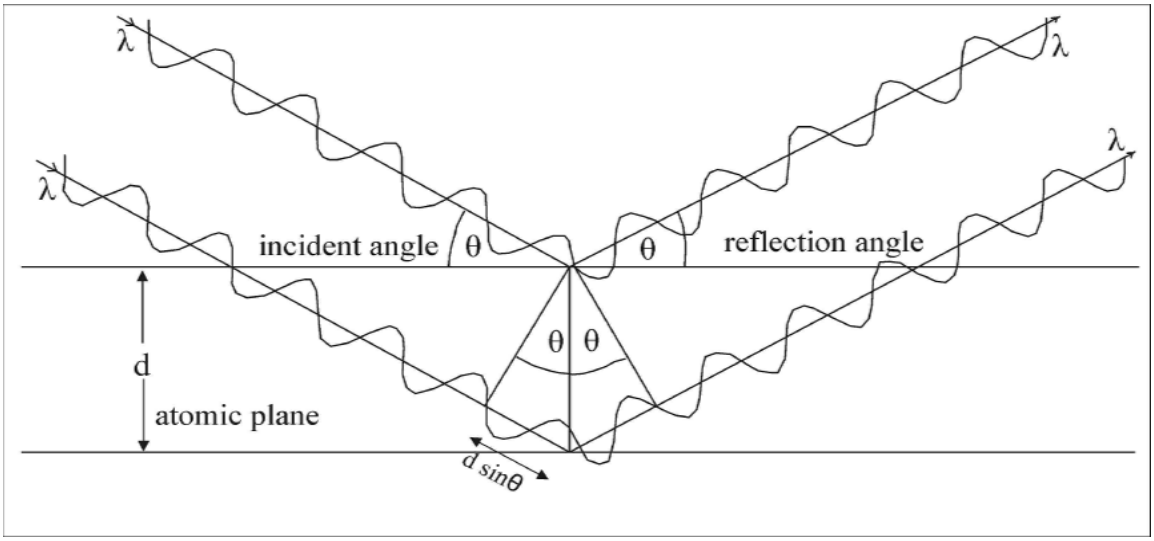

Fig. 6 Reflection of X-ray beams from the crystal plane

Through measurement of the d-spacings, the building-in or intercalation of a drug can be determined. In a drug-carrier system, the intercalation of the drug results in an expansion of the basal spacing of the carrier (Fig. 7). If the bonding between the drug and the auxiliary material is strong, the drug release can be slowed down [96-100]. Thus, it is useful to determine the change in the d-spacing of the carrier after treatment.

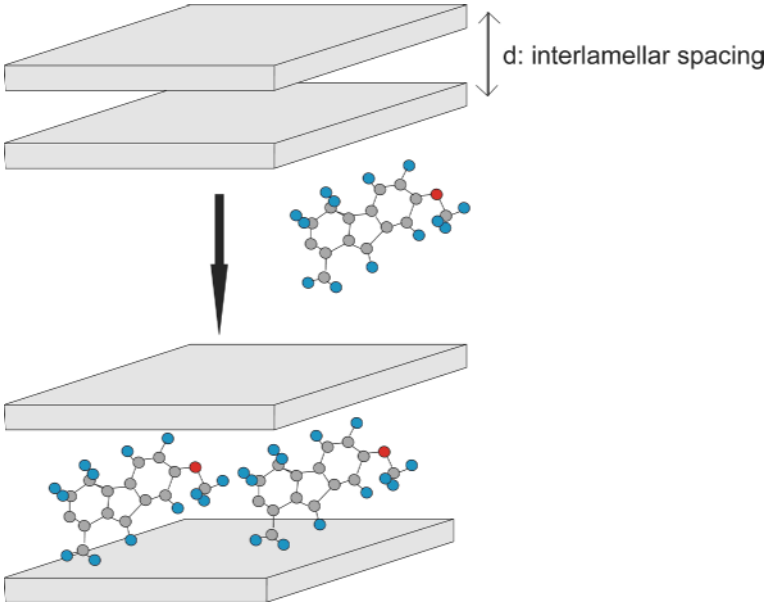

Fig. 7 Intercalation of drug molecule between the carrier lamellas

4.3.6. Rheological analysis

If a carrier exhibits swelling behaviour, this property is of great importance in the drug-release process. Hence, rheological measurement of a swollen carrier before and after inclusion of the drug is a useful characterization method [101]. For rheological analysis, 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^{o}; truncation, 49 μm). During the measurements, the temperature of the samples was modulated from 25 ^{o}C to 40 ^{o}C at a heating rate of 1 ^{o}C min^{-1}, while the resulting viscosity changes were recorded.

4.3.7. Contact angle measurements

All materials act, react and interact at surfaces; hence surface characterization can be vital for an understanding of the behaviour of any type of material. Surface characterization of powders can be undertaken by a variety of techniques, of which contact angle determination is

the most commonly used. Contact angle data may be used to estimate the surface energy of the powder. If surface energies are known for both drug and excipient, then interactions can be predicted [102, 103]. 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), and the method of Wu, in which two liquids with known polar (γ_l^p) and dispersion (γ_l^d) components are used for measurement [104]. 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. (4):

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

where Θ is the contact angle, γ_s is the solid surface free energy and γ_l is the liquid surface tension. The percentage polarity can be calculated from the γ^p and γ values: $(\gamma^p/\gamma)*100$ [105]. The liquids used for our contact angle measurements were bidistilled water (γ^p = 50.2 mN m^{-1}, γ^d = 22.6 mN m^{-1}) and diidomethane (γ^p = 1.8 mN m^{-1}, γ^d = 49 mN m^{-1}).

4.3.8. *In vitro* drug release study

Melt technology is commonly used to enhance the dissolution of poorly water-soluble drugs, or to control drug release. Hence, *in vitro* drug-release studies are often used to examine solid dispersions [106]. For the dissolution tests, ME-SE(melt) or DS-SE(melt) was 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 = 7.5±0.05) at 37 °C (±0.5 °C) was used. The drug contents of the samples were measured spectrophotometrically (λ_{ME} = 362 nm; λ_{DS} = 276 nm) (Unicam UV/Vis spectrophotometer).

5. RESULTS

5.1. Characterization of the sucrose esters

The objective of the experiments presented in this chapter was to investigate the structural and thermal properties of SEs and to demonstrate the differences between SEs with various HLB values. Time-dependent solid-state changes (crystalline-amorphous phases and polymorphism) were also observed. A further aim was the characterization of the swelling behaviour of the SEs.

5.1.1. Thermoanalytical investigations

In measurements with the derivatograph, the TG results showed that the mass loss of the examined SEs heated to 100 °C was less than 1%, *i.e.* they did not include water adsorbed on their surface or any volatile component.

To determine the melting points, DSC studies were performed. The DSC scans (Fig. 8, curves 1, first heating) revealed that the melting points and melting ranges of P1670 and S1670 and their enthalpies were very similar, while the melting of SEs with lower HLB values (S970, S370 and B370) was prolonged, with more peaks (Table 4). The probable cause of this was that the studied SEs with high HLB values included only mono-, di- and triesters, while the SEs with lower HLB values additionally contained tetra- and pentaesters (Table 3).

Table 4 Thermal parameters of SEs during first heating

SE	Melting range [°C]	Mp [°C]	Total enthalpy [J g^{-1}]
P1670	41-62	51	-66.6
S1670	45-62	54	-66.7
S970	36-65	50 and 54	-75.7
S370	45-66	54 and 64	-55.7
B370	51-79	66 and 77	-68.4

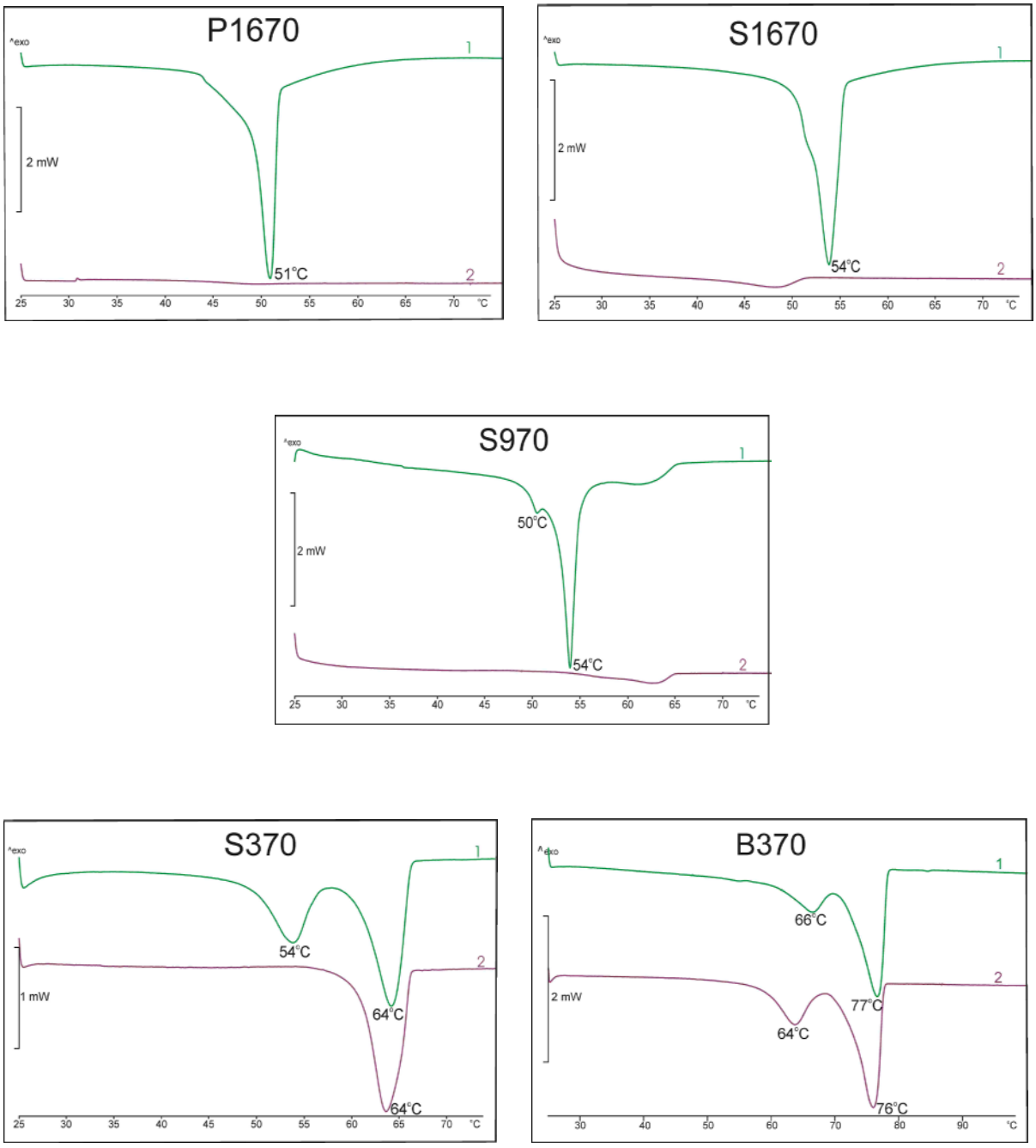

Fig. 8 DSC scans of different SEs (curve 1: first heating; curve 2: second heating)

The effects of a second heating were also studied. The melted SE in the DSC pan (after the first heating) was cooled to 25 °C at a rate of 2 °C min^{-1}, and then heated again at a heating rate of 1 °C min^{-1} to 100 °C (second heating). The results are illustrated in Fig. 8 by curves 2, and summarized in Table 5.

Table 5 Thermal parameters of SEs during second heating

SE	Melting range [°C]	Mp [°C]	Total enthalpy [J g^{-1}]
P1670	—	—	—
S1670	—	—	—
S970	—	—	—
S370	54-66	64	-31
B370	52-79	64 and 76	-63.9

The DSC curve of second heating demonstrated that there were no more endothermic changes for P1670, and for S1670 and S970 the changes were negligibly small. Accordingly, the crystal structures of SEs with high (P1670 and S1670) or moderate (S970) HLB values, which can be characterized by melting points (Fig. 8, curves 1), broke down during the first heating and could not recrystallize during cooling. Thus, curves 2 in Fig. 8 (second heating) exhibit the characteristics of amorphous materials. S370 has two endothermic peaks, but during the second heating one peak disappeared and the melting range decreased. B370 seemed to be the most stable material: the melting ranges in the first and second heatings were the same and the shapes of the curves did not change; only the total enthalpy decreased slightly (<5 J g^{-1}). Consequently, there were probably changes in the structures of the SEs with high HLB values during heating. The structures of the SEs broke down and were built up again during the heating and cooling processes. SEs with low HLB values (S370 and B370) displayed faster recrystallization, but the rearrangement of the structures of SEs with high (P1670 and S1670) or moderate (S970) HLB values was very long. Accordingly, this led to an amorphous state. Amorphous materials can be characterized by the glass transition temperature (*T*g) instead of the melting point (Mp). The determination of *T*g by the conventional DSC method is difficult, because *T*g is often concealed by or overlaps with other

thermal events taking place in parallel. The results of our MTDSC measurements revealed that SEs with high (P1670 and S1670) or moderate (S970) HLB values undergo glass transitions, which coincide with the melting points of the materials (Table 6) [**I, II and V-VII**].

Table 6 Melting points and glass transitions during first and second heatings

	First heating		Second heating	
	Mp [°C]	*T*g [°C]	Mp [°C]	*T*g [°C]
P1670	51	—	—	50
S1670	54	—	—	51
S970	50 and 54	—	—	53
S370	54 and 64	—	64	—
B370	66 and 77	—	64 and 76	—

To visualize the changes in the samples during heating, HSM was used. The photographs in Fig. 9 show the morphology of SEs with high (S1670) or low (S370) HLB values before heating (at 25 °C) and after their melting (S1670: 65 °C, and S370: 70 °C). While SEs with high HLB values (*e.g.* S1670) merely became soft, but did not flow, lipophilic SEs (*e.g.* S370) melted. SEs with high or medium HLB values did not melt during the first heating; their melting points detected in the DSC curves were truly their glass transitions (Table 6). During the preparation of the melts, the SEs with high (P1670 and S1670) or moderate (S970) HLB values did not become fluid even at 100 °C, in contrast with the lipophilic (S370 and B370) SEs, as expected from the HSM study (Fig. 9c,f). If we wish to prepare a solid dispersion of a drug with a high melting point, this can be a problem if SEs with high HLB values are used, as their melts do not flow.

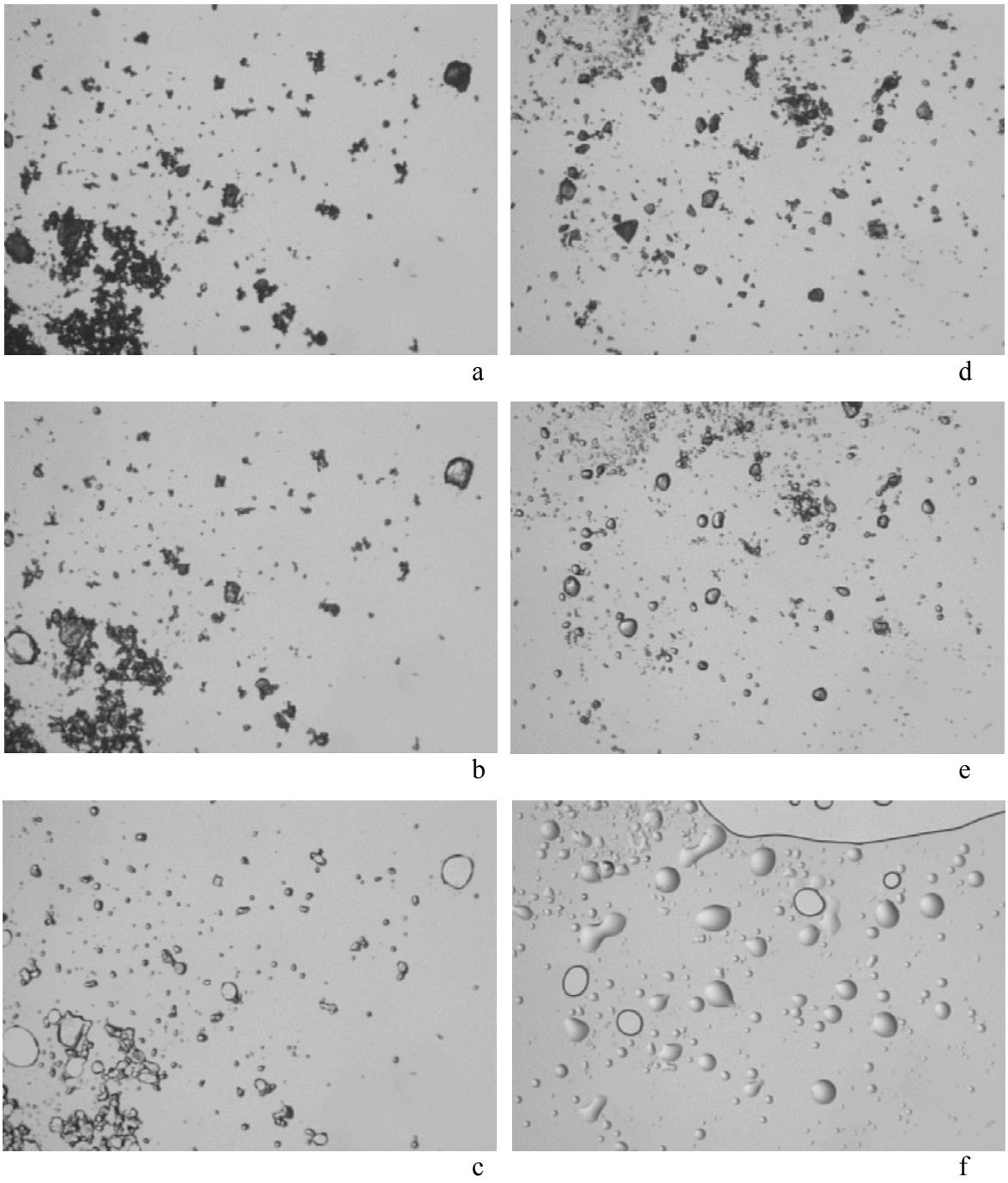

Fig. 9 HSM pictures of S1670 at 25 °C (a), 65 °C (b) and 100 °C (c), and of S370 at 25 °C (d), 70 °C (e) and 100 °C (f)

With respect to the processing, it is important to know whether the changes in structure of these materials are irreversible, or whether the original morphology of the samples is recovered in time. To study this, melts of SEs were prepared and their changes in

time were examined in comparison with the initial state. The melting ranges of melted and solidified (melt) and aged (A1week and A4weeks) samples were measured, their normalized enthalpies were compared with the enthalpy of the untreated SE, and the *CI*s were calculated.

The melting behaviour of samples after melting and solidification differed from that of untreated samples, and it changed in time (Figs 10-14, Table 7). P1670(melt) started to melt 2 °C earlier than the untreated P1670 and its melting also finished earlier. In the DSC curve of solidified P1670, a small peak appeared after 1 week (P1670(A1week)), which was not characteristic of the untreated P1670 (Fig. 10). After 4 weeks (P1670(A4weeks)), the sizes of the two peaks had changed: the melting point had drawn nearer to that for the untreated sample, but was lower; on the other hand, the enthalpy determined by the melting range was the same as that for the untreated P1670.

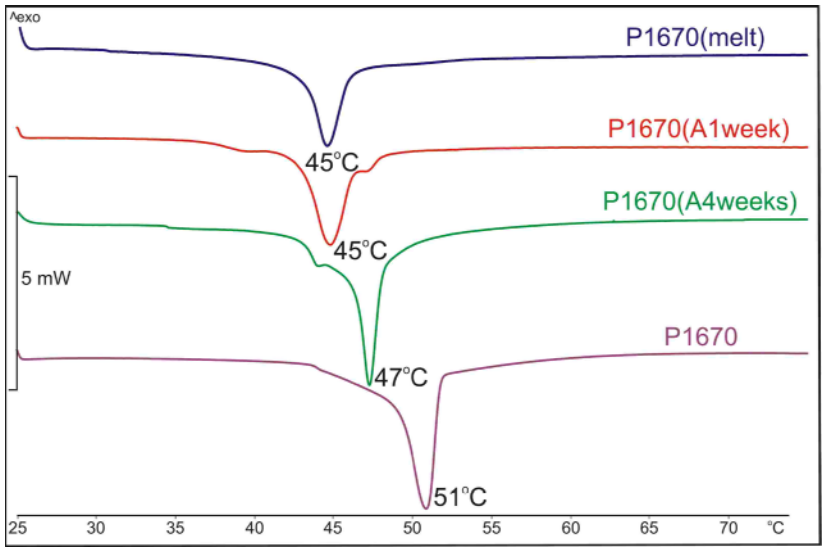

Fig. 10 DSC curves of untreated, melted and solidified, and aged P1670

The melting points of S1670(melt), S1670(A1week) and S1670(A4weeks) were decreased by 2 °C as compared with that of the untreated S1670, but the shape of the curve did not change considerably: it was characterized by one sharp peak (Fig. 11).

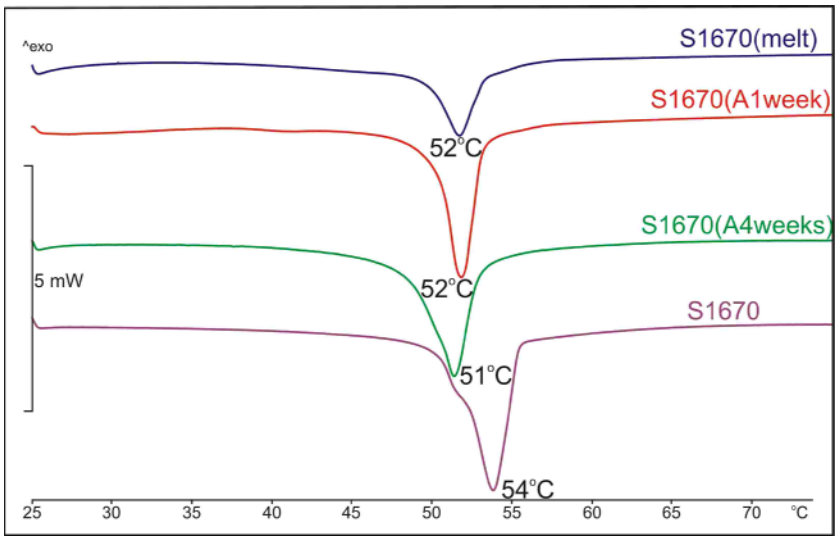

Fig. 11 DSC curves of untreated, melted and solidified, and aged S1670

S970 crystallized very slowly after melting and solidification; in contrast with the other SEs, its CI was not 100% restored after 4 weeks (Table 7, Fig. 12).

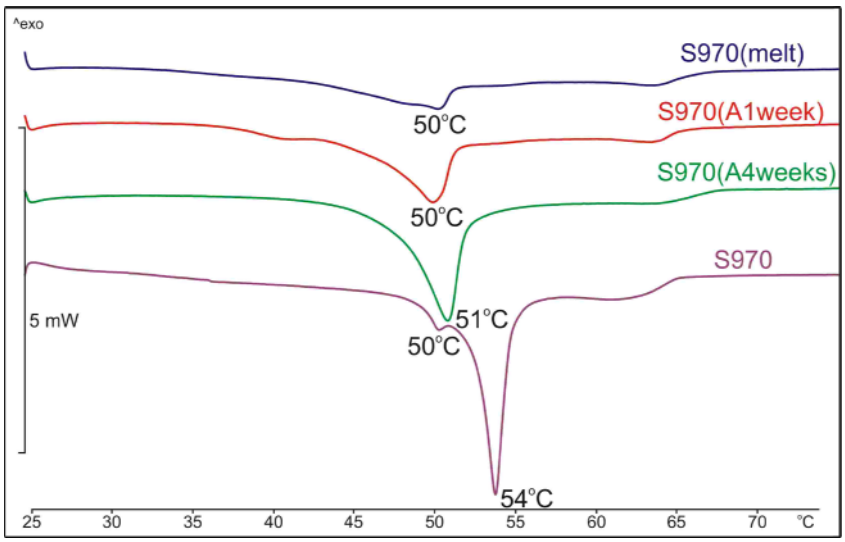

Fig. 12 DSC curves of untreated, melted and solidified, and aged S970

S370(melt) exhibited only one endothermic peak after solidification, but after 1 week (S370((A1week)) the other peak characteristic of the untreated sample appeared. The melting started 7 °C earlier, and thus the melting range was increased as compared with that for the untreated S370 (Fig. 13, Table 7).

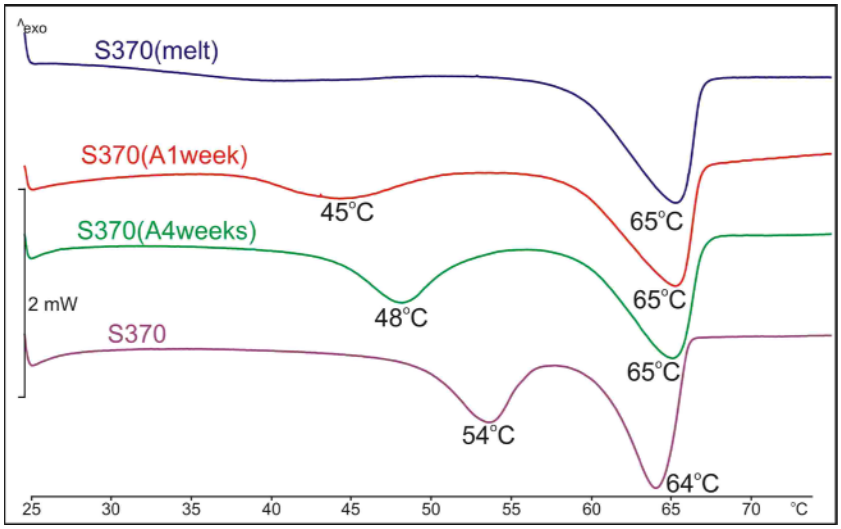

Fig. 13 DSC curves of untreated, melted and solidified, and aged S370

For B370, one of the two peaks likewise disappeared after melting and solidification (B370(melt)), and did not appear even after 1 week (B370((A1week)) or 4 weeks (B370(A4weeks)) (Fig. 14). However, the normalized enthalpy nearly reached the enthalpy of the untreated B370 (Table 7).

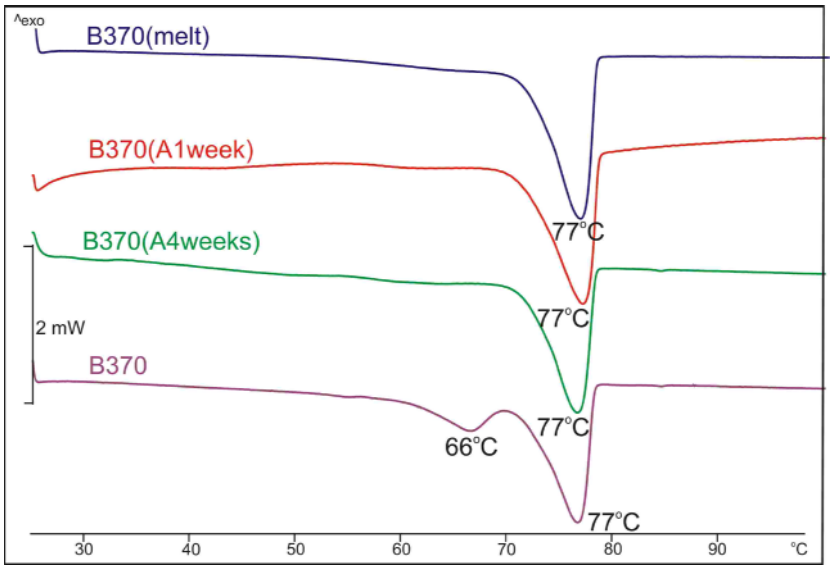

Fig. 14 DSC curves of untreated, melted and solidified, and aged B370

It is probable that, similarly to other fatty acid derivatives, SEs transform from one polymorph to another during storage. After storage for 4 weeks (A4weeks), the heats of fusion of aged samples drew near to the enthalpy of the untreated sample, which means that the structures of all the SEs were apparently restored in time. This is in accordance with the finding of Laine *et al*. [107] that solidified triglycerides have partially amorphous layered structures which gradually crystallize during storage. DSC measurements indicated that, even if the total enthalpies of aged samples reached the enthalpy of the untreated sample, the shape of the DSC curves was different from that of the curve of the initial material, *i.e*. the original structure was not recovered.

Table 7 Effects of treatment and storage of SEs

Sample name	Melting range [°C]	Total enthalpy [J g^{-1}]	*CI* [%]
P1670(melt)	39-56	-37	55.6
P1670(A1week)	37-52	-42.3	63.5
P1670(A4weeks)	35-61	-66.6	100
P1670	41-62	-66.6	100
S1670(melt)	39-60	-35.7	53.5
S1670(A1week)	38-61	-49.6	74.4
S1670(A4weeks)	38-62	-64.3	96.4
S1670	45-62	-66.7	100
S970(melt)	33-68	-30	39.6
S970(A1week)	35-68	-52.9	69.9
S970(A4weeks)	34-68	-63.8	84.3
S970	36-65	-75.7	100
S370(melt)	59-67	-35.2	63.2
S370(A1week)	38-69	-50.3	90.3
S370(A4weeks)	39-69	-55.7	100
S370	45-66	-55.7	100
B370(melt)	55-78	-57.5	84.1
B370(A1week)	56-79	-63.6	93
B370(A4weeks)	55-78	-66.4	97.1
B370	51-79	-68.4	100

Hence, even if the molecular dispersion of a drug in SEs is successful, it is not sure that this advantageous state can be maintained, because the structure of the SE is continuously changing [**I, II and VII**].

5.1.2. Structural characterization

To confirm the DSC results, X-ray analysis was performed on untreated SEs, melted and solidified SEs and aged samples. The measurements were carried out until 40º 2θ, from which it was determined that between 10 and 40º 2θ the SEs display only one peak, at the same position (2θ = 21.04° (P1670); 21.24° (S1670); 21.28° (S970); 21.08° (S370); and 21.3° (B370)). According to the measured basal spacing (0.42 nm), an alpha form with a hexagonal structure was characteristic for all SEs. There are also some peaks at small angles in different positions and with various basal spacings, as indicated in Fig. 15.

The DSC curves of P1670 and S1670 were similar (Fig. 8, curves 1), and the same can be said about their X-ray diffraction patterns. Both SEs have ordered structures: at small angles, they demonstrate four distinct peaks (P1670: 2θ = 2.2°, 4.5°, 6.8° and 9.2°; S1670: 2θ = 2.2°, 4.4°, 6.6° and 8.9°) and nearly the same basal spacing, characteristic of stearic acid (Fig. 15). S970 has a more complex structure: it contains more di- and triester, and also a little tetraester. Moreover, S370 and B370 include the pentaester too (Table 3). In consequence of the presence of these components, the characteristic diffraction peaks disappeared from the X-ray diffractograms and the interlayer spacings increased. The untreated S970 had three (2θ = 1.6°, 2° and 4.4°), S370 had two (2θ = 1.5° and 4.5°), and B370 had three (2θ = 1.3°, 1.9° and 3.9°) characteristic peaks at small angles (Fig. 15).

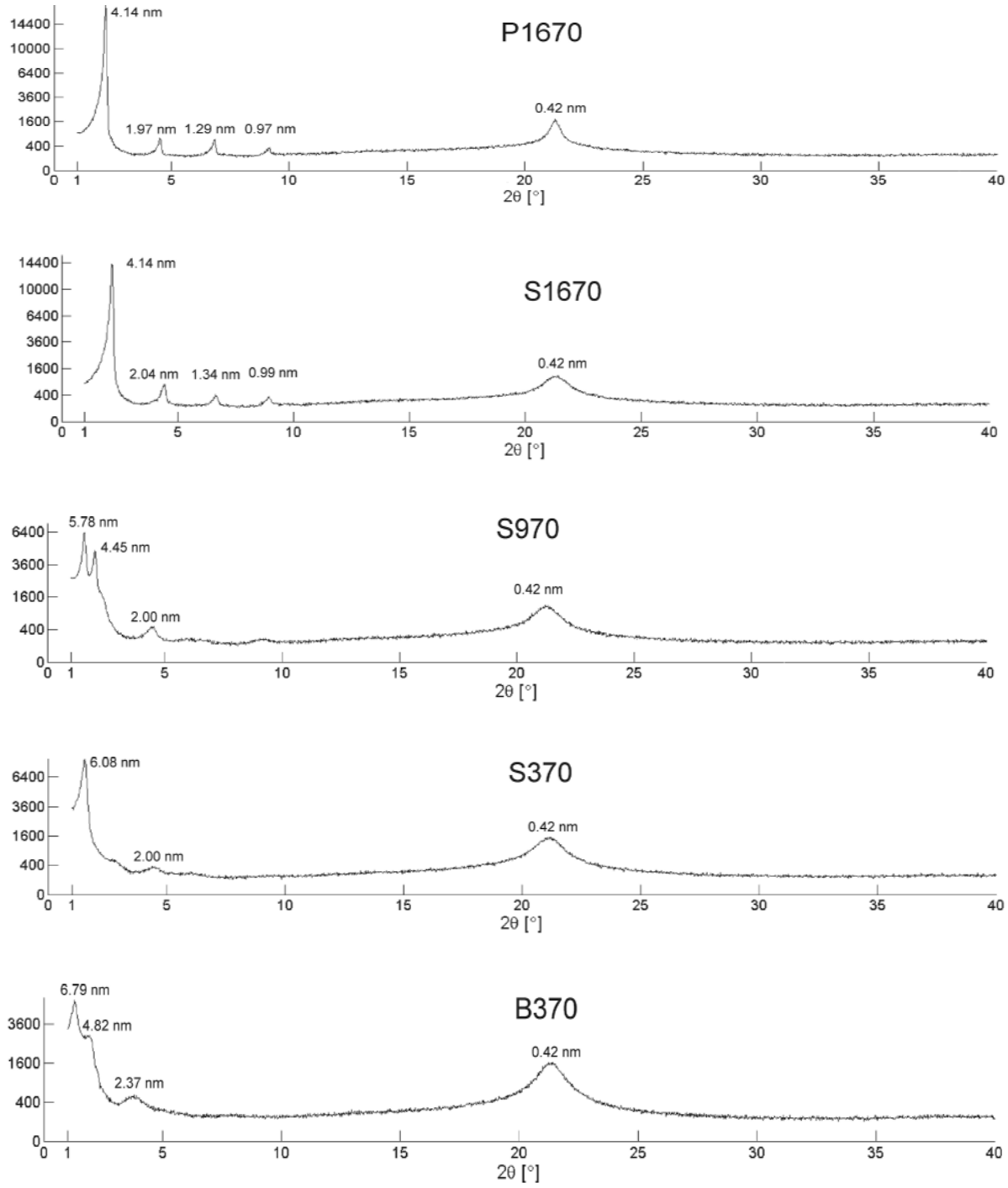

Fig. 15 X-ray diffractograms of SEs

After melting and solidification, the structures of all the SEs were changed, the basal spacings and counts were modified and in almost all cases one of the characteristic peaks had

disappeared, which was probably induced by the polymorphism of the fatty acids (Figs 16-20).

In the diffractograms of melted P1670 and S1670, only three peaks were observed, whereas four peaks were found for the untreated sample. The P1670 peak at 9.2° 2θ (Fig. 16), and the S1670 peak at 8.9° 2θ disappeared (Fig. 17). The peak intensities decreased (practically only the first signal could be seen) and the basal spacings increased.

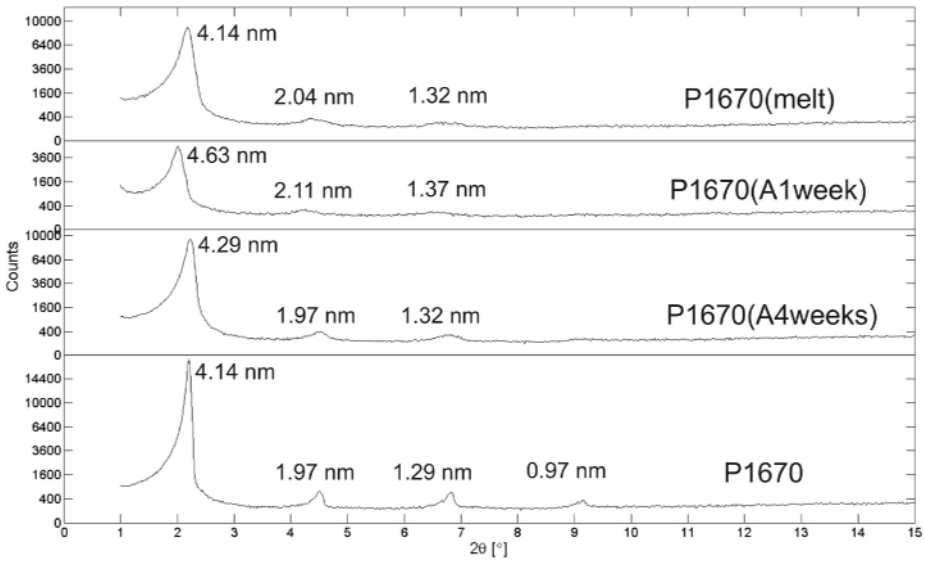

Fig. 16 X-ray patterns of untreated, melted and solidified, and aged P1670

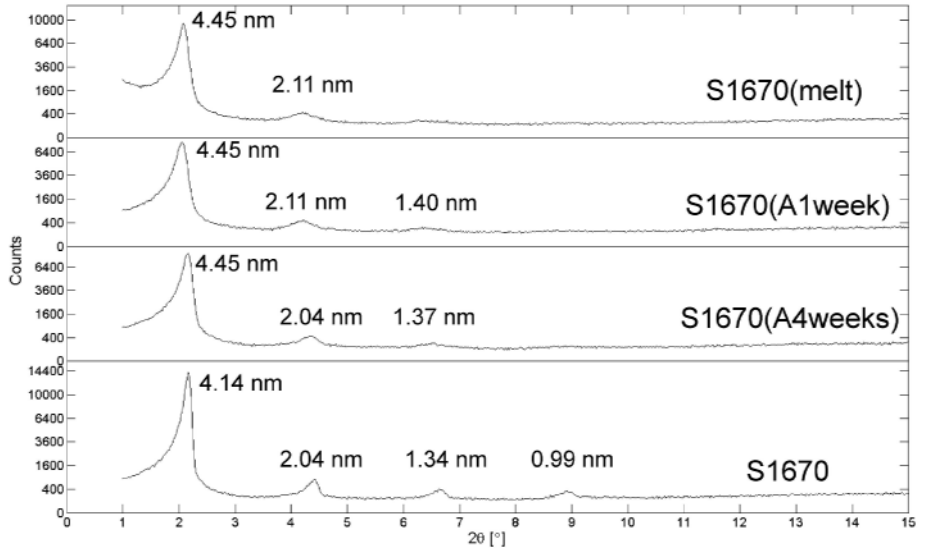

Fig. 17 X-ray patterns of untreated, melted and solidified, and aged S1670

Of the three peaks of untreated S970, after melting and solidification the second signal ($2\theta = 2°$) had disappeared and was not recovered even 4 weeks later (Fig. 18).

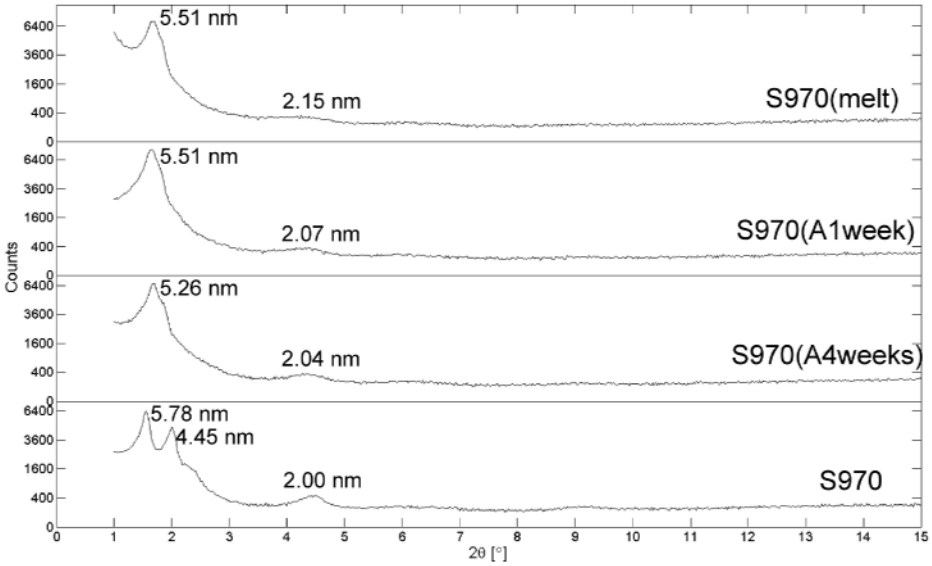

Fig. 18 X-ray patterns of untreated, melted and solidified, and aged S970

The X-ray pattern of S370 did not exhibit such a large change in counts as for SEs with high HLB values, but the basal spacings were modified in this case too (Fig. 19).

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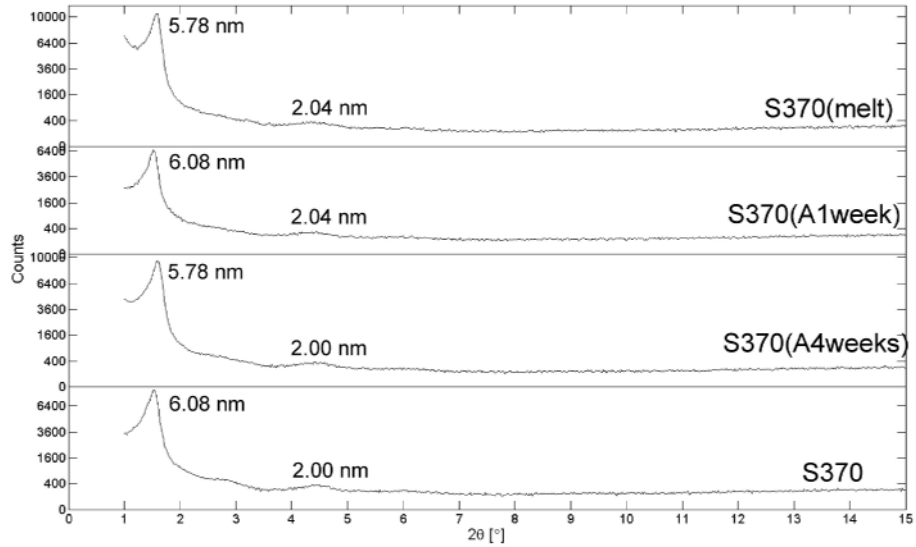

Fig. 19 X-ray patterns of untreated, melted and solidified, and aged S370

The change in degree of crystallinity for B370 was smaller, and the count fluctuation was slight, but the second signal (2θ = 1.9°) disappeared and the morphology of the untreated sample was not restored (Fig. 20).

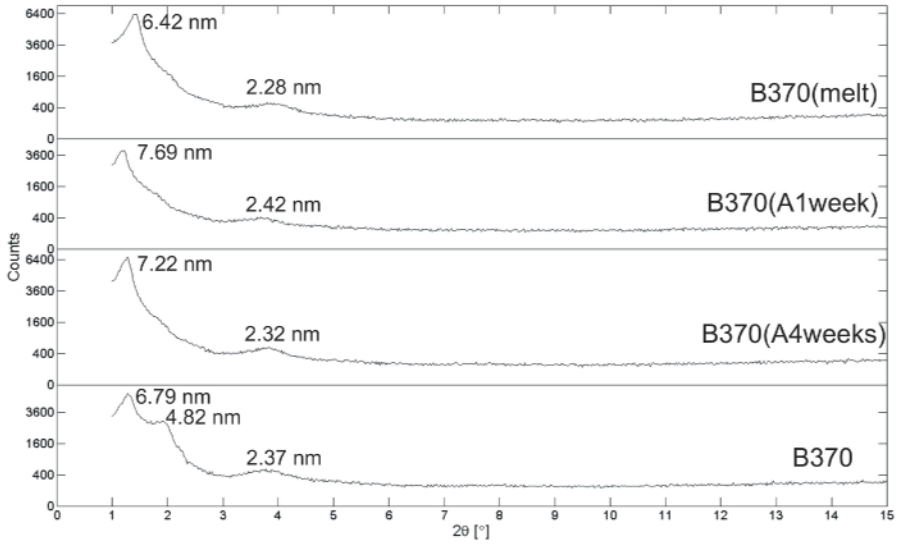

Fig. 20 X-ray patterns of untreated, melted and solidified, and aged B370

These X-ray observations are in accordance with the DSC results, since the shapes of the DSC curves changed continuously, the melting range varied after treatment and the original shape of the curve (characteristic of the untreated sample) was not regained even after storage for one month [**I, II and V**].

5.1.3. Swelling characterization

According to the recently published literature data [42], SEs have gelling behaviour which can influence the drug release. Hence, the examined SEs were dispersed in water (5%) and the viscosity of the suspension was measured as a function of temperature (Fig. 21). These rheological measurements revealed that the different SEs have various swelling properties.

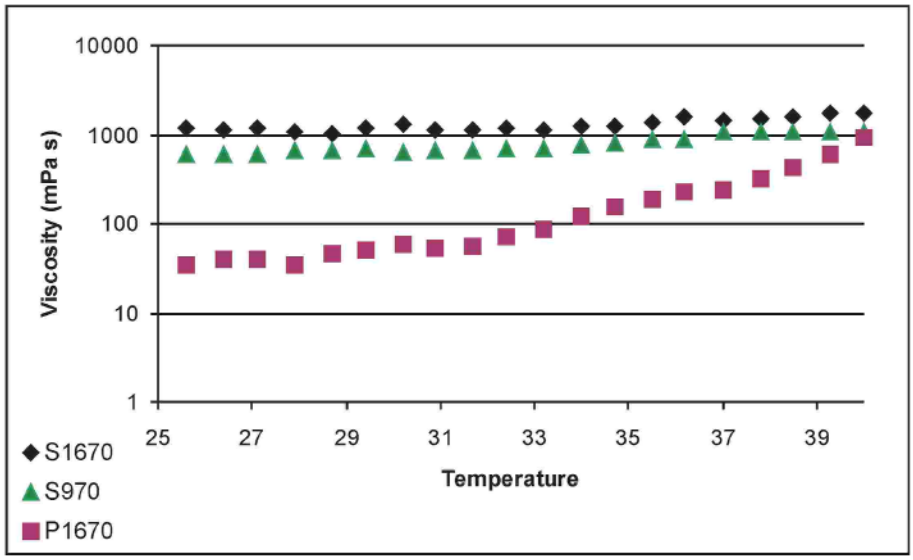

Fig. 21 Viscosities of the hydrophilic SEs in water

It was found that the stearate (C18)-containing S1670 and S970 displayed high viscosity at room temperature, which did not change appreciably on increase of the temperature (Fig. 21). P1670 (where the main fatty acid is palmitate (C16)) has a lower viscosity at 25 °C, which increased considerably on increase of the temperature. Presumably the longer fatty acid chains in the SEs result in the higher viscosity. Lipophilic S370 and B370 have poor wetting properties in water, and their viscosity did not increase with increase of the temperature. If the SE particles are situated close to the drug particles (*e.g.* in hard gelatine capsule or tablet dosage forms), the drug release can be sustained due to the gel-forming behaviour of the hydrophilic SEs. In these cases, therefore, it is important to consider not only the polarity and wetting effect of the SEs, but also their swelling behaviour, because this can influence the drug release to a great extent.

5.1.4. Conclusion

The DSC and HSM results revealed that SEs with high (P1670 and S1670) or moderate (S970) HLB values exhibit a glass transition temperature instead of a melting point. They soften during heating, whereas SEs with low HLB values (S370 and B370) melt and then quickly recrystallize from their melts. However, the original structure does not return

either for SEs with high or moderate, or for SEs with low HLB values: after melting and solidification, their melts continuously change, probably because polymorphs are undergoing transformation. The DSC scans and X-ray patterns of samples stored for up to 4 weeks do not display the same picture as that for the untreated samples. These results demonstrate that changes in morphology must be considered during research and development. This is especially important as concerns molecularly dispersed materials (amorphous state) in SEs. In consequence of the changes in structure, a drug can partially or completely assume a crystalline form, which can entail a lower dissolution rate or the appearance of an undesirable polymorph form [**I, II and VII**].

The drug release can be influenced not only by the thermal and structural behaviour of the SEs, but also by the swelling properties of the materials. According to our rheological measurements, it can be predicted that prompt drug release may not be achieved even with the hydrophilic SEs because of their swelling at body temperature.

5.2. Investigation of drug-SE solid dispersions prepared by melt technology

The aim of the present work was to examine the effects of active agents on the thermal behaviour and the effects of structural changes in the SEs and the drug-SE solid-state interactions on drug release. SE samples (P1670, S970 and B370) were chosen on the basis of the HLB classification system because the ratio of the hydrophilic and lipophilic groups influences their processibility by hot-melt technology as well as the bioavailability of the drug material. Both model active agents (ME and DS) are BCS class II drugs, but they have appreciably different polarities and solubilities.

5.2.1. Thermoanalytical investigation

The DSC results on the SE melts revealed that the drug brought about considerable structural changes in the SEs, to different extents for the three SEs (Table 8).

Table 8 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

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.

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).

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 8) [**III, IV and VIII-X**].

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 263 °C, and that of DS is 291 °C, and the measurements were therefore performed in the range 25-300 °C. However, the SEs can

undergo pyrolysis above 200 °C [108], so the curves were not plotted above this temperature (Figs 22-24). 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. 22). The DS, which did not dissolve in the SE, must have melted before the pyrolysis of P1670.

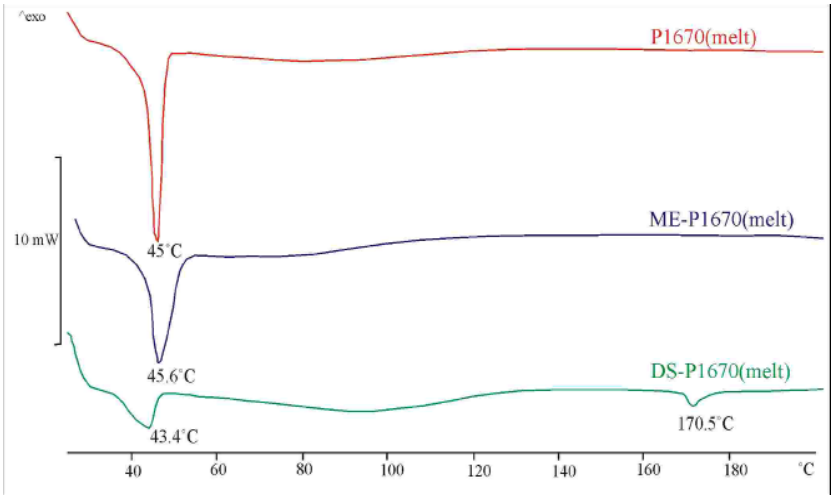

Fig. 22 DSC curves of P1670(melt) and drug-P1670 melted products

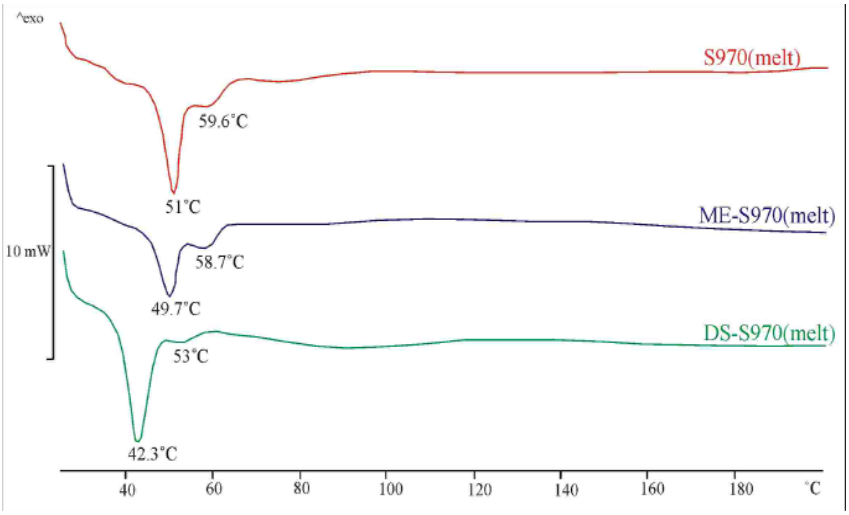

Fig. 23 DSC curves of S970(melt) and drug-S970 melted products

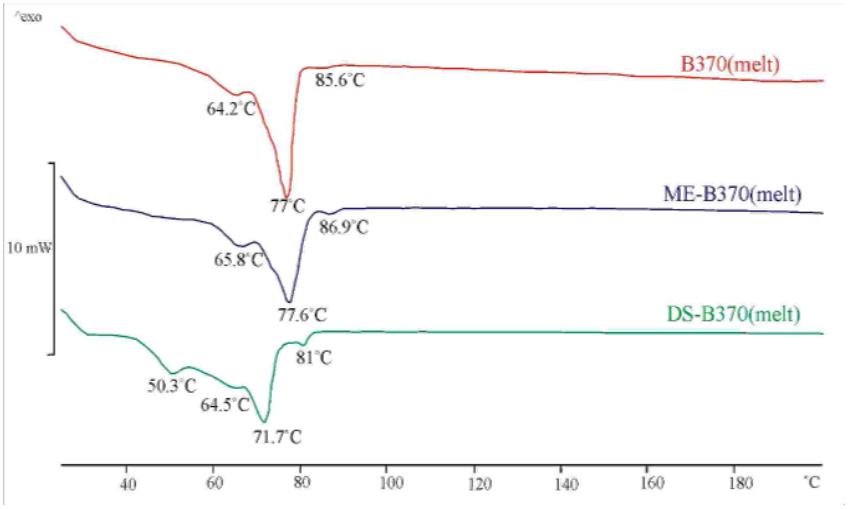

Fig. 24 DSC curves of B370(melt) and drug-B370 melted products

5.2.2. Structural characterization

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 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. By virtue of the size of their molecules, both ME [109] and DS [110] 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.

The positions of the peaks of the SEs at small angles and their intensities are listed in Table 9, and plotted in Figs 25-27, where the basal spacings are also indicated.

Table 9 X-ray data on SEs, SE melts and drug-SE melted products

	2θ	Counts
P1670	2.2	10692
P1670(melt)	2.2	9101
ME-P1670(melt)	2.2	2852
DS-P1670(melt)	2.2	2190
S970	1.6 and 2.1	4597 and 3648
S970(melt)	1.6	6939
ME-S970(melt)	1.6	1739
DS-S970(melt)	2.2	1640
B370	1.3 and 1.9	5184 and 2841
B370(melt)	1.4	6352
ME-B370(melt)	1.3	1303
DS-B370(melt)	2	955

For P1670, neither the position of the characteristic peak of SE nor the basal spacing changed considerably; only the degree of crystallinity decreased to a third as compared with P1670(melt), both for ME-P1670(melt) and for DS-P1670(melt) (Fig. 25).

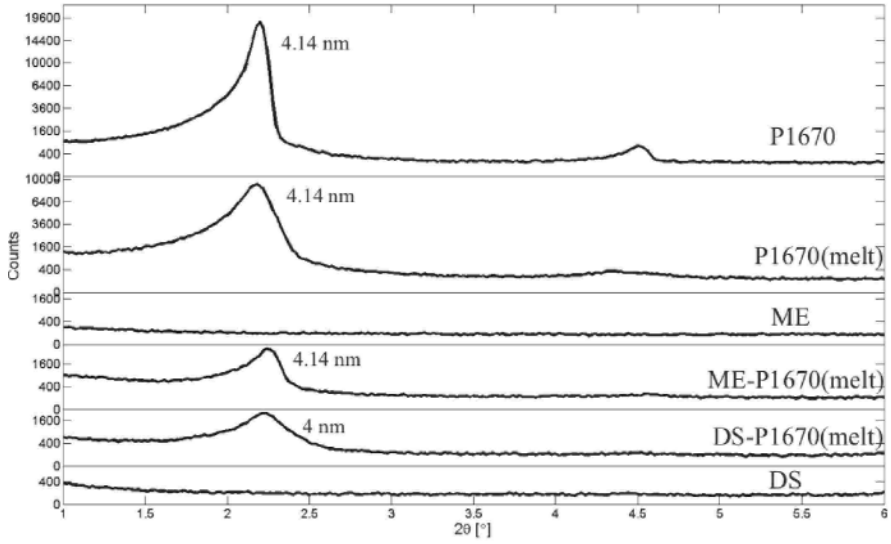

Fig. 25 X-ray diffractograms of drugs, P1670 and drug-P1670 melted products

For ME-S970(melt), the degree of crystallinity decreased to a quarter relative to S970(melt), just as in the case of the DS-S970(melt). It is clear from Fig. 26 that only one characteristic peak of the SEs appeared for the products, at different positions for the two drugs.

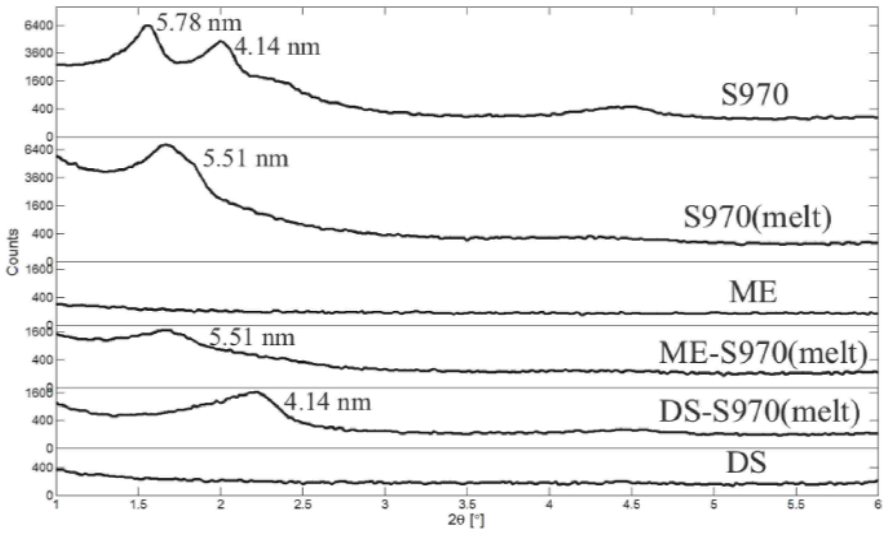

Fig. 26 X-ray diffractograms of drugs, S970 and drug-S970 melted products

The greatest decrease in crystallinity was that for drug-B370(melt) as compared with B370(melt); the drugs are best distributed in this SE. The characteristic peak of B370 appeared in different positions, as a result of the effects of the two drugs (Fig. 27).

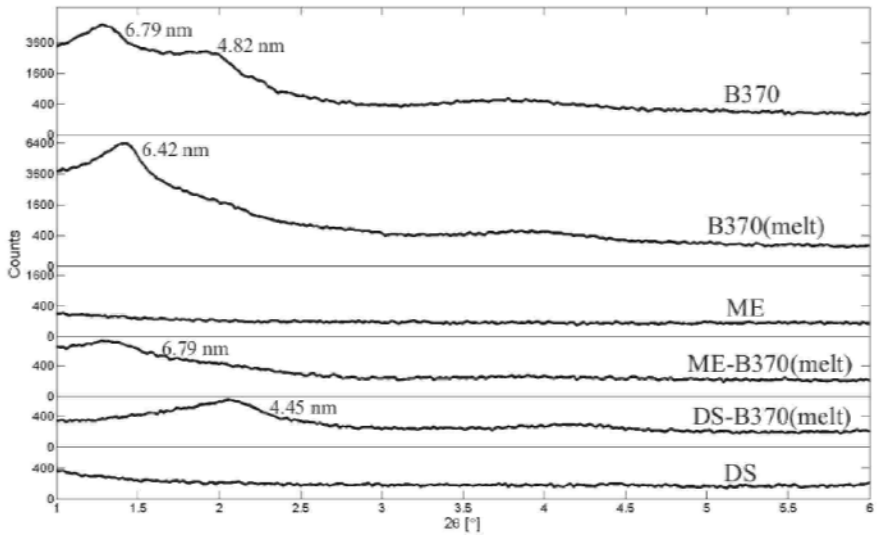

Fig. 27 X-ray diffractograms of drugs, B370 and drug-B370 melted products

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 [**III and VIII-X**].

5.2.3. Contact angle measurements

The drug release may be influenced by many factors (*e.g.* the swelling of the carriers, the polarities and the wetting properties of the 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 10.

Table 10 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

The contact angles of the two drugs in water were very different (θ_{water}(ME) = 61.56; θ_{water}(DS) = 16.8), and the SEs influenced the wetting behaviour of the drugs according to their HLB values or polarity. From these results, it is predictable how SEs can change the dissolution of these two drugs.

5.2.4. *In vitro* drug release

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 hours 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 hours 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 an HLB of 16. In the cases of the hydrophilic SE-containing products (ME-P1670(melt) and ME-S970(melt)), a gel-like residue could be seen in the capsule holder at the end of the examinations. For ME-B370(melt), the drug release was greatly slowed down: only 15% of the ME was dissolved in 2 hours, instead of 30% (Fig. 28).

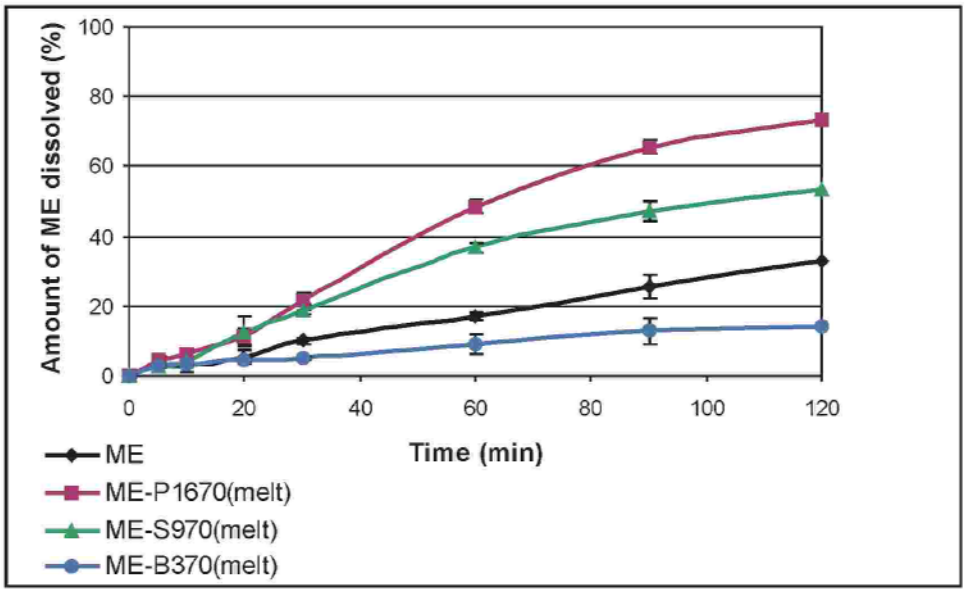

Fig. 28 Dissolution of ME and ME-SE melted products

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 release of DS was delayed by S970, but the drug was completely dissolved in 1 hour. The dissolution of DS was greatly

decreased by the lipophilic B370: the quantity of drug dissolved in 2 hours was < 50% (Fig. 29).

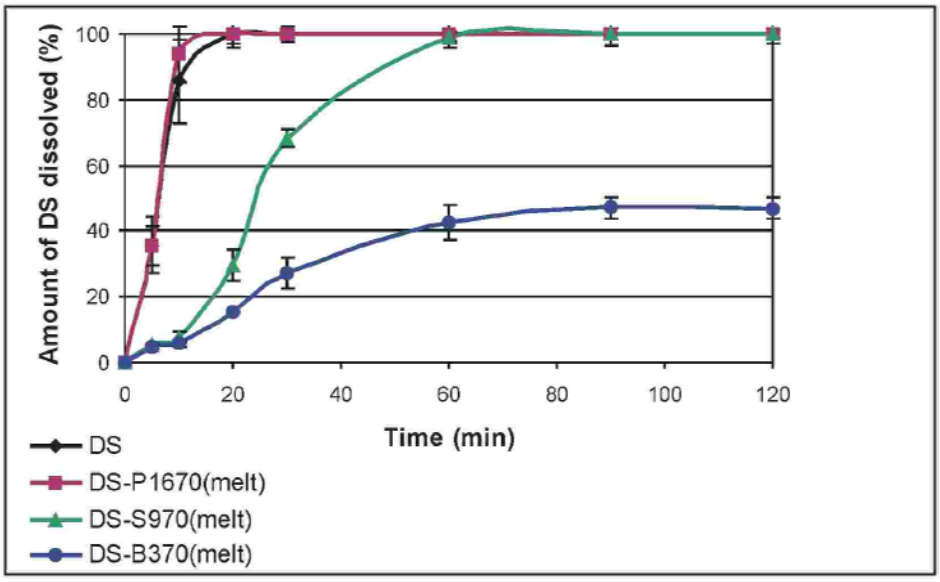

Fig. 29 Dissolution of DS and DS-SE melted products

The dissolution studies indicated that the dissolution of the different drugs was influenced differently by the SEs. The hydrophilic P1670 increased the dissolution of ME considerably, but 100% drug release could not be achieved. Our rheological measurements showed that P1670 gelled at 37 ºC (Fig. 21), which explains why 100% release could not be attained in the case of ME despite the high HLB value. S970, with a medium HLB value, slightly increased the dissolution of ME due to its polarity and wetting effect, but because of its gel-forming property, the drug release was sustained. The lipophilic B370 has a low viscosity in aqueous medium; in this case, only the HLB value plays a role, and it decreases the dissolution of ME.

DS was dissolved in the intestinal juice within a few minutes, and the effect of the hydrophilic P1670 was not manifested here. In spite of the gel-forming property of P1670, the dissolution of DS could not be delayed with this SE. S970 has a medium HLB value and is dispersed less in water, and it slows down the dissolution of DS. B370 has the lowest HLB value among the SEs examined; it decreases the dissolution of DS because of its polarity [**III and VIII-X**].

5.2.5. Study the effects of the drugs on the swelling of SE

It emerged from the *in vitro* dissolution studies that, in the case of ME-P1670(melt)), the swelling of the SE played a role and the ME release was sustained because of the gel-forming properties of the P1670. On the other hand, P1670 did not have any significant effect on the dissolution of DS in artificial enteric juice. The DS release could not be delayed with P1670: there is presumably an interaction between the drug and the SE; DS possibly has a salting-out effect on the gel structure of this SE.

In order to study the effects of the drugs on the gelling of P1670, rheological measurements were made. The viscosity of P1670 was measured in artificial enteric juice (at pH = 7.5), alone and in the presence of the drugs.

It can be clearly seen that the viscosity of P1670 is constant between 25 and 35 °C, but it increases appreciably above 35 °C. In the presence of ME, the swelling process of P1670 is similar to that without this drug (Fig. 30). In this case, the drug has no an effect on the gelling of P1670.

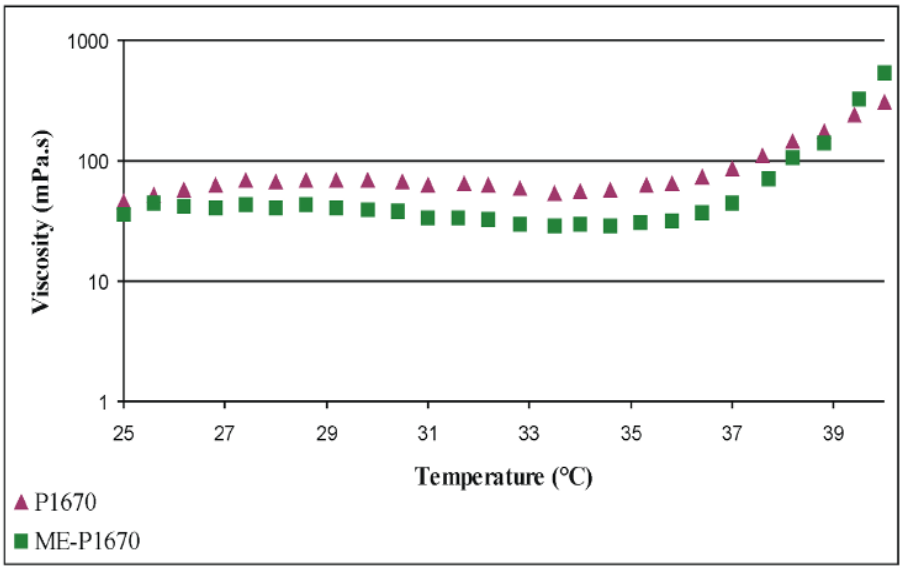

Fig. 30 Viscosity of P1670 and ME-P1670 in enteric juice

On the other hand, in the presence of DS, the viscosity of P1670 is lower (about 10 mPa s) at 25 °C than that of P1670 without DS, and it did not change appreciably on increase of the temperature (Fig. 31). In this case, the drug has a great effect on the gel structure of P1670, and this interaction can be influenced to a large extent by the dissolution of DS.

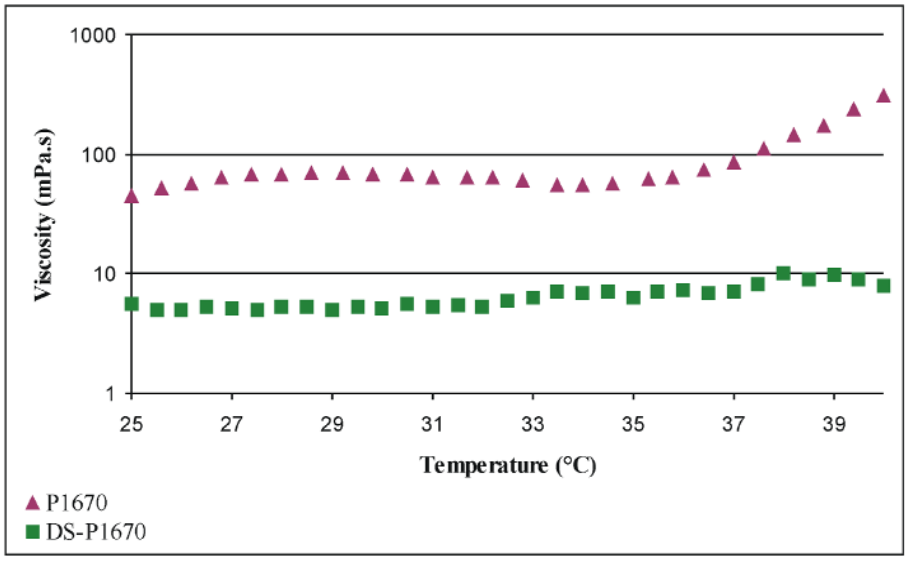

Fig. 31 Viscosity of P1670 and DS-P1670 in enteric juice

For a better understanding of the interaction between DS and P1670, the swelling process of this SE was observed by means of HSM, too. The photos in Fig. 32 show P1670 particles in enteric juice during heating (at 25 °C, 33 °C, 37 °C and 40 °C). The P1670 particles are swollen at room temperature and the gelling process persists and is more expressed at body temperature.

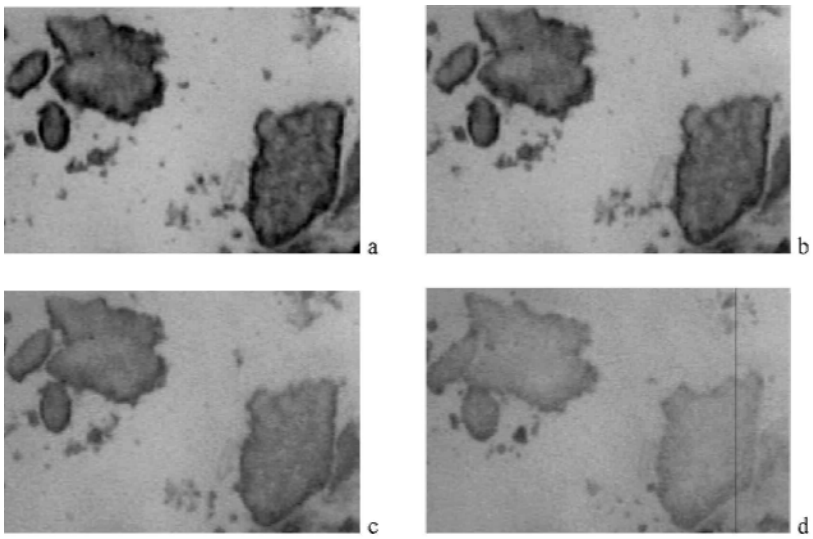

Fig. 32 Effects of heating on P1670 in enteric juice.
HSM pictures at 25 °C (a), 33 °C (b), 37 °C (c) and 40 °C (d)

In contrast, in the presence of DS, P1670 starts to swell at lower temperature, but its structure is destroyed because of the salting-out effect of DS (Fig. 33a,b). It can be seen that, in this case, P1670 is dissolved in the enteric juice at body temperature (Fig. 33c). This explains why the viscosity of P1670 in enteric juice is constant in the presence of DS (Fig. 31) and why P1670 has no effect on the dissolution of DS (Fig. 29).

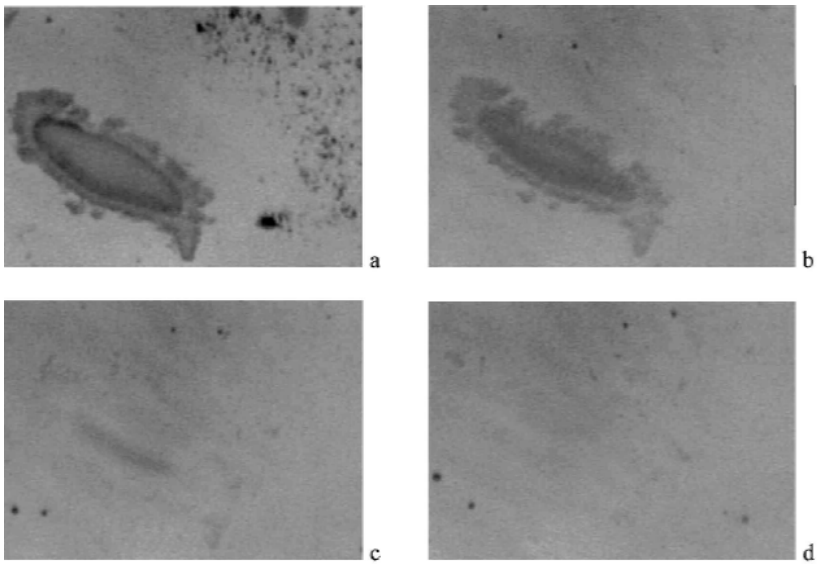

Fig. 33 Effects of heating on P1670 in enteric juice, in the presence of DS.
HSM pictures at 25 °C (a), 33 °C (b), 37 °C (c) and 40 °C (d)

5.2.6. Conclusion

The DSC and X-ray examinations indicated 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. Comparison of the changes caused by the two drugs demonstrated that, in accord with the results of the DSC examinations, the X-ray signal of SE appeared 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 appeared at a different position. Thus, DS brings about a greater structural rearrangement in the SE than ME does. 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.

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 serve as suitable carrier to enhance the rate of dissolution 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 these can influence the structure of the SE or the gel structure formed [**III and VIII-X**].

6. SUMMARY

The objective of this thesis was to characterize and investigate the applicability of SEs as possible carriers in melt technology.

A . Characterization of the SEs

The structure and thermal behaviour of some SEs (P1670, S1670, S970, S370 and B370) with different HLB values were studied. The results revealed that SEs with high or medium HLB values were vitrified by melting. Their *T*g values were determined by means of MTDSC. To visualize the changes in the samples during heating, HSM was used. Hydrophilic SEs were only softened, while lipophilic SEs were melted by heating. After melting and solidification, SEs have partially amorphous layered structures, which slowly crystallize in time. Time-dependent solid-state changes (crystalline and amorphous phases) were observed, and analysed by means of DSC and XRPD. The DSC scans and X-ray patterns of samples stored for up to 4 weeks do not display the same picture as that for the untreated samples. These results demonstrate that changes in morphology must be considered during research and development. This is especially important as concerns molecularly dispersed materials (amorphous state) in SEs. In consequence of the changes in structure, a drug can partially or completely assume a crystalline form, which can entail a lower dissolution rate or the appearance of an undesirable polymorph form.
The swelling of the SEs in aqueous medium was also determined by means of rheological measurements. It was found that hydrophilic SEs exhibit gelling behaviour at body temperature, which can influence the drug release.

B. Investigation of drug-SE solid dispersions prepared by melt technology

After the thermal and structural characterization of the SEs, the effects of active agents on the structures of the SEs were also studied. Drug-SE products were prepared by melt technology and investigated by DSC, XRPD, contact angle measurements, dissolution tests and rheological measurements. ME and DS as model drugs and three SEs with different polarities (P1670, S970 and B370) were chosen for the preparation of the products.

Considerable melting range and enthalpy decreases were observed in the DSC curves for the drug-SE melted products. The structures of the products were rearranged and their degrees of crystallinity were decreased. The molecules of dissolved drugs broke down the structures of the SEs, but did not build 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 drugs and the interactions between the drugs and SEs.

C. Practical relevance of the results

The results presented in this thesis furnish information on the structures and thermal behaviour of the SEs and demonstrate the differences between the properties of the SEs with various HLB values. Moreover, the effects of active agents on the structures of the SEs and the effects of the SEs on drug release were studied.

The results allow the following practical conclusions:

- After melting and solidification, the structures of the SEs break down, and then slowly rearrange. The original structure does not return either for SEs with high or moderate, or for SEs with low HLB values: after melting and solidification, their melts continuously change, probably because polymorphs are undergoing transformation. SEs are semicrystalline carriers, with both amorphous and crystalline regions. During the preparation of solid dispersions, the drugs are built into the amorphous phases of the SEs.

- In the melt technology, mainly the lipophilic SEs may be suggested as carriers. They display characteristic melting, whereas SEs with high or moderate HLB values only soften during heating. The hydrophilic SEs dissolve well in organic solvents, so they can be used to form solid dispersions by the solvent method.

- With respect to the HLB values, hydrophilic SEs (P1670 and S1670) can serve as suitable carriers to enhance the rate of dissolution of drugs with poor water-solubility, while the lipophilic SEs (S370 and 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 the basis of their gel-forming properties, SEs with high (S1670 and P1670) or medium HLB values (S970) can be suitable for delaying the release of certain drugs.

Figure 34 summarizes the main results of this thesis, and emphasizes the common and the different properties of the hydrophilic and lipophilic SEs.

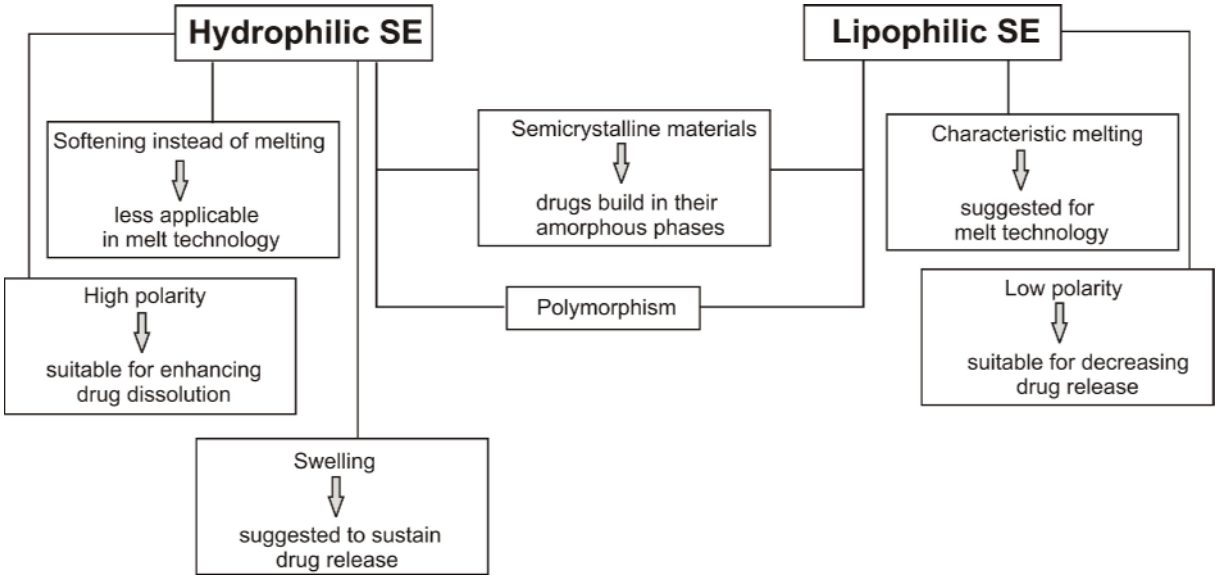

Fig. 34 Common and different behaviour of the SEs

It may be concluded that SEs, and especially lipophilic SEs, can be recommended as carriers in hot-melt technology. The use of hydrophilic SEs in the melt method is complicated, because of their vitrifying, but, due to their higher polarity, they can be used as excipients to form solid dispersions by the solvent method. In recent years, new SEs have been produced, such as ER-190 (sucrose erucate, HLB = 1), or POS-135 (SE of mixed fatty acids, HLB = 1), but very little information is available on these materials. It appears interesting and useful to characterize them, because they may be valuable future materials in the "green" hot-melt method.

REFERENCES

1. Sekiguchi, K., Obi, N., Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man, Chem. Pharm. Bull., 9 (1961) 866-872.
2. Vasconcelos, T., Sarmento, B., Costa, P., Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs, Drug Discovery Today, 12 (2007) 1068-1075.
3. Mitsubishi- Kagaku Foods Corporation, 1982. Ryoto Sugar Ester Technical Information. Nonionic surfactant/Sucrose fatty acid ester/Food additive
4. Jackson, F. L., Lutton, E.S., The polymorphism of certain behenyl mixed triglycerides. A new metastable crystalline form of triglycerides, J. Am. Chem. Soc., 72, (1950) 4519-4521.
5. Chapman, D., Polimorphism of glycerides, Chem. Rev., 62 (1962) 433-456.
6. Larsson, K., Classification of glyceride crystal forms, Acta Chem. Scand., 20 (1966) 55-2260.
7. Ollivon, M., Perron, R., Measurements of enthalpies and entropies of unstable crystalline forms of saturated even monoacid triglycerides, Thermochim. Acta, 53 (1982) 183-194.
8. Hagemann, J. W., Thermal behaviour and polymorphism of acylglycerides. In: Garti, N., Sato, K. (Eds), Crystallization and Polymorphism of Fats and Fatty Acids, Marcel Dekker, New York, USA (1988) pp. 29-67
9. Kellens, M., Meeussen, W., Riekel, C., Reynaers, H., Time resolved X-ray diffraction studies of the polymorphic behaviour of tripalmitin using synchrotron radiation, Chemistry and Physics of Lipids, 52 (1990) 79-98.
10. Westesen, K., Siekmann, B., Koch, M.H.J., Investigations on the physical state of lipid nanoparticles by synchrotron radiation X-ray diffraction, Int. J. Pharm, 93 (1993) 189-199.
11. Sato, K., Crystallization of fats and lipids-a review, Chem. Eng. Sci., 56 (2001) 2255-2265.
12. Kalnin, D., Garnaud, G., Amenitsch, H., Ollivon, M., Monitoring fat crystallization in aerated food emulsions by combined DSC and time-resolved synchrotron X-ray diffraction, Food Res. Int., 35 (2002) 927-934.

13. Foubert, I., Dewettinck, K., Janssen, G., Vanrolleghem, P. A., Modelling two-step isothermal fat crystallization, J. Food Eng., 75 (2006) 551-559.
14. Himawan, C., Starov, V. M., Stapley, A. G. F., Thermodynamic and kinetic aspects of fat crystallization, Adv. Coll. Interface Sci, 122 (2006) 3-33.
15. Piska, I., Zárubová, M., Loužecký, T., Karami, H., Filip, V., Properties and crystallization of fat blends, J. Food Eng., 77 (2006) 433-438.
16. Hill, K., Rhode, O., Sugar-based surfactants for consumer products and technical applications, Fett/Lipid, 1 (1999) S25-33
17. Godshall, M. A., The Potential for Sucrose Esters In Detergent Compositions-A report, Sugar Processing Research Institute, Inc., New Orleans, Louisiana, USA (2005)
18. Akoh, C. C., Emulsification properties of polyesters and sucrose ester blends I: Carbohydrate fatty acid polyesters, J. Am. Oil Chem. Soc., 69 (1992) 9-13.
19. Mutoh, T., Kubouchi, H., Noda, M., Shiinoki, Y., Matsumura, Y., Effect of oil-soluble emulsifiers on solidification of thermally treated creams, Int. Dairy J., 17 (2007) 24-28.
20. Oh, J., Swanson, B. G., Polymorphic transitions of cocoa butter affected by high hydrostatic pressure and sucrose polyesters, J. Am. Oil. Chem. Soc., 83 (2006) 1007-1014.
21. Garti, N., Aserin, A., Fanun, M., Non-ionic sucrose esters microemulsions for food applications. Part 1. Water solubilization, Coll. Surf. A., 164 (2000) 27-38.
22. Kato, A., Arima, K., Inhibitory effect of sucrose ester of lauric acid on the growth of Escherichia coli, Biochem. Biophys. Res. Commun., 42 (1971) 596-601.
23. Awad, T., Kato, S., Acceleration of crystallization of palm cernel oil in oil-in-water emulsion by hydrophobic emulsifier additives, Coll. Surf. B., 25 (2002) 45-53.
24. Arima, S., Ueji, T., Ueno, S., Ogawa, A., Sato K., Retardation of crystallization-induced destabilization of PMF-in-water emulsion with emulsifier additives, Coll. Surf. B., 55 (2007) 98-106.
25. Garti, N., Clement, V., Leser, M., Aserin, A., Fanun, M., Sucrose Ester Microemulsions, J. Molec. Liqu., 80 (1999) 253-296.
26. Bolzinger, M. A., Carduner, T. C., Poelman, M. C., Bicontinuous sucrose ester microemulsion: a new vehicle for topical delivery of niflumic acid, Int. J. Pharm., 176 (1998) 39-45.

27. Huang, J., Moriyoshi, T., Preparation of stabilized lidocaine particles by a combination of supercritical CO_2 technique and particle surface control, J. Mater. Sci., 43 (2008) 2323-2327.
28. Shibata, D., Shimada, Y, Yonezawa, Y., Sunada, H., Otomo, N., Kasahara, K., Application and evaluation of sucrose fatty acid esters as lubricants in the production of pharmaceuticals, J. Pharm. Sci. Technol., 62 (2002) 133-145.
29. Dredán, J., Csóka, G., Marton, S., Antal, I., Határfelületi tulajdonságok jelentősége a gyógyszertechnológiában, Acta Pharm. Hung., 73 (2003) 147-151.
30. Lehmann, L., Keipert, S., Gloor, M., Effects of microemulsions on the stratum corneum and hydrocortisone penetration, Eur. J. Pharm. Biopharm., 52 (2001) 129-136.
31. Ganem Quintanar, A., Quintanar-Guerrero, D., Falson-Rieg, F., Buri, P., Ex vivo oral mucosal permeation of lidocaine hydrochloride with sucrose fatty acid esters as absorption enhancers, Int. J. Pharm, 173 (1998) 203-210.
32. Ayala-Bravo, H. A., Quintanar-Guerrero, D., Naik, A., Kalia, Y. N., Cornejo-Bravo, J. M., Ganem-Quintanar, A., Effects of sucrose oleate and sucrose laurate on in vivo human stratum corneum permeability, Pharm. Res., 20 (2003) 1267-1273.
33. Okamoto, H., Takashi, S., Kazumi, D., Effect of sucrose fatty acid esters on transdermal permeation of lidocaine and ketoprofen, Biol. Pharm. Bull., 28 (2005) 1689-1694.
34. Csóka, G., Marton, S., Zelko, R., Otomo, N., Antal, I., Application of sucrose fatty acid esters in transdermal therapeutic systems, Eur. J. Pharm. Biopharm., 65 (2007) 233-237.
35. Ntawukulilyayo, J. D., Bouckaert, S., Remon, J. P. 1993. Enhancement of dissolution rate of nifedipine using sucrose ester coprecipitates, Int. J. Pharm., 93, 209-214.
36. Otsuka, M., Matsuda, Y., Effect of cogrinding with various kinds of surfactants on the dissolution behavior of phenytoin, J. Pharm. Sci., 84 (1995) 1434-1437.
37. Otsuka, M., Ofusa, T., Matsuda, Y., Dissolution improvement of water-insoluble glybuzole by co-grinding and co-melting with surfactants and their physicochemical properties, Colloids Surf. B., 10 (1998) 217-226.
38. Marton, S., Auner, A., Csóka, G., Increased solubility applying solid-in-solid solutions, Eur. J. Pharm. Sci., 25S1 (2005) S155-S157.

39. Csóka, G., Marton, S., Klebovich, I., Study of solid in solid mixtures of ibuprofen and different sugar fatty acid esters. 1st BBBB Conference on Pharmaceutical Sciences, Programme Book, (2005) pp. 119-122.
40. Seiler, F., Burton, J. S., Dressman, J. B., Characterization of CR matrix formulations based on sucrose-fatty-acid-esters processed by hot-melt extrusion. BPC Science Abstracts, J. Pharm. Pharmacol., 57 (Suppl.) (2005) S28-S29.
41. Ntawukulilyayo, J. D., Demuynck, C., Remon, J. P., Microcrystalline cellulose-sucrose esters as tablet matrix forming agents, Int. J. Pharm., 121 (1995) 205-210.
42. Ullrich, S., Metz, H., Mäder, K., Sucrose ester nanodispersions: Microviscosity and Viscoelastic properties, Eur. J. Pharm. Biopharm., 70 (2008) 550-555.
43. Abd-Elbary, A., El-laithy, H. M., Tadros, M. I., Sucrose stearate-based proniosome-derived niosomes for the nebulisable delivery of cromolyn sodium, Int. J. Pharm., 357 (2008) 189-198.
44. Rote Liste® - Arzneimittelverzeichnis für Deutschland, Rote Liste® Service GmbH, Frankfurt a. M. (2002)
45. Chiou, W. L., Riegelman, S., Pharmaceutical applications of solid dispersion systems, J. Pharm.Sci, 60 (1971) 1281-1302.
46. El-Egakey, M. A., Soliva, M., Speiser, P., Hot extruded dosage forms, Pharm. Acta Helv., 46 (1971) 31-52.
47. Ford, J., The current status of solid dispersions, Pharm. Acta Helv., 61 (1986) 69-88.
48. Follonier, N., Doelker, E., Cole, E. T., Evaluation of Hot-melt-extrusion as a new technique for the production of polymer-based pellets for sustained release capsules containing high loadings of freely soluble drugs, Drug Dev. Ind. Pharm., 20 (1994) 1323-1339.
49. Grünhagen, H-H., Polymer/drug melt extrusion: therapeutic and technological appeal, Pharm. Tech. Eur, 8 (1996) 22-28.
50. Sprockel, O. L., Sen, M., Shivanand, P., Prapaitrakul, W., A melt-extrusion process for manufacturing matrix drug delivery systems, Int. J. Pharm., 155 (1997) 191-199
51. Serajuddin, A. T. M., Solid dispersion of Poorly Water-Soluble Drugs, J. Pharm. Sci, 88 (1999) 1058-1066.
52. Repka, M. A., McGinity, J. W., Zhang, F., Koleng, J. J., Hot-melt extrusion technology, In: Swarbick, J., Boylan, J. (Eds), Encyclopedia of Pharmaceutical Technology, Marcel Dekker, New York, (2002), pp. 203-266

53. Breitenbach, J., Melt extrusion: from process to drug delivery technology, Eur. J. Pharm. Biopharm., 54 (2002) 107-117.
54. Breitenbach, J., Lewis, J., Two concepts, one technology: Controlled-release and solid dispersion with Meltrex, in: Modified-Release Drug Delivery Technology, Drugs and the Pharmaceutical Sciences, Vol. 126, Hadgraft, J., Rathbone, M. J., Roberts, M. S. (Eds.), Marcel Dekker, New York, Basel (2003) pp. 125-134
55. Bashiri-Shahroodi, A., Szabó-Révész, P., Erős, I., Dropping Method Solution for Formulating Solid Dispersions, Pharm. Tech. Eur., 2003. December 1 (http://www.ptemag.com/pharmtecheurope)
56. Chokshi, R., Zia, H., Hot –Melt Extrusion Technique: A Review, Iran J Pharm Res., 3 (2004) 3-16.
57. Sutananta, W., Craig, D. Q. M., Newton, J. M., An investigation into the effects of preparation conditions and storage on the rate of drug release from pharmaceutical glyceride bases, J. Pharm. Pharmacol., 47 (1995) 355-359.
58. Pallagi, E., Vass, K., Pintye-Hódi, K., Kása Jr., P., Falkay, G., Erős, I., Szabó-Révész, P., Iron(II) sulfate release from drop-formed lipophilic matrices developed by special hot-melt technology, Eur. J. Pharm. Biopharm., 57 (2004) 287-294.
59. Bikiaris, D., Papageorgiou, G. Z., Stergiou, A., Pavlidou, E., Karavas, E., Kanaze, F., Georgarakis, M., Physicochemical studies on solid dispersions of poorly water-soluble drugs: Evaluation of capabilities and limitations of thermal analysis techniques, Thermochim. Acta, 439 (2005) 58-67.
60. Vilhelmsen, T., Eliasen, H., Schæfer, T., Effect of a melt agglomeration process on agglomerates containing solid dispersions, Int. J. Pharm., 303 (2005) 132–142.
61. Karanth, H., Shenoy, V. S., Murthy, R. R., Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions: A Technical Report, AAPS PharmSciTech., 7(4) (2006) article 87
62. Reisi Nassab, P, Rajkó, R., Szabó-Révész, P., Physicochemical characterization of meloxicam-mannitol binary systems, J. Pharm. Biomed. Anal., 41 (2006) 1191-1197.
63. Kanig, J. L., Properties of fused mannitol in compressed tablets, J. Pharm.Sci., 53 (1964) 188-192.
64. Beech, D. V., Booth, C., Dodgson, D. V., Sharpe, R. R., Warring, J. R. S., Melting of low molecular weight polyethylene oxide, Polymer, 13 (1972) 73-77.
65. Buckley, C. P., Kovacs, A. J., Melting behaviour of low molecular weight polyethylene oxide fractions, Coll. Polym. Sci., 254 (1976) 695-715.

66. Craig, D. Q. M., Newton, J. M., Characterisation of polyethylene glycols using differential scanning calorimetry, Int. J. Pharm., 74 (1991) 33-41.
67. Morris, K. R., Knipp, G. T., Serajuddin, A. T. M., Structural properties of polyethylene glycol - polysorbate 80 mixture, a solid dispersion vehicle, J. Pharm. Sci., 81 (1992) 1185-1188.
68. Pitkänen, I., Perkkalainen, P., Rautiainen, H., Thermoanalytical studies on phases of D-mannitol, Thermochim. Acta, 214 (1993) 157-162.
69. Sutananta, W., Craig, D. Q. M., Newton, J. M., The effects of ageing on the thermal behaviour and mechanical properties of pharmaceutical glycerides, Int. J. Pharm., 111 (1994) 51-62.
70. Sutananta, W., Craig, D. Q. M., Newton, J. M., An investigation into the effect of preparation conditions on the structure and mechanical properties of pharmaceutical glyceride bases, Int. J. Pharm., 110 (1994) 75-91.
71. Craig, D. Q. M., The use of glycerides as controlled release matrices. In: Karsa, D. R., Stephenson, R. A. (Eds.), Excipients and delivery systems for pharmaceutical formulations, The Royal Society of Chemistry, Cambridge, (1994) pp.148-170
72. Ginés, J. M., Arias, M. J., Rabasco, A. M., Novák, C., Ruiz-Conde, A., Sánchez-Soto, P. J., Thermal characterization of polyethylene glycols applied in the pharmaceutical technology using differential scanning calorimetry and hot stage microscopy, J. Therm. Anal., 46 (1996) 291-304.
73. Yu , L., Mishra, D. S., Rigsbee, D. R., Determination of the glass properties of D-mannitol using sorbitol as an impurity, J. Pharm. Sci, 87 (1998) 774-777.
74. Siniti, M., Jabrane, S., Létoffé, J. M., Study of the respective binary phase diagrams of sorbitol with mannitol, maltitol and water, Thermochim. Acta, 325 (1999) 171-180.
75. Leuner, C., Dressman, J., Improving drug solubility for oral delivery using solid dispersions, Eur. J. Pharm. Biopharm., 50 (2000) 47-60.
76. Talja, R. A., Roos, Y. H., Phase and state transition effects on dielectric, mechanical and thermal properties of polyols, Thermochim. Acta, 380 (2001) 109-121.
77. Gombás, Á., Szabó-Révész, P., Regdon Jr., G., Erős, I., Study of thermal behaviour of sugar alcohols, J. Therm. Anal. Cal., 73 (2003) 615-621.
78. Hamdani, J., Moës, A. J., Amighi, K., Physical and thermal characterisation of Precirol® and Compritol® as lipophilic glycerides used for the preparation of controlled-release matrix pellets, Int. J. Pharm., 260 (2003) 47-57.

79. Brubach, J. B., Jannin, V., Mahler, B., Bourgaux, C., Lessieur, P., Roy, P., Ollivon, M., Structural and thermal characterization of glyceryl behenate by X-ray diffraction coupled to differential calorimetry and infrared spectroscopy, Int. J. Pharm., 336 (2007) 248-256.
80. van den Mooter, G., Weuts, I., de Ritter, T., Blaton, N., Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs, Int. J. Pharm. 316 (2006) 1–6.
81. Karavas, E., Georgarakis, M., Docoslis, A., Bikiaris, D., Combining SEM, TEM, and micro-Raman techniques to differentiate between the amorphous molecular level dispersions and nanodispersions of a poorly water-soluble drug within a polymer matrix, Int. J. Pharm., 340 (2007) 76-83.
82. van Drooge, D. J., Hinrichs, W. L. J., Visser, M. R., Frijlink, H. W., Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques, Int. J. Pharm., 310 (2006) 220-229.
83. Erős, I., Felületaktív anyagok gyógyszerformákban és biológiai rendszerekben II., Acta Pharm. Hung., 75 (2005) 161-167.
84. Vitez, I. M., Newman, A. W., Davidovich, M., Kiesnowski, C., The evolution of hot-stage microscopy to aid solid-state characterizations of pharmaceutical solids, Thermochim. Acta, 324 (1998) 187-196.
85. Giron, D., Thermal analysis of drugs and drug products, in: Encyclopedia of Pharmaceutical Technology, Second Edition, Swarbrick, J., Boylan, J. C. (Eds.), Marcel Dekker, New York, Basel, (2002) pp. 2766-2793.
86. Harmathy, Zs., Konkoly, I., Modern termoanalitikai módszerek alkalmazása a gyógyszeranalízisben, Acta Pharm. Hung., 64 (1994) 9-15.
87. Pereczes, J., Zelkó, R., A differenciál szkening kalorimetria (DSC) gyógyszertechnológiai alkalmazási lehetőségei, Gyógyszerészet, 44 (2000) 403-406.
88. Khan, N., Craig, D. Q. M., The influence of drug incorporation on the structure and release properties of solid dispersions in lipid matrices, J. Control. Rel., 93 (2003) 355-368.
89. Coleman, N. J., Craig, D. Q. M., Modulated temperature differential scanning calorimetry: a novel approach to pharmaceutical thermal analysis, Int. J. Pharm., 135 (1996) 13–29.

90. Craig, D. Q. M., Royall, P. G., The use of modulated temperature DSC for the study of pharmaceutical systems: Potential uses and limitations, Pharm. Res., 15 (1998) 1152–1153.
91. Yu, L., Amorphous pharmaceutical solids: preparation, characterization and stabilization, Adv. Drug Deliv. Rev., 48 (2001) 27-42.
92. Stephenson, G. A., Forbes, R. A., Reutzel-Edens, S. M., Characterization of the solid state: quantitative issues, Adv. Drug Deliv. Rev., 48 (2001) 67-90.
93. Vippagunta, S.R., Brittain, H. G., Grant, D. J. W., Crystalline solids, Adv. Drug Deliv. Rev., 48 (2001) 3-26.
94. Pfeffer-Hennig, S., Piechon, P., Bellus, M., Goldbronn, C., Tedesco, E., Physico-chemical characterization of an active pharmaceutical ingredient. Crystal polymorphism and structural analysis, J. Therm. Anal. Cal., 77 (2004) 663–679.
95. Suryanaranyanan, R., Rastogi, S., X-ray powder diffractometry, in: Encyclopedia of Pharmaceutical Technology, Second Edition, Swarbrick, J., Boylan, J. C. (Eds.), Marcel Dekker, New York, Basel, (2002) pp. 3005-3019
96. Kata, M., Erős, I., Dékány, I., Fejér, I., Gyógyszertartalmú agyagásvány-komplexek, Gyógyszerészet, 45 (2001) 70-76.
97. Ambrogi, V., Fardella, G., Grandolini, G., Perioli, L., Tiralti, M. C., Intercalation Compounds of hydrotalcite-like anionic clays with anti-inflammatory agents, II: Uptake of diclofenac for a controlled release formulation, AAPS PharmSciTech, 3 (2002) article 26
98. Makai, M., Csányi, E., Németh, Zs., Pálinkás, J., Erős, I., Structure and drug release of lamellar liquid crystals containing glycerol, Int. J. Pharm., 256 (2003) 95-107.
99. Li, B., He, J., Evans, D. G., Duan, X., Inorganic layered double hydroxides as a drug delivery system—intercalation and in vitro release of fenbufen, Appl. Clay Sci., 27 (2004) 199-207.
100. Zheng, J. P., Luan, L., Wang, H. Y., Xi, L. F., Yao, K. D., Study on ibuprofen/montmorillonite intercalation composites as drug release system, Appl. Clay Sci., 36 (2007) 297-301.
101. Francois, N. J., Rojas, A. M., Daraio, M. E., Bernik, D. L., Dynamic rheological measurements and drug release kinetics in swollen scleroglucan matrices, J. Control. Rel., 90 (2003) 355-362.

102. Buckton, G., Characterisation of powder surfaces, pp. 59-74, in: Excipients and delivery systems for pharmaceutical formulations, Eds: D.R.Karsa, R.A. Stephenson, The Royal Society of Chemistry (1995)
103. Nassab, P. R., Tüske, Zs., Kása jr., P., Bashiri-Shahroodi, A., Szabó-Révész, P., Influence of work of adhesion on dissolution rate in binary solid systems, J. Adhesion, 83 (2007) 799-810.
104. Wu, S., Calculation of interfacial tension in polymer systems, J. Polym. Sci., 34 (1971) 19-30.
105. Oh, E. , Luner, P. E., Surface free energy of ethylcellulose films and the influence of plasticizers, Int. J. Pharm., 188 (1999) 203-219.
106. Craig, D. C. M., The mechanism of drug release from solid dispersions in water-soluble polymers, Int. J. Pharm., 231 (2002) 131-144.
107. Laine, E., Auramo, P., Kahela, P., On the structural behaviour of triglycerides with time, Int. J. Pharm., 43 (1988) 241-247.
108. Ushikusa, T., Maruyama, T., Niiya, I., Okada, M., Pyrolysis Behavior and Thermostability of Sucrose Ester of Fatty Acids, Yukagaku, 39 (1990) 38–41.
109. Luger, P., Daneck, K., Engel, W., Trummlitz, G., Wagner, K., Structure and physicochemical properties of meloxicam, a new NSAID, Eur. J. Pharm. Sci., 4 (1996) 175-187.
110. Muangsin, N., Prajaubsook, M., Chaichit, N., Siritaedmukul, K., Hannongbua, S., Crystal structure of a unique sodium distorted linkage in diclofenac sodium pentahydrate, Anal. Sci., 18 (2002) 967-968.

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ANNEX

I.

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Study of thermal behaviour of sugar esters

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Abstract

Sugar esters (SEs) are widely used in the pharmaceutical and food industries. They have a wide range of HLB values (1–16), and hence they can be applied as surfactants, or as solubility or penetration enhancers. SEs can be employed in hot-melt technology, because their melting points are low and they decompose only above 220 °C. The aims of this work were to study the thermal properties of SEs and to demonstrate differences between SEs with various HLB values. The results revealed that SEs with high or medium HLB values were vitrified by melting. Their glass transitions (T_g) were determined by modulated differential scanning calorimetry. To visualize the changes in the samples during heating, hot-stage microscopy was used. Hydrophilic SEs were only softened, while lipophilic SEs were melted by heating. After melting and solidification, SEs have partially amorphous layered structures which slowly crystallize in time. Time-dependent solid-state changes (crystalline and amorphous phases) were observed, and analysed by means of differential scanning calorimetry and X-ray powder diffraction.

Keywords: Glass transition; Hot-stage microscopy; Sugar esters; Thermal analysis; X-ray powder diffraction

1. Introduction

Sugar esters (SEs) have been known since 1960s, but they are relatively new materials in pharmaceutical technology. They are tasteless, odourless and non-toxic, and thus they are good emulsifiers for foodstuffs. They are also suitable for medications and cosmetics, because they are non-irritant to the eyes and skin.

SEs are non-ionic surface-active agents consisting of sucrose as hydrophilic group and fatty acids as lipophilic groups, i.e. sucrose fatty acid esters. Sucrose contains 8 hydroxy groups, and it is therefore possible to manufacture SEs with various HLB values by controlling the degree of esterification (Mitsubishi-Kagaku Foods Corporation, 1982; Molinier et al., 2005). Depending on their HLB values, they are available with a range of properties: O/W and W/O emulsifying properties, solubilizing and foaming properties (Husband et al., 1998; Garti et al., 2000), enhancement or inhibition of crystal growth in fat (Awad and Sato, 2002), antibacterial effects (Kato and Arima, 1971), and lubrication and releasing properties (Hahn and Sucker, 1989; Ntawukulilyayo et al., 1993; Otsuka et al., 1998; Marton et al., 2005).

The melting points of most sugars are high, so that preparations by the hot-melt method are problematic (Leuner and Dressman, 2000), but SEs have melting points of 40–79 °C and are very stable to heat, and hence they can be employed to prepare solid dispersions by the melt technology. In fact, it is very important to know the thermal behaviour of these materials, so that the changes in the base materials can be predicted during storage and technological processes such as the preparation of solid dispersions by melting.

The aims of this study were to evaluate the thermal properties of SEs, to observe and analyse the time-dependent solid-state changes (crystalline–amorphous phases) and to demonstrate the differences between SEs with various HLB values. SE samples were chosen by HLB classification system because the ratio of the hydrophilic and lipophilic groups influences their processibility by hot melt technology as well as the bioavailability of the drug material.

2. Materials and methods

2.1. Materials

Ryoto SEs (Mitsubishi-Kagaku Foods Corporation, Japan) are a family of vehicles consisting of sucrose and mixtures of

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Table 1
Data of SEs by Mitsubishi-Kagaku Foods Corporation

Name of SE	Fatty acid	HLB	mp (°C)	Decomposition temperature (°C)
P1670	Palmitate (C16)	16	48	235
S1670	Stearate (C18)	16	56	237
S970	Stearate (C18)	9	56	234
S370	Stearate (C18)	3	58 and 69	238
B370	Behenate (C22)	3	63 and 79	241

mono- to octaesters of fatty acids. According to Aulton (2002), excipients with high HLB (10–18) are hydrophilic (water soluble), with medium HLB (7–9) are water dispersible and with low HLB (0–6) are hydrophobic (oil soluble). SEs with high or moderate HLB can be used in preparation of fast release and SEs with low HLB in preparation of sustained release formulation. So, we selected SEs for study that have high (P1670 and S1670), medium (S970) and low HLB values (S370 and B370). The longer the fatty acid chains in the SEs and the higher the degree of esterification result in the lower the HLB value (Tables 1 and 2).

2.2. Sample preparation

Three types of samples were prepared for the physical evaluation of SEs:

- Untreated samples (U): samples without any special treatment (commercial).
- Freshly solidified samples (F): samples were melted in a porcelain dish in an oven (Factory for Laboratory Equipment, Budapest, Hungary, Labor type 123) from 25 to 100 °C, and then allowed to recrystallize at room temperature.
- Aged samples (A): the freshly solidified samples were stored for up to 1 month at room temperature (20 ± 2 °C) to detect any physical aging effect.
  - A1week: samples stored for 1 week.
  - A4week: samples stored for 4 weeks.

For the comparison of sample properties (e.g. by X-ray), it is important that the particle sizes should be similar. These were therefore determined by sieve analysis (Retsch vibrating apparatus, amplitude: 1, interval: 60 s, time: 5 min, three times). The average particle size of the untreated samples was 100–300 μm. After melting and solidification, the freshly solidified samples were pulverized in a mortar to achieve the same particle size as that of the untreated samples.

Table 2
Data on compositions of different SEs by Mitsubishi-Kagaku Foods Corporation

	P1670	S1670	S970	S370	B370
Monoester (%)	80	77	48	19	15
Diester (%)	17	20	34	33	24
Triester (%)	3	3	14	30	28
Tetraester (%)			4	15	22
Pentaester (%)				3	11

2.3. Derivatography

Fifty milligrams SE and 50 mg inert Al_2O_3 were placed into the platinum container of a Derivatograph-C apparatus (MOM, Hungary). The instrument was calibrated by using $CuSO_4 \cdot 5H_2O$. The TG, DTG and DTA curves were determined. The samples were heated from 25 to 100 °C at a heating rate of 5 °C min^{-1}.

2.4. Differential scanning calorimetry (DSC)

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 Ar atmosphere at a flow rate of 100 ml min^{-1}. The samples were heated from 25 to 100 °C at a heating rate of 1 °C min^{-1}. For analysis of the recrystallization process, samples were heated up to 100 °C as described above, then cooled down to 25 °C at a rate of 2 °C min^{-1}, and reheated to 100 °C at a heating rate of 1 °C min^{-1}.

The crystallinity index for freshly solidified sample (CI_F) and the aged sample (CI_A) was calculated from the heats of fusion:

$$CI_F\,(\%) = \frac{\Delta H_F}{\Delta H_U} \times 100$$

$$CI_A\,(\%) = \frac{\Delta H_A}{\Delta H_U} \times 100$$

where ΔH_F = normalized enthalpy (J g^{-1}) of freshly solidified sample, ΔH_U = normalized enthalpy (J g^{-1}) of untreated sample, and ΔH_A = normalized enthalpy (J g^{-1}) of aged sample.

Modulated-temperature DSC is a method that allows the relaxation endotherm and glass transition to be separated into non-reversing and reversing signals, respectively. Hence, it is possible to visualize T_g in isolation (Coleman and Craig, 1996; Craig and Royall, 1998; Yu, 2000). In modulated DSC the measurement conditions were as follows: start temperature: 25 °C, heating rate: 1 °C min^{-1}, amplitude: 1 °C, period: 60 s, and end temperature: 75 °C.

2.5. Hot-stage microscopy (HSM)

HSM observations of morphological features and changes during heating were carried out with a Leica MZ6 microscope (Wetzlar GmbH, Germany) equipped with a Leica 350 heating stage and a JVC TK-128OE (Japan) colour video camera. The different types of samples (untreated, freshly solidified and aged) were observed under the microscope by using a scanning speed of 1 °C min^{-1}. Data were imported into a computer and captured images were analysed by using the Leica Q500MC program.

2.6. X-ray powder diffraction (XRPD)

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 (λ = 0.15418 nm),

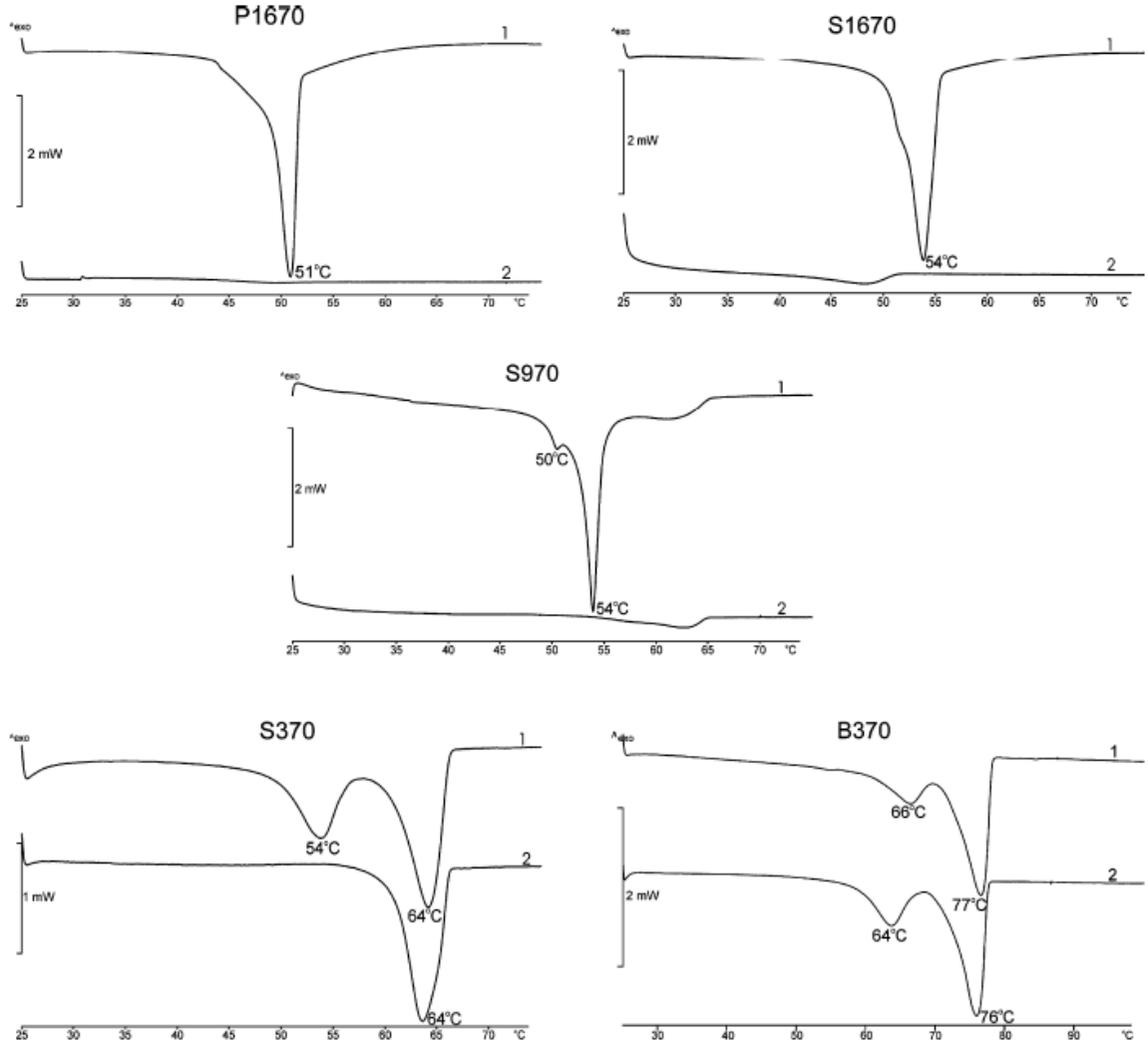

Fig. 1. DSC curves of untreated samples (U); curve 1: first heating; curve 2: second heating.

40 kV, 35 mA. The basal spacing (d_L) was calculated from the diffraction peaks by using the Bragg equation. The XRPD patterns were determined on untreated, freshly solidified and aged samples.

3. Results

The TG, DTG and DTA curves of untreated samples were determined by investigations with a derivatograph. The TG results showed that the mass loss of samples heated to 100 °C was less than 1%, i.e. the SEs did not include water adsorbed on their surface or any volatile component. In response to heating, endothermic changes were observed in the DTA curves of all the SEs, and more peaks were manifested by SEs with lower HLB values.

To determine the exact melting points, DSC studies were performed. The DSC scans (Fig. 1, curves 1) revealed that the melting points (mp) and melting ranges of P1670 and S1670 and their enthalpies were very similar, while the melting of SEs with lower HLB values was prolonged, with more peaks (Table 3). The probable cause of this was, that the studied SEs with high HLB values included only mono-, di- and triesters, while the SEs with lower HLB values contained tetra- and pentaesters too (Table 2).

The effects of a second heating were also studied. The melted SE in the DSC pan (after the first heating) was cooled to 25 °C

Table 3
Thermal parameters of SEs during first heating

SE	Melting range (°C)	mp (°C)	Total enthalpy (J g^{-1})
P1670	41–62	51	−66.6
S1670	45–62	54	−66.7
S970	36–65	50 and 54	−75.7
S370	45–66	54 and 64	−55.7
B370	51–79	66 and 77	−68.4

at a rate of 2 °C min^{-1}, and then heated again at a heating rate of 1 °C min^{-1} to 100 °C (second heating). The results are illustrated in Fig. 1 by curves 2. The DSC curve of second heating demonstrated that there were no more endothermic changes for P1670, and for S1670 and S970 the changes were negligibly small. Accordingly, the crystal structures of SEs with high (P1670 and S1670) or moderate (S970) HLB values, which can be characterized by melting points (Fig. 1, curves 1) broke down during the first heating and could not recrystallize during cooling. Thus, curves 2 in Fig. 1 (second heating) exhibit the characteristics of amorphous materials. S370 has two endothermic peaks, but during the second heating one peak disappeared and the melting range decreased. B370 seemed to be the most stable material: the melting ranges in the first and second heatings were the same and the shapes of the curves did not change; only the total enthalpy decreased slightly (<5 J g^{-1}) (Table 4).

Table 4
Thermal parameters of SEs during second heating

SE	Melting range (°C)	mp (°C)	Total enthalpy (J g^{-1})
P1670	–	–	–
S1670	–	–	–
S970	–	–	–
S370	54–66	64	−31
B370	52–79	64 and 76	−63.9

Consequently, there was probably a change in the structures of the SEs with high HLB values during heating. According to XRPD investigation, alpha form of the SEs with a hexagonal structure was characterized for all excipients which broke down and built up during the heating and cooling processes. SEs with low HLB values (S370 and B370) had faster recrystallization but the rearrangement of the stucture of SEs with high (P1670 and

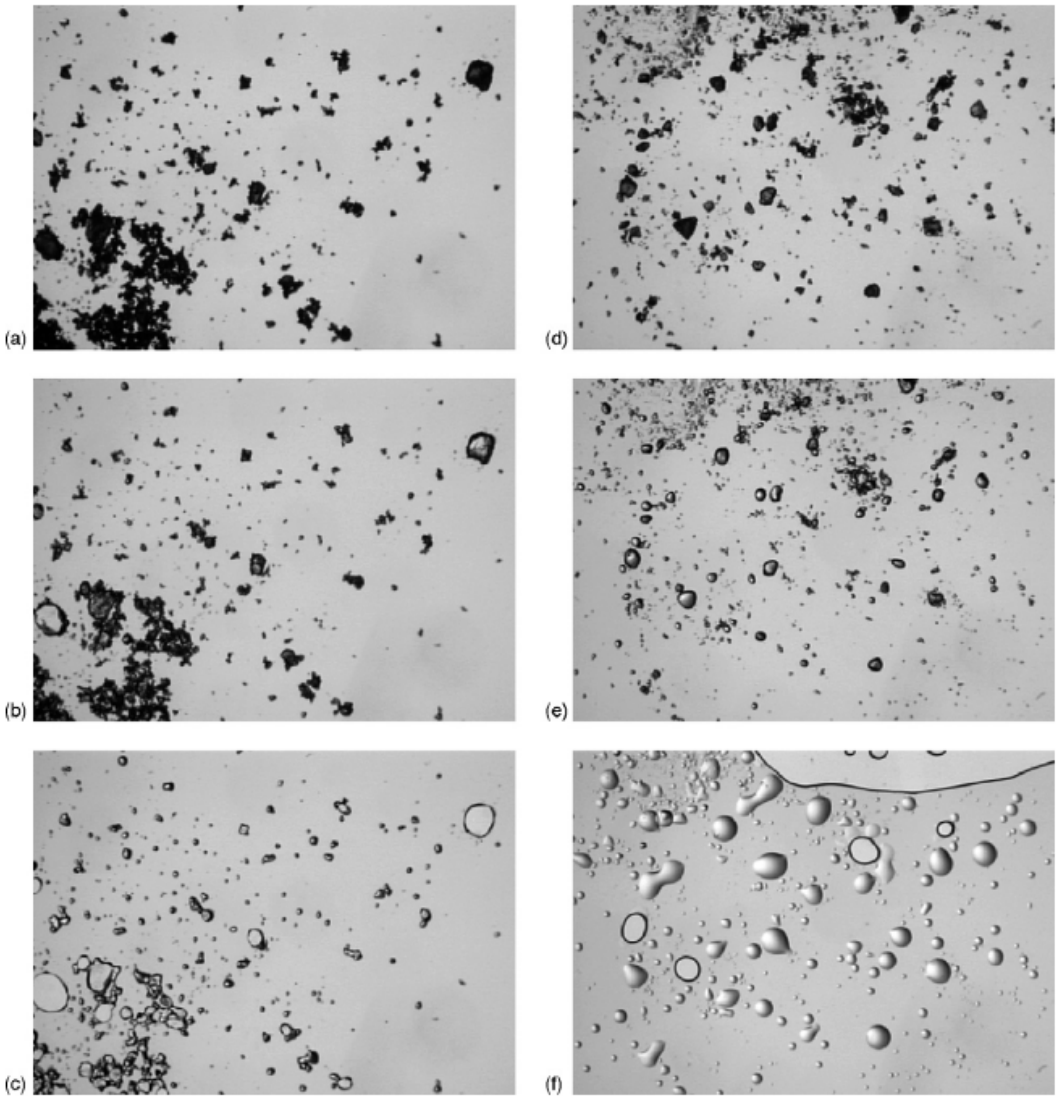

Fig. 2. HSM pictures of untreated S1670 at 25 °C (a), 65 °C (b) and 100 °C (c), and of untreated S370 at 25 °C (d), 70 °C (e) and 100 °C (f).

S1670) or moderate (S970) HLB values was very long. So, this led to an amorphous state. Amorphous materials can be characterized with the glass transition temperature (T_g) instead of the melting point. The determination of T_g by the conventional DSC method is difficult, because T_g is often concealed by or overlapped with other thermal events which take place in parallel. The results of our MTDSC measurements revealed that SEs with high (P1670 and S1670) or moderate (S970) HLB values undergo a glass transition, which coincides with the melting points of the materials (Table 5).

To visualize the changes in the samples during heating, HSM was used. This technique is complementary to DSC and may help in the interpretation of the DSC results. The photographs in Fig. 2 shows the morphology of SEs with high (S1670) or low (S370) HLB values before heating (at 25 °C) and after their melting (S1670: 65 °C, and S370: 70 °C). While SEs with high HLB values (e.g. S1670) only became soft, but did not flow, lipophilic SEs (e.g. S370) melted. SEs with high or medium HLB values did not melt during the first heating; their melting points detected in the DSC curves were truly their glass transitions (Table 5).

Table 5
Melting points and glass transitions during first and second heatings

	First heating		Second heating	
	mp (°C)	T_g (°C)	mp (°C)	T_g (°C)
P1670	51	–	–	50
S1670	54	–	–	51
S970	50 and 54	–	–	53
S370	54 and 64	–	64	–
B370	66 and 77	–	64 and 76	–

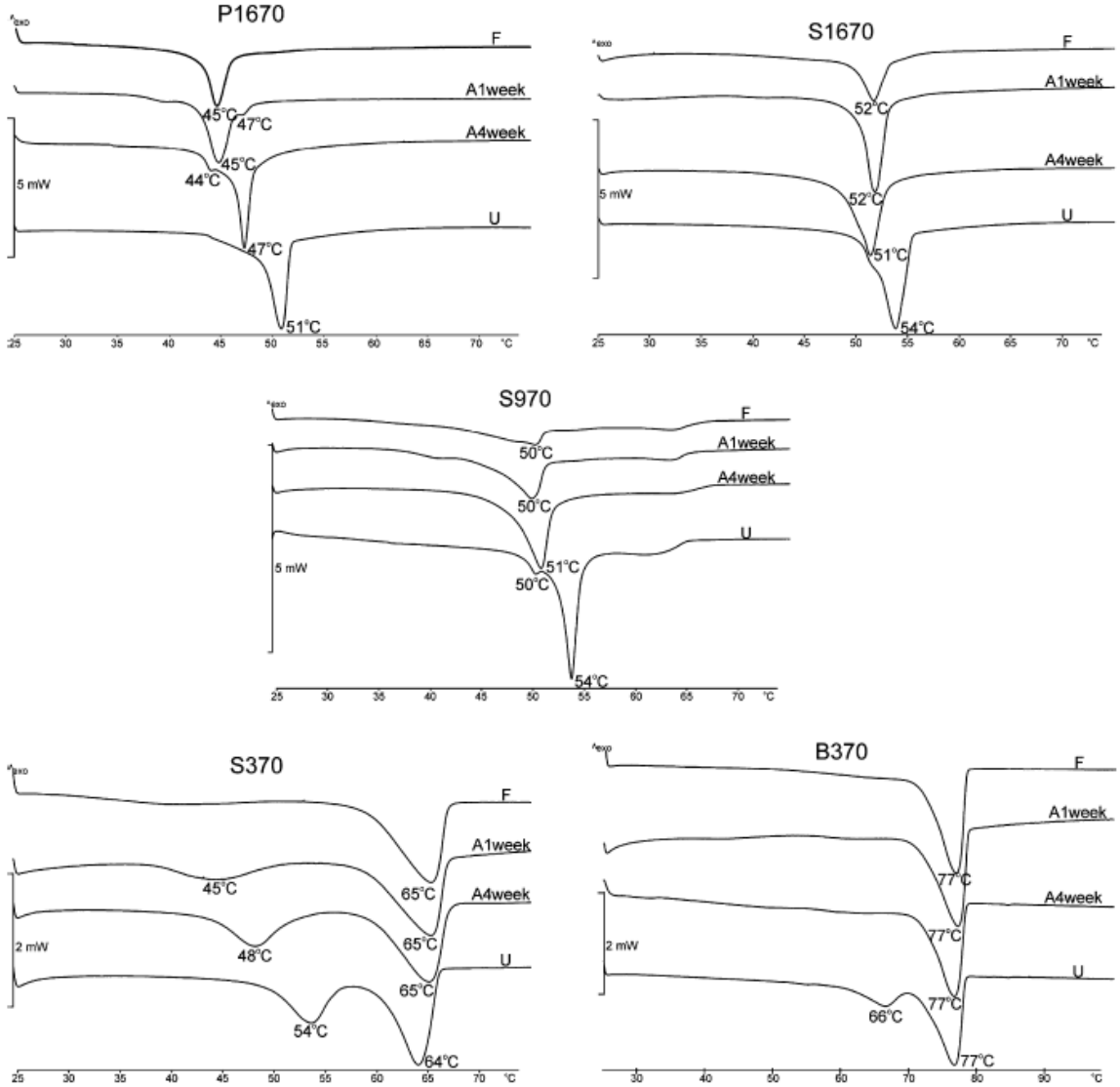

Fig. 3. DSC heating curves of SEs obtained from untreated (U), freshly solidified (F), and aged (A1week and A4week) samples.

During the preparation of the melts the SEs with high (P1670 and S1670) or moderate (S970) HLB values did not become fluid even at 100 °C, in contrast with the lipophilic (S370 and B370) SEs, as expected from the HSM study (Fig. 2c and f). If we wish to prepare a solid dispersion of a drug with a high melting point, this can be a problem if SEs with high HLB values are used, as their melts do not flow.

With respect to the processing, it is important to know whether the changes in structure of these materials are irreversible, or whether the original morphology of the samples is recovered in time. To study this, melts of SEs were prepared and their changes in time were examined in comparison with the initial state. The melting ranges of freshly solidified (F) and aged (A1week or A4week) samples were measured, their normalized enthalpies were compared with the enthalpy of the untreated sample (U), and the crystallinity index (CI) was calculated.

The melting behaviour of samples after melting and solidification differed from that of untreated samples, and it changed in time (Fig. 3 and Table 6). The freshly solidified (F) P1670 started to melt 2 °C earlier than the untreated (U) sample and its melting also finished earlier. In the DSC curve of the solidified sample, a small peak appeared after 1 week (A1week), which was not characteristic of the untreated sample (U). After 1 month (A4week), the sizes of the two peaks had changed: the melting point had drawn nearer to that for the untreated sample, but was lower; on the other hand, the enthalpy determined by the melting range was the same as that for the untreated sample. The melting points of the freshly solidified (F) and aged (A1week and A4week) S1670

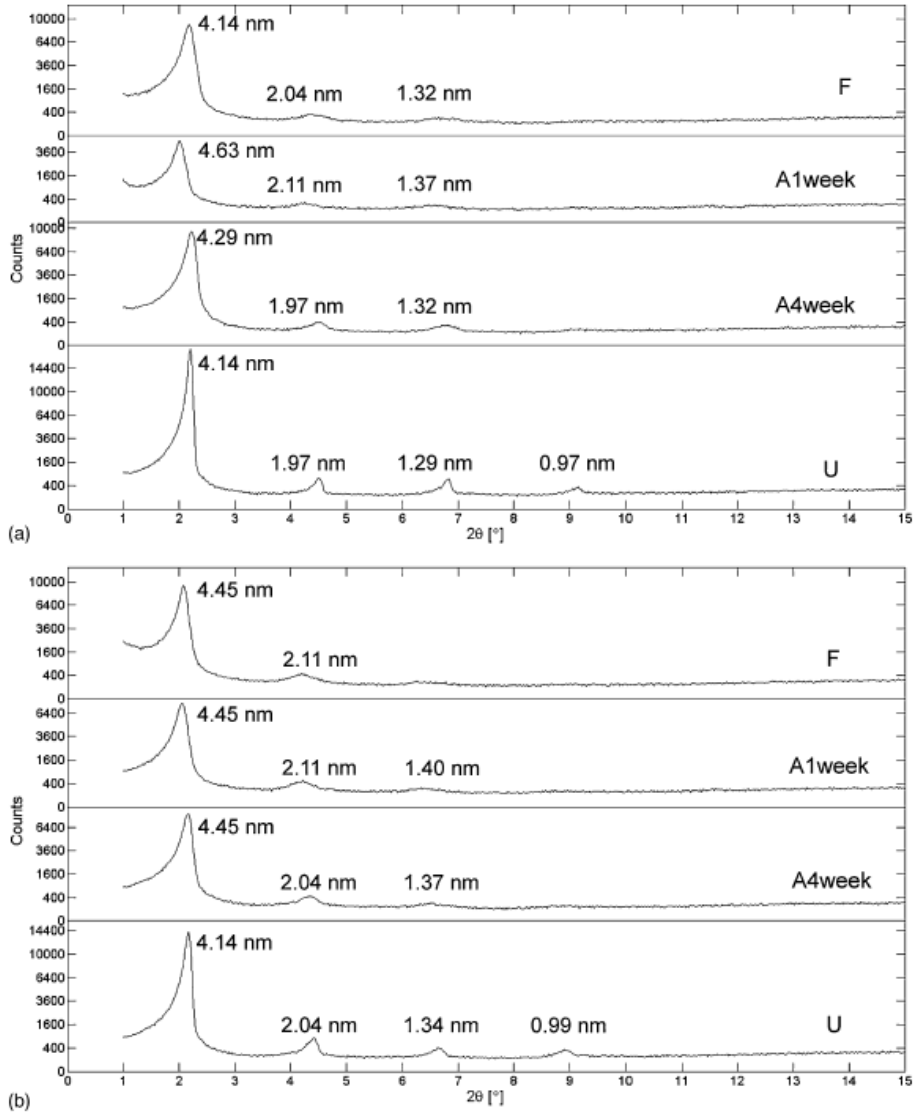

Fig. 4. X-ray patterns of SEs with high HLB values, obtained on untreated (U), freshly solidified (F) and aged (A1week and A4week) samples (a) P1670, (b) S1670.

Table 6
Effects of treatment and storage of SEs

		Melting range (°C)	Enthalpy (J g^{-1})	CI (%)
P1670	F	39–56	−37	55.6
	A1week	37–52	−42.3	63.5
	A4week	35–61	−66.6	100
	U	41–62	−66.6	100
S1670	F	39–60	−35.7	53.5
	A1week	38–61	−49.6	74.4
	A4week	38–62	−64.3	96.4
	U	45–62	−66.7	100
S970	F	33–68	−30	39.6
	A1week	35–68	−52.9	69.9
	A4week	34–68	−63.8	84.3
	U	36–65	−75.7	100
S370	F	59–67	−35.2	63.2
	A1week	38–69	−50.3	90.3
	A4week	39–69	−55.7	100
	U	45–66	−55.7	100
B370	F	55–78	−57.5	84.1
	A1week	56–79	−63.6	93
	A4week	55–78	−66.4	97.1
	U	51–79	−68.4	100

were decreased by 2 °C as compared with that of the untreated sample, but the shape of the curve did not change considerably: it was characterized by one sharp peak. S970 crystallized very slowly after melting and solidification; in contrast with the other SEs, its CI was not 100% restored after 1 month (Table 6). The melted S370 had only one endothermic peak after solidification (F), but after 1 week (A1week) the other peak characteristic of the untreated sample appeared. The melting started 7 °C earlier, and thus the melting range was increased as compared with that for the untreated sample. For B370, one of the two peaks likewise disappeared after melting and solidification (F), and did not appear even after 1 week (A1week) or 1 month (A4week) later. However, the normalized enthalpy nearly reached the enthalpy of the untreated sample (Table 6). It is probable that, similarly to other fatty acid derivatives, SEs transform from one polymorph to another during storage (Hagemann, 1988; Siekmann and Westesen, 1994; Sutananta et al., 1994; Hamdani et al., 2003; Schubert et al., 2005).

After storage for 1 month (A4week), the heats of fusion of aged samples drew near to the enthalpy of the untreated sample, which means that the structures of all the SEs are apparently restored in time. This is in accordance with the finding of Laine et al. (1988), that solidified triglycerides have partially amorphous layered structures, which gradually crystallize during storage. DSC measurements indicated that, even if the total enthalpies of aged samples reached the enthalpy of the untreated sample, the shape of the DSC curves was different from that of the curve of the initial material, i.e. the original structure was not recovered.

Hence, even if the molecular dispersion of a drug in SEs is successful, it is not sure that this advantageous state can be maintained, because the structure of the SE is continuously changing.

To confirm the DSC results, X-ray analysis was performed on untreated (U), freshly solidified (F) and aged (A1week and A4week) samples. The DSC curves of P1670 and S1670 were similar (Fig. 1, curve 1), and the same can be said about their X-ray diffraction patterns (Fig. 4a and b, U). Both SEs have ordered structures: four distinct peaks (P1670: $2\theta = 2.2°$, 4.5°, 6.8° and 9.2°; S1670: $2\theta = 2.2°$, 4.4°, 6.6° and 8.9°) and nearly the same basal spacing (these are given in Figs. 4–6, in nm), characteristic of stearic acid. S970 has a more complex structure: it contains more di- and triester, and also a little tetraester. Moreover, S370 and B370 include pentaester too (Table 2). In consequence of the presence of these components, the characteristic diffrac-

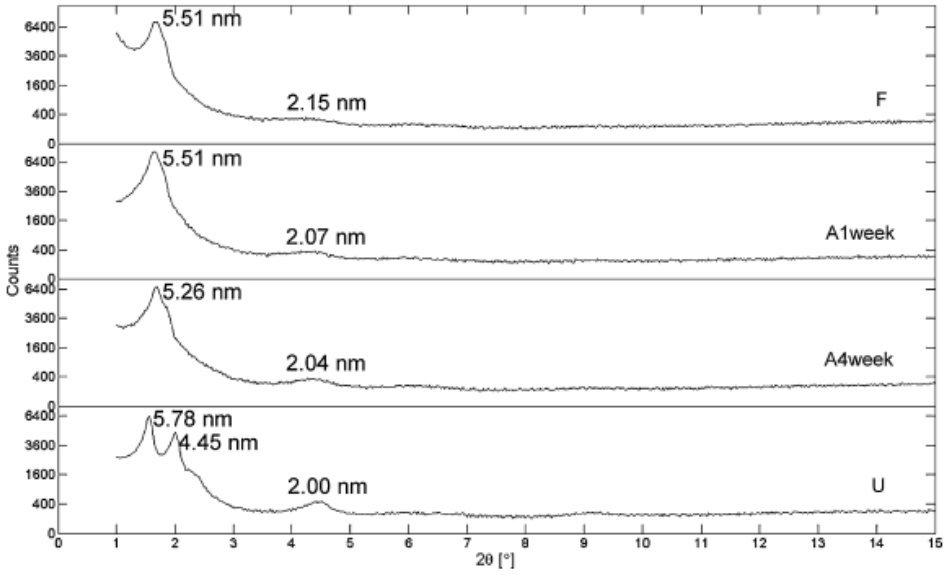

Fig. 5. X-ray patterns of S970, obtained on untreated (U), freshly solidified (F) and aged (A1week and A4week) samples.

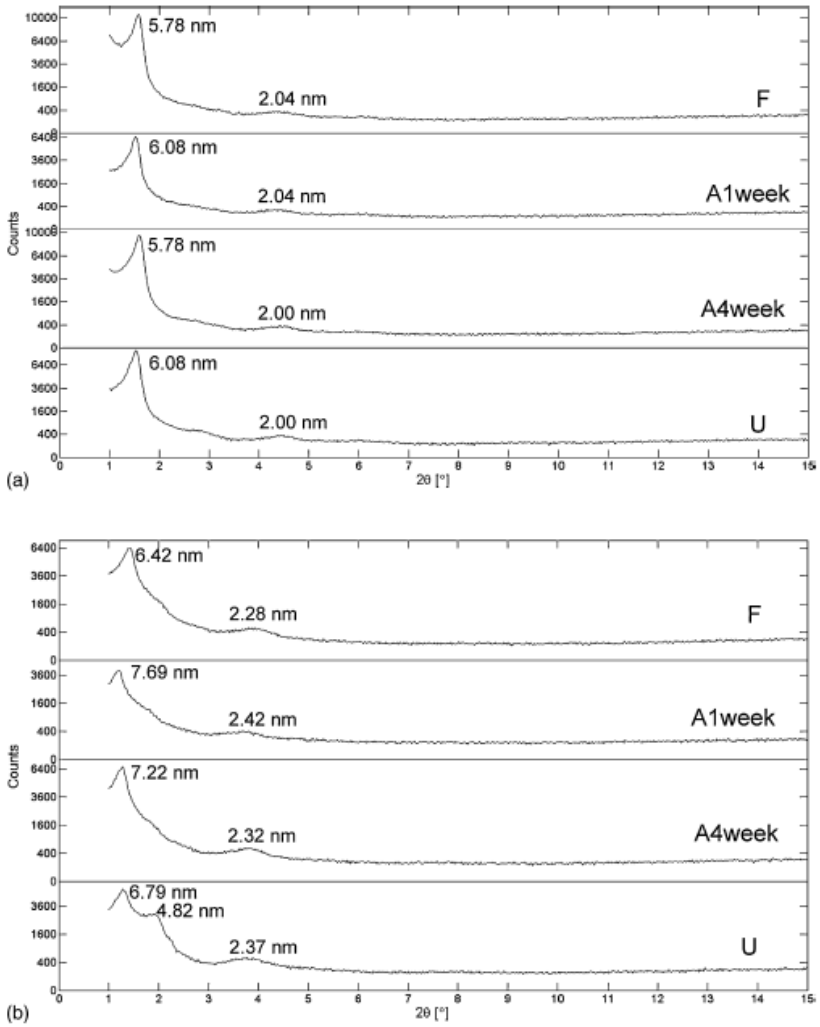

Fig. 6. X-ray patterns of SEs with low HLB values, obtained on untreated (U), freshly solidified (F) and aged (A1week and A4week) samples; (a) S370, (b) B370.

tion peaks disappeared from the X-ray diffractograms and the interlayer spacings increased. The untreated S970 (Fig. 5, U) had three ($2\theta = 1.6°$, 2° and 4.4°), S370 (Fig. 6a, U) had two ($2\theta = 1.5°$ and 4.5°), and B370 (Fig. 6b, U) had three ($2\theta = 1.3°$, 1.9° and 3.9°) characteristic peaks. After melting and solidification, the structures of all the SEs were changed, the basal spacings and counts were modified and in almost all cases one of the characteristic peaks had disappeared, which was probably induced by the polymorphism of the fatty acids. In the diffractograms of melted P1670 and S1670, only three peaks were observed in comparison with the untreated sample, where four peaks were found. The P1670 peak at 9.2°, and the S1670 peak at 8.9° disappeared (Fig. 4a and b). The peak intensities decreased (practically only the first signal could be seen) and the basal spacings increased. Of the three peaks of untreated S970, after melting and solidification the second signal ($2\theta = 2°$) had disappeared and was not recovered even 1 month later (Fig. 5). The X-ray pattern of S370 (Fig. 6a) did not exhibit such a large change in counts as for SEs with high HLB values, but the basal spacings were modified in this case too. The change in degree of crystallinity for B370 was smaller, and the count fluctuation was slight, but the second signal ($2\theta = 1.9°$) disappeared and the morphology of the untreated sample was not restored (Fig. 6b). These X-ray observations are in accordance with the DSC results, since the shapes of the DSC curves changed continuously, the melting range varied after treatment and the original shape of the curve (characteristic of the untreated sample) was not regained even after storage for 1 month.

4. Discussion

The aims of this work were to study the thermal properties of SEs and to evaluate their applicability in hot-melt technology. SEs with various HLB values can be used to influence (increase or decrease) the rate of dissolution of drugs, and hence to change the development of the effect. Due to their low melting points,

they are promising carriers for the melting method. For this reason, we searched for a relation between their thermal behaviour and HLB values.

The results of DSC and HSM revealed that SEs with high (P1670 and S1670) or moderate (S970) HLB values have a glass transition temperature (T_g) instead of a melting point. They soften during heating, whereas SEs with low HLB values (S370 and B370) melt and then quickly recrystallize from their melts. However, the original structure does not return either for SEs with high or moderate, or for SEs with low HLB values: after melting and solidification, their melts continuously change. The DSC scans and X-ray patterns of samples stored for up to 1 month do not display the same picture as that for the untreated samples. There are other excipients which are used in hot melt technology and change during aging. Shimpi et al. (2004) and Sutananta et al. (1995) studied the effect of preparation condition and storage on the rate of drug release from the hydrophobic Gelucire and they reported an increase in drug release caused by phase transformation. Saers et al. (2002) examined the effect of storage on drug dissolution from solid dispersions with PEG 3000 or xylitol and observed that the dissolution rate of drug was unchanged during storage. These results demonstrate that changes in morphology must be considered during research and development. This is especiall important as concerns molecular dispersed materials (amorphous state) in SEs. In consequence of the changes in structure, a drug can partially or completely assume a crystalline form, which can entail a lower dissolution rate or the appearance of an undesirable polymorph form.

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References

Aulton, M.E., 2002. Pharmaceutics, The Science of Dosage form Design, 2nd ed. Churchill Livingstone, Edinburgh, London, New York, Oxford, Philadelphia, St. Louis, Sydney, Toronto, p. 96.

Awad, T., Sato, K., 2002. Acceleration of crystallisation of palm kernel oil in oil-in-water emulsion by hydrophobic emulsifier additives. Colloids Surf. B 25, 45–53.

Coleman, N.J., Craig, D.Q.M., 1996. Modulated temperature differential scanning calorimetry: a novel approach to pharmaceutical thermal analysis. Int. J. Pharm. 135, 13–29.

Craig, D.Q.M., Royall, P.G., 1998. The use of modulated temperature DSC for the study of pharmaceutical systems: potential uses and limitations. Pharm. Res. 15, 1152–1153.

Garti, N., Aserin, A., Faunn, M., 2000. Non-ionic sucrose esters microemulsions for food applications. Part 1. Water solubilization. Colloids Surf. A 164, 27–38.

Hagemann, J.W., 1988. Thermal behaviour and polymorphism of acylglycerides. In: Garti, N., Sato, K. (Eds.), Crystallization and Polymorphism of Fats and Fatty Acids. Marcel Dekker, New York, USA, pp. 29–67.

Hahn, L., Sucker, H., 1989. Solid surfactant solutions of active ingredients in sugar esters. Pharm. Res. 6, 958–960.

Hamdani, J., Moës, A.J., Amighi, K., 2003. Physical and thermal characterisation of Precirol® and Compritol® as lipophilic glycerides used for the preparation of controlled-release matrix pellets. Int. J. Pharm. 260, 47–57.

Husband, F.A., Sarney, D.B., Bamard, M.J., Wilde, P.J., 1998. Comparison of foaming and interfacial properties of pure sucrose monolaurate, dilaurate and commercial preparations. Food Hydrocolloids 12, 237–244.

Kato, A., Arima, K., 1971. Inhibitory effect of sucrose ester of lauric acid on the growth of Escherichia coli. Biochem. Biophys. Res. Commun. 42, 596–601.

Laine, E., Auramo, P., Kahela, P., 1988. On the structural behaviour of triglycerides with time. Int. J. Pharm. 43, 241–247.

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.

Marton, S., Anner, A., Csoka, G., 2005. Increased solubility applying solid-in-solid solutions. Eur. J. Pharm. Sci. 25S1, S155–S157.

Mitsubishi-Kagaku Foods Corporation, 1982. Ryoto Sugar Ester Technical Information. Nonionic surfactant/Sucrose fatty acid ester/Food additive.

Molinier, V., Fenet, B., Fitremann, J., Bouchu, A., Qeneau, Y., 2005. PFGSE-NMR study of the self-diffusion of sucrose fatty acid monoesters in water. J. Colloid Interf. Sci. 286, 360–368.

Ntawukulilyayo, J.D., Bouckaert, S., Remon, J.P., 1993. Enhancement of dissolution rate of nifedipine using sucrose ester coprecipitates. Int. J. Pharm. 93, 209–214.

Otsuka, M., Ofusa, T., Matsuda, Y., 1998. Dissolution improvement of water-insoluble glybuzole by co-grinding and co-melting with surfactants and their physicochemical properties. Colloids Surf. B 10, 217–226.

Saers, S.E., Nyström, C., Aldén, M., 2002. Physicochemical aspects of drug release. XVI. The effect of storage on drug dissolution from solid dispersions and the influence of cooling rate and incorporation of surfactant. Int. J. Pharm. 90, 105–118.

Schubert, M.A., Schicke, B.C., Müller-Goymann, C.C., 2005. Thermal analysis of the crystallisation and melting behaviour of lipid matrices and lipid nanoparticles containing high amounts of lecithin. Int. J. Pharm. 298, 242–254.

Shimpi, S., Chauhan, B., Mahadik, K.R., Paradkar, A., 2004. Preparation and evaluation of diltiazem hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. AAPS PharmSciTech. 5, 43, http://www.pharmscitech.com/journal.

Siekmann, B., Westesen, K., 1994. Thermoanalysis of the recrystallization process of melt-homogenized glyceride nanoparticles. Colloids Surf. B 3, 159–175.

Sutananta, W., Craig, D.Q.M., Newton, J.M., 1994. The effects of ageing on the thermal behaviour and mechanical properties of pharmaceutical glycerides. Int. J. Pharm. 111, 51–62.

Sutananta, W., Craig, D.Q.M., Newton, J.M., 1995. An investigation into the effect of preparation condition and storage on the rate of drug release from pharmaceutical glycerides bases. J. Pharm. Pharmacol. 47, 355–359.

Yu, L., 2000. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv. Drug Deliv. Rev. 48, 27–42.

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Cukorészterek alkalmazhatósága az olvadéktechnológiában*

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Summary

Szűts, A., O. Laczkovich, P. Reisi Nassab, Z. Aigner, P. Szabó–Révész: ***A applicability of sugar esters in hot-melt technology***

One of the most important tasks in pharmaceutical technology is the optimization of drug release. The hot-melt technology is an important method with which to modify the bioavailability. Sugar esters (SEs) have a wide range of HLB values (1-16). Due to their low melting points, they are promising carriers for the melting method.

The aims of the present work were to study the thermal properties (DSC) and the structures (XRPD) of SEs with low, medium or high HLB values, and to evaluate their applicability in the hot-melt technology. Relationships were found between the HLB value, the structure and the thermal behaviour. After melting and solidification, the SEs have partially amorphous layered structures which slowly crystallize in time; the original structure does not return for SEs with high, moderate, or low HLB values. These results demonstrate that changes in morphology must be considered during research and development. During the examination of meloxicam-SE melted products the SEs influenced the drug release, depending on their HLB values. In the cases of ibuprofen-SE melted products, the SEs did not influence the drug release. Here, a change in the drug distribution was the predominant effect, which was accompanied by movement in the SE structure.

Összefoglalás

A gyógyszertechnológiai kutatás fontos feladata a hatóanyagfelszabadulás optimálása. Az olvadéktechnológia a biológiai hatáskifejlődés módosításának egyik fontos módszere. Az olvadéktechnológia ígéretes segédanyagai a cukorészterek, amelyek alacsony olvadáspontú és széles HLB spektrummal (1-16) rendelkező segédanyagok.

Munkánk során kis, közepes és nagy HLB értékű cukorészterek termikus viselkedését (DSC), szerkezetét (porröntgen) és olvadéktechnológiai alkalmazhatóságát vizsgáltuk. Összefüggéseket találtunk a HLB érték, a szerkezet és a termikus viselkedés között. Megállapítottuk, hogy olvasztás és dermesztés után a cukorészterek szerkezete folyamatosan változik, amit nem szabad figyelmen kívül hagyni a kutató és fejlesztő munka során. Meloxicam-cukorészter olvadékok esetében a cukorészterek HLB értéküknek megfelelően módosították a hatóanyagfelszabadulást. Ibuprofen-cukorészter olvadékok vizsgálata alapján viszont megállapítható volt, hogy a cukorészterek HLB értéke nem befolyásolta a hatóanyag kioldódását. Ez utóbbi esetben a cukorészterek szerkezeti változását kísérő hatóanyag-eloszlás megváltozása volt a meghatározó.

Bevezetés

A cukorészterek jól ismert segédanyagok az élelmiszer- és kozmetikai iparban, s alkalmazásuk egyre inkább előtérbe kerül a gyógyszerészetben is. Színtelenek, szagtalanok, nem toxikusak, nem irritálják a szemet és a bőrt, biodegradábilisak. Attól függően, hogy milyen hosszú szénláncú zsírsav észterezi a szacharózt és mekkora az észterezettség foka, különböző HLB értékű (1-16) termékek állíthatók elő [1]. Ez a széles HLB spektrum sokirányú alkalmazást tesz lehetővé. Gyógyszertechnológiai vonatkozásban lehetnek emulgensek [2], kristályosodás-gátlók [3], lubrikánsok [4], nedvesítőszerek és oldódást elősegítő vagy retardizáló segédanyagok [5-11].

Szerkezetük nagyon összetett. Miután a szacharóz 8 hidroxil-csoporttal rendelkezik, 8 zsírsavval észteresíthető, melyek szénláncának hossza is változtatható. Minél nagyobb az észterezettség foka, annál kisebb a HLB érték, vagyis annál lipofilebb a cukorészter (*1. ábra*).

Az 1995-ben bevezetett biofarmáciai osztályozási rendszer (BCS) alapján a hatóanyagok 4 csoport-

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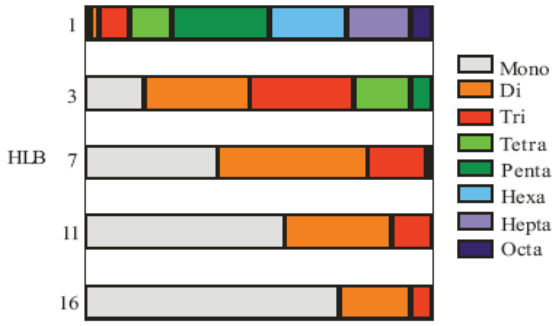


1. ábra: Cukorészterek észterezettségi foka és HLB értéke közötti összefüggés

ba oszthatók oldékonyságuk és permeabilitásuk alapján [12]. Amennyiben gyors hatású készítményt szeretnénk formulálni, a rossz vízoldékonyságú hatóanyagok (II., IV. osztály) oldódási sebességét növelni kell. Ha pedig a hatás megnyújtása a cél, a jó vízoldékonyságú farmakonok (I., III. osztály) oldódási sebességét szükséges csökkenteni. Az előbbi esetben nagy HLB-jű, hidrofil segédanyagok, az utóbbi esetben pedig a kis HLB értékű, lipofil hordozók alkalmazásával érhetünk el eredményt.

Célunk volt megvizsgálni, hogy használhatók-e a cukorészterek farmakonok oldódási sebességének módosítására olvadéktechnológiai módszerek alkalmazásával. Miután az irodalomban ismeretlen volt ezen segédanyagok termikus viselkedése és fizikai-kémiai sajátságai, így ennek felderítésére termoanalitikai méréseket és porröntgen vizsgálatokat végeztünk, majd tanulmányoztuk a cukorészterek HLB értékének befolyását a *meloxicam* és az *ibuprofen* oldódási sebességére.

Kísérleti rész

Anyagok

Vizsgálatainkban nagy (S1670), közepes (S970) és kis (S370) HLB-jű cukorésztereket (*I. táblázat*) alkalmaztunk, amelyek szerkezetét, termikus viselkedését és oldódási sebességet befolyásoló hatását hasonlítottuk össze.

A hatóanyag-felszabadulás vizsgálatához modellanyagként, a nem szteroid gyulladáscsökkentő, rossz vízoldékonyságú *meloxicam*ot és *ibuprofen*t (BCS II. osztály) használtuk. A *meloxicam* olvadáspontja magas (258 °C), míg az *ibuprofen*é 78 °C, tehát közel esik a cukorészterek olvadáspontjához.

Minták előállítása

A hatóanyag nélküli olvadékok előállításánál a cukorésztereket porcelántégelyben, szárítószekrényben megolvasztottuk (100 °C), az olvadékot hűtve dermesztettük, majd porítottuk és szitáltuk (200 μm), s szobahőmérsékleten (20 ± 2°C) tároltuk.

A hatóanyagtartalmú olvadékok esetén a megolvasztott cukorészterben azonos mennyiségű *meloxicam*ot, illetve *ibuprofen*t keveréssel eloszlattunk (1:1 arány), az olvadékot hűtve dermesztettük, porítottuk és szitáltuk (200 μm), s szintén szobahőmérsékleten tároltuk.

Vizsgálati módszerek

Termoanalitikai vizsgálatok

A cukorészterek termikus viselkedését Mettler Toledo 821^e készülékkel végeztük, argon gáz alkalmazásával. 10 mg cukorésztert melegítettünk zárt DSC tégelyben, 25 °C-tól 100 °C-ig, 1 °C/perc fűtési sebességgel.

A cukorészterek üvegesedési hőmérsékletét (Tg) modulált DSC alkalmazásával határoztuk meg. E mérés során 25 °C és 75 °C között, 1 °C/perc fűtési sebességet alkalmazva vizsgáltuk az anyagokat.

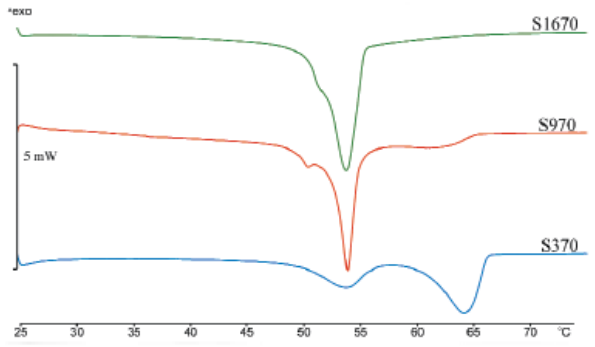
Porröntgen vizsgálatok

A Rtg-diffrakciós méréseket Philips X-ray diffraktometer (PW 1930 generátor, PW 1820 goniométer) készülékkel végeztük. A mérési paraméterek a következők voltak: CuKα sugárzás (λ = 0.15418 nm), 40 kV, 35 mA. A laptávolságok meghatározása a Bragg egyenlet segítségével történt.

I. táblázat

Cukorészterek gyártó által megadott adatai [1]

Cukorészter	Észterező zsírsav	HLB	Op [°C]	Észterezettség foka
S1670	sztearát (C18)	16	56	mono-,di-,triészter
S970	sztearát (C18)	9	56	mono-, di-, tri-, tetraészter
S370	sztearát (C18)	3	58 és 69	mono-, di-, tri-, tetra-, pentaészter



2. ábra: Cukorészterek DSC felvétele (1. fűtés)

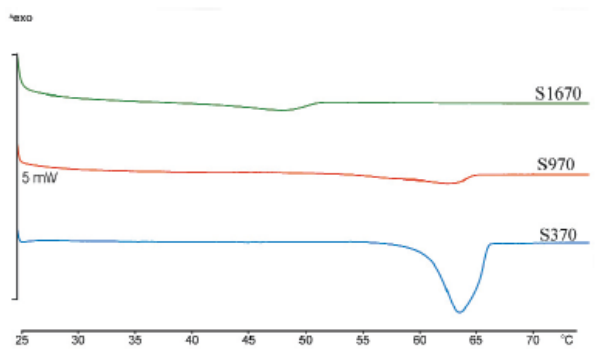
Hatóanyag-kioldódási vizsgálatok

A vizsgálatokat kapszula gyógyszerformából, Pharmatest forgólapátos kioldó készülékkel végeztük (100 rpm, 37 ± 0,5 °C). Mintákat 5, 10, 20, 30, 60, 90 és 120 perc után vettünk. A hatóanyag-tartalom meghatározása spektrofotometriásan (Unicam UV/Vis spektrofotométer) történt [λ = 362 nm (*meloxicam*) és λ = 264 nm (*ibuprofen*)].

A kioldó közeg *meloxicam* esetében 900 ml mesterséges bélnedv (pH = 7,5 ± 0,05), *ibuprofen* esetében pedig 900 ml mesterséges gyomornedv (pH = 1,1 ± 0,05) volt.

Eredmények

A cukorészterek olvadáspont meghatározásához DSC-vizsgálatokat végeztünk. A kapott görbék (*2. ábra*) alapján megállapítható, hogy a kisebb HLB-jű cukorészterek olvadása elhúzódóbb és két endoterm csúcsot is mutat, szemben a nagyobb HLB-jű



3. ábra: Cukorészterek DSC felvétele (2. fűtés)

cukorészterekkel, melyek DSC görbéjén csak egy éles endoterm peak figyelhető meg. Ennek oka az lehet, hogy míg a nagy HLB-jű cukorészterek csak mono-, di- és triészterekből épülnek fel, addig a kis HLB-jű termékek tetra- és pentaésztereket is tartalmaznak (lásd *I. táblázat*).

Megvizsgáltuk az újbóli fűtés hatását is a cukorészterekre. A DSC tégelyben megolvadt cukorésztert (*1. fűtés*) lehűtöttük 25 °C-ra, majd ismételten melegítettük 1 °C/perc sebességgel (*2. fűtés*). Az eredményeket a *3. ábra* szemlélteti.

A görbék lefutása alapján megállapítható, hogy a nagy (S1670) és a közepes (S970) HLB-jű termékek szerkezete az első fűtésnél letört és nem volt lehetősége a hűtéssel egyidőben visszarendeződni, vagyis amorf anyagra jellemző görbéket látunk a második fűtés során. Az S370 két olvadásponttal jellemezhető, de a lehűlés és újbóli fűtés hatására az egyik csúcs eltűnik, s ezzel együtt az olvadási tartomány is lecsökken.

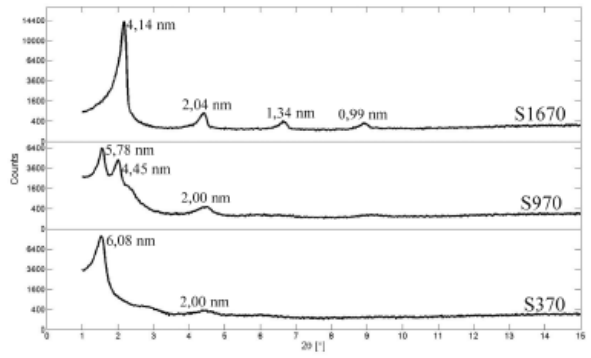
II. táblázat

Olvadáspont és üvegesedési hőmérséklet értékek az első és második fűtés során

Cukorészter	Első fűtés		Második fűtés	
	Op [°C]	Tg [°C]	Op [°C]	Tg [°C]
S1670	54	–	–	51
S970	50 és 54	–	–	53
S370	54 és 64	–	64	–

Modulált DSC segítségével kimutattuk, hogy a nagy (S1670) és a közepes (S970) HLB-jű cukorészterek rendelkeznek üvegesedési hőmérséklettel, és ez egybeesik az első fűtéskor tapasztalt olvadáspontjukkal (*II. táblázat*).

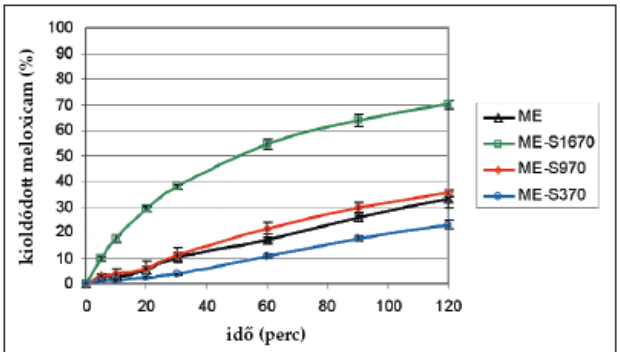
Az eltérő észterezettségi foknak megfelelően Rtg-diffraktogramjuk különböző mértékű rendezettségre utal. A kisebb észterezettségi fokkal rendelkező sztearátszármazék, az S1670 Rtg-diffraktogramján a sztearinsavra jellemző reflexiósor jelenik meg, rendezett szerkezet jellemzi, jól kimérhető laptávolságokkal (4,14 nm, 2,04 nm, 1,34 nm, 0,99 nm, 2θ = 2,2°, 4,4°, 6,6°, 8,9°). A több komponens hatására az S970 Rtg felvételén nem különülnek el olyan karakteresen a reflexiós pontok, kevésbé rendezett szerkezet jellemzi (5,78 nm, 4,45 nm, 2,00 nm, 2θ = 1,6°, 2°, 4,4°). A legösszetettebb S370 esetében megszűnnek a rendezett szerkezetre utaló reflexiós pontok, csak két csúcs jelenik meg (6,08 nm, 2,00 nm, 2θ = 1,5°, 4,5°) (*4. ábra*).



4. ábra: Cukorészterek Rtg-felvétele

A feldolgozás szempontjából fontos tudni, hogy az anyagok szerkezetében bekövetkező változások megmaradnak vagy esetleg idővel visszaalakul a kezdeti állapot. Ennek tanulmányozására cukorészter-olvadékokat készítettünk és egy hónapig vizsgáltuk a változást a kiindulási állapothoz képest. Olvasztás és dermesztés után mindegyik cukorészter szerkezete megváltozik, módosulnak a laptávolságok, a kristályos és amorf fázisok arányát tükröző ütésszámok és majdnem minden esetben megszűnik az anyagra jellemző valamely karakterisztikus csúcs a Rtg-diffraktogramon, amit a bennük lévő zsírsavak polimorfiája okozhat. A DSC görbék alapján megállapítható, hogy az olvasztás majd dermesztés után kapott minták olvadási tulajdonsága is eltér a kiindulási anyagétól [13].

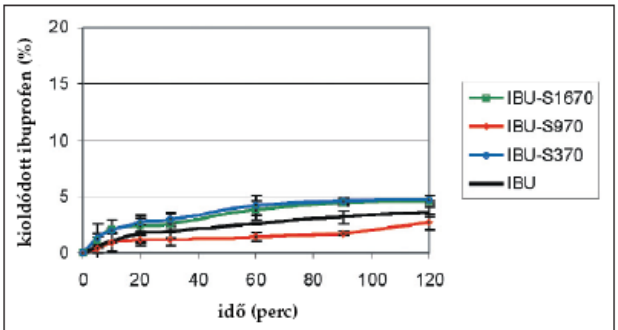
Az eltérő HLB értékű cukorészterek alkalmasak lehetnek a farmakonok oldódási sebességének befolyásolására (növelésére, csökkentésére), s ezzel a hatás kifejlődésének megváltoztatására. Modellanyagként a nem szteroid gyulladáscsökkentő *meloxicam*ot és *ibuprofen*t használva, olvadékokat készítettünk a különböző HLB értékű cukorészterekkel és megvizsgáltuk, hogyan befolyásolják a hatóanyag-felszabadulást. A hatóanyag és a cukorészter aránya az olvadékban 1:1 volt.



5. ábra: Meloxicam és meloxicam-cukorészter olvadékok (1:1) kioldódási görbéi

Vizsgálataink alapján megállapítottuk, hogy a tisztán *meloxicam*ot tartalmazó kapszulából, bélnedvben, 2 óra alatt, mindössze 33%-a szabadul fel a hatóanyagnak. A hidrofil S1670 és *meloxicam* 1:1 arányú olvadék esetén 70%-a, az S970 esetén 35,5%-a oldódott fel a hatóanyagnak. A lipofil S370 lassította a hatóanyag-felszabadulást, alkalmazásakor a *meloxicam* 23%-a oldódott fel mesterséges bélnedvben a vizsgált 2 óra alatt (*5. ábra*).

Vizsgálataink alapján megállapítható, hogy a nagy HLB-jű, hidrofil S1670 jelentősen meggyorsítja, míg a kis HLB-jű, lipofil S370 lassítja a *meloxicam* kioldódását. A közepes HLB értékkel rendelkező S970 csak kis mértékben módosította a hatóanyag-felszabadulást. Ezen eredmények azt mutatják, hogy



6. ábra: Ibuprofen és ibuprofen-cukorészter olvadékok (1:1) kioldódási görbéi

a különböző HLB-jű cukorészterek alkalmas segédanyagok lehetnek az olvadéktechnológiában, hatóanyagok oldódási sebességének módosítására. Az oldódási sebességet a hatóanyag–segédanyag arányának változtatásával is lehet módosítani, a cukorészterek arányának növelésével tovább növelhető vagy csökkenthető a hatóanyag-felszabadulás mértéke [11].

Nem minden hatóanyag esetében érvényesül azonban a cukorészterek oldódási sebesség módosító hatása. Jó példa erre a szintén rossz vízoldékonyságú *ibuprofen*nel előállított termékek vizsgálata, ahol a kis HLB értékkel rendelkező S370 ugyanolyan irányban és mértékben (nagyon kicsi növekedés) változtatta az *ibuprofen* kioldódását, mint a nagy HLB-jű S1670. Ebben az esetben a cukorészterek nem a HLB értéküknek megfelelően módosították a hatóanyag kioldódását, tehát nem érvé-

nyesült a cukorészterek nagy HLB értékéből adódó szolubilizáló hatás. Érvényesült viszont a cukorészterek szerkezeti változásával összefüggő hatóanyag eloszlás megváltozása (*6. ábra*).

Következtetések

Kísérleteink alapján megállapítható, hogy a cukorészterek alkalmazhatók az olvadéktechnológiában, de nem minden hatóanyag esetében. HLB értéküktől függően képesek módosítani egyes hatóanyagok oldódási sebességét (*meloxicam*), s ezáltal a biológiai hatáskifejlődést. A nagy HLB-jű cukorészterek ajánlhatók rossz vízoldékonyságú, a kis HLB-jűek pedig jó vízoldékonysággal rendelkező hatóanyagok oldódási sebességének módosítására. Amennyiben gyorsítani szeretnénk valamely hatóanyag kioldódását, leginkább a nagy monoésztertartalmú, rövid szénláncú zsírsavakkal észterezett cukorészterek ajánlhatók erre a célra. Azonban a cukorészterekben bekövetkező szerkezetváltozást nem szabad figyelmen kívül hagyni a gyógyszerfejlesztés során, mert a szerkezeti változás miatt a hatóanyag részben vagy egészében kristályos formát ölthet (*ibuprofen*), ami együtt járhat annak rosszabb oldódási sebességével vagy egy nem kívánatos polimorf forma megjelenésével.

Köszönetnyilvánítás

Köszönet illeti *dr. Dékány Imre* akadémikus urat, aki lehetővé tette, hogy a Rtg-vizsgálatokat az általa vezetett SZTE Kolloidkémiai Intézetben végezzük el.

A munka az OTKA (T047166) támogatásával készült.

IRODALOM

1. *Mitsubishi- Kagaku Foods Corporation*: Ryoto Sugar Ester Technical Information. Nonionic surfactant/Sucrose fatty acid ester/Food additive (1982)
2. *Garti, N., Aserin, A., Faunn, M.*: Colloids Surf. A. *164*, 27-38 (2000)
3. *Awad, T., Sato, K.*: Colloids Surf. B. *25*, 45-53 (2002)
4. *Shibata, D., Shimada, Y., Yonezawa, Y., Sunada, H., Kasahara, K.*: J. Pharm. Sci. Technol. Japan *62*, 133-145 (2002)
5. *Dredán, J., Csóka, G., Marton, S., Antal, I.*: Acta Pharm. Hung. *3*, 147-151 (2003)
6. *Csóka,G., Marton, S., Klebovich, I.*: Study of solid in solid mixtures of ibuprofen and different sugar fatty acid esters. 1st BBBB Conference on Pharmaceutical Sciences, pp. 119-122 (2005)
7. *Csóka, G., Marton, S., Zelko, R., Otomo, N., Antal, I.*: Eur. J. Pharm. Biopharm. *65*, 233-237 (2007)
8. *Hahn, L., Sucker, H.*: Pharm. Res. *6*, 958-960 (1989)
9. *Ntawukulilyayo, J. D., Bouckaert, S., Remon, J. P*: Int. J. Pharm. *93*, 209-214 (1993)
10. *Otsuka, M., Ofusa, T., Matsuda, Y.*: Colloids Surf. B. *10*, 217-226 (1998)
11. *Marton, S., Anner, A., Csoka, G.*: Increased solubility applying solid-in-solid solutions. 6th Central European Symposium on Pharmaceutical Technology and Biotechnology. Eur. J. Pharm. Sci. *25S1*, S155-S157 (2005)
12. *Pouton, C. W.*: Eur. J. Pharm. Sci. 29, 278-287 (2006)
13. *Szűts, A., Pallagi, E., Regdon, G. jr., Aigner, Z., Szabó-Révész, P.*: Int. J. Pharm. 336, 199-207 (2007)

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III.

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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).

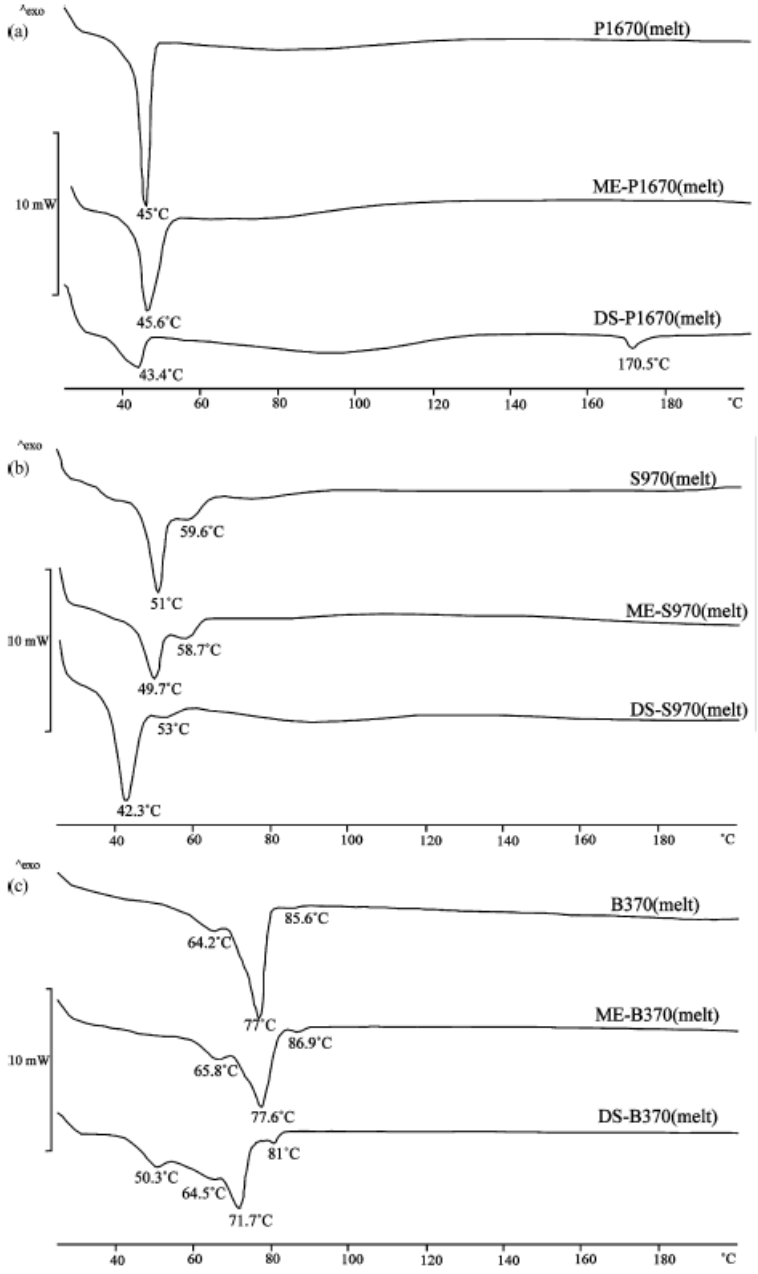

Fig. 1. DSC curves of SE melts and drug–SE melted products. (a) P1670(melt) and drug–P1670(melt), (b) S970(melt) and drug–S970(melt) and (c) B370(melt) and drug–B370(melt).

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

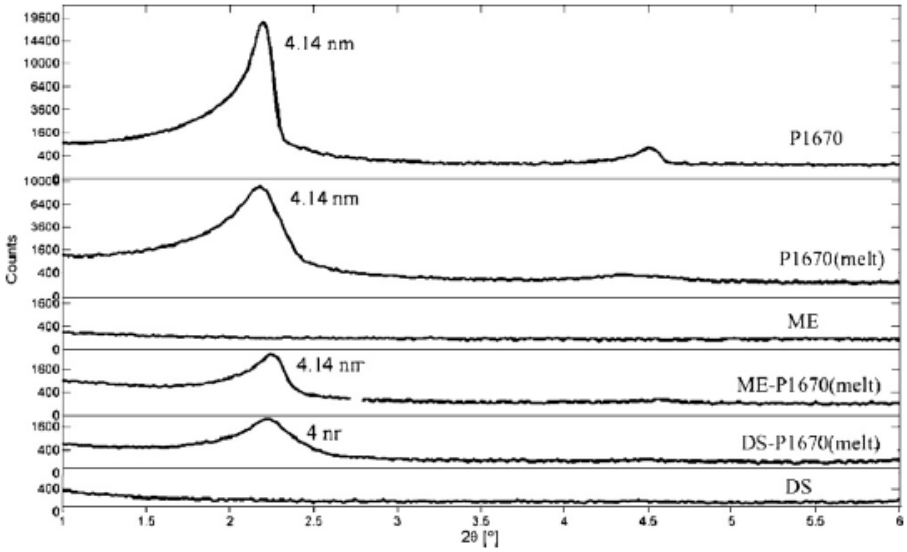

Fig. 2. X-ray diffractograms of drugs, P1670 and drug–P1670 melted products.

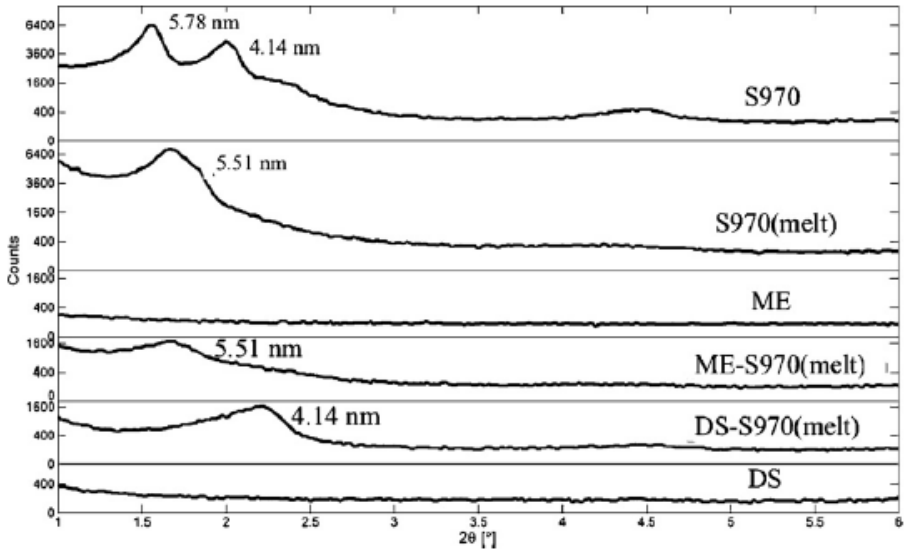

Fig. 3. X-ray diffractograms of drugs, S970 and drug–S970 melted products.

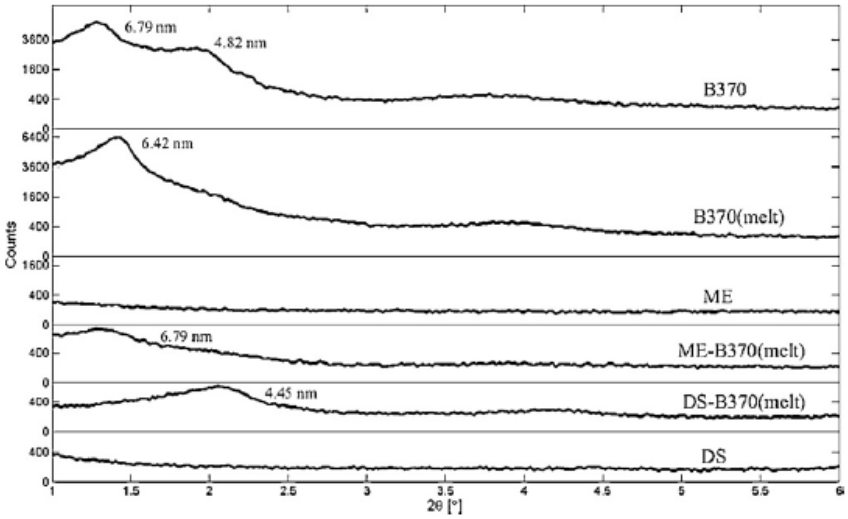

Fig. 4. X-ray diffractograms of drugs, B370 and drug–B370 melted products.

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

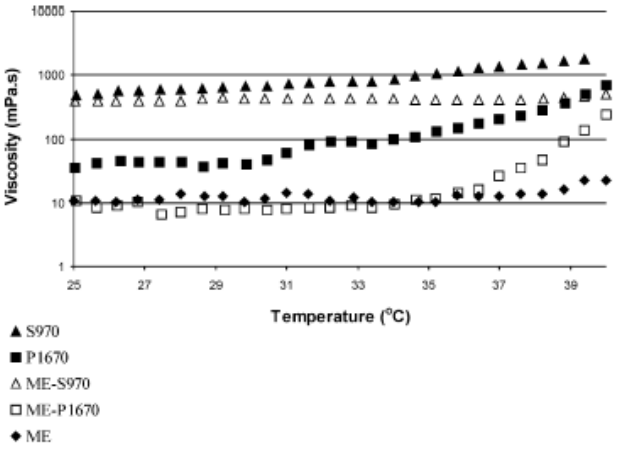

Fig. 5. Viscosity of ME, SEs and ME–SEs in water.

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.

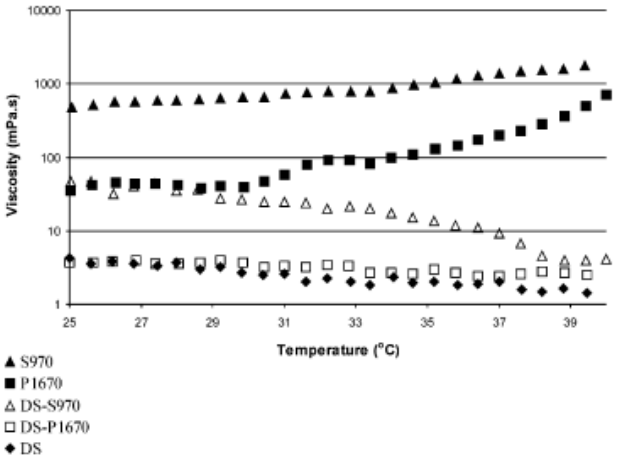

Fig. 6. Viscosity of DS, SEs and DS–SEs in water.

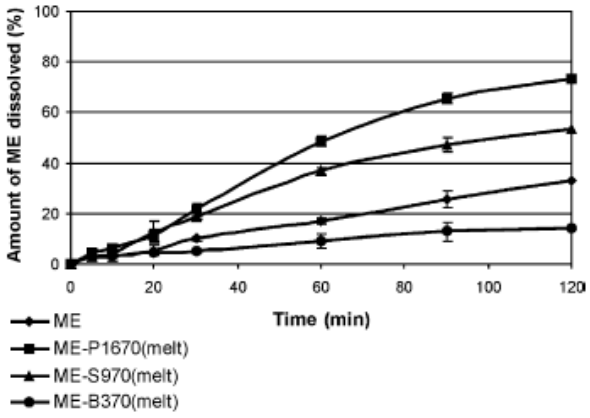

Fig. 7. Dissolution of ME and ME–SE melted products.

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

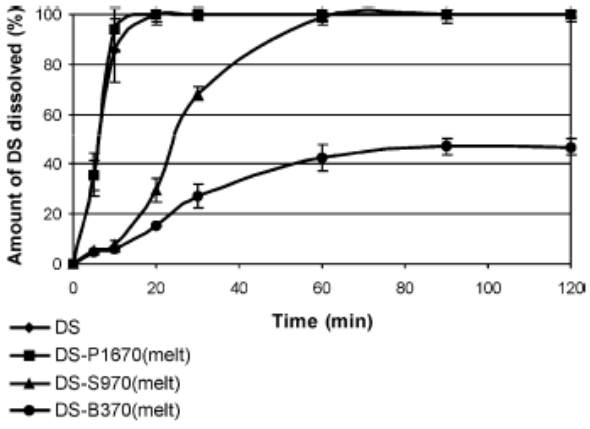

Fig. 8. Dissolution of DS and DS–SE melted products.

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.

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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. Szücs, A. Szabó, I. Erös, 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.

IV.

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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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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

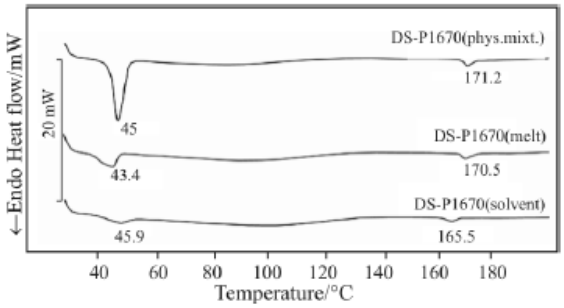

Fig. 1 DSC curves of DS-P1670 products

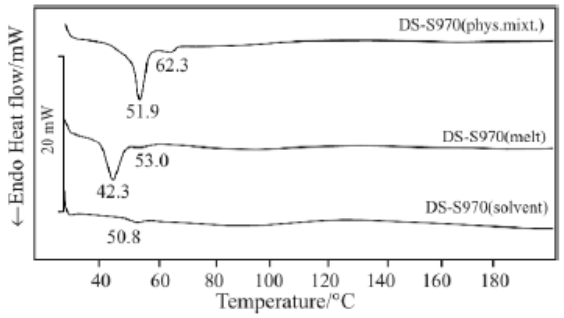

Fig. 2 DSC curves of DS-S970 products

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

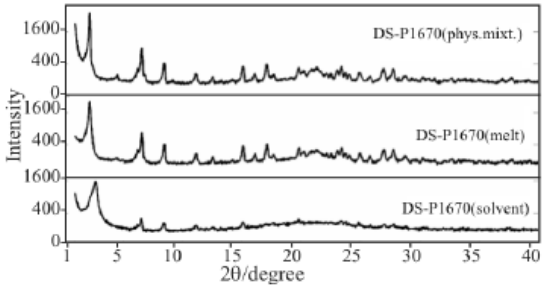

Fig. 3 X-ray diffractograms of DS-P1670 products

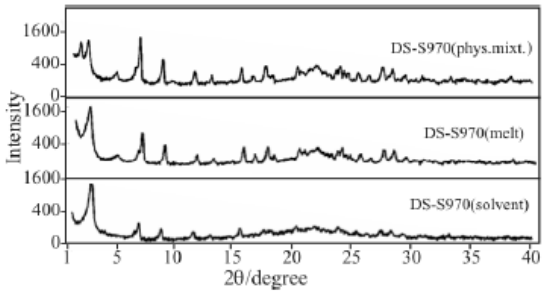

Fig. 4 X-ray diffractograms of DS-S970 products

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.

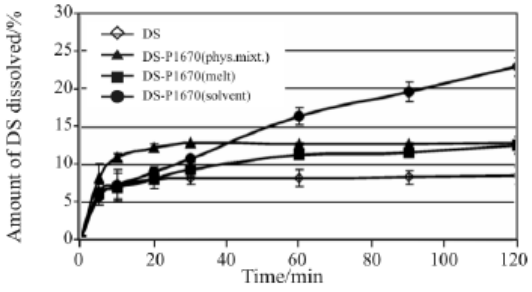

Fig. 5 Dissolution of DS and DS-P1670 products

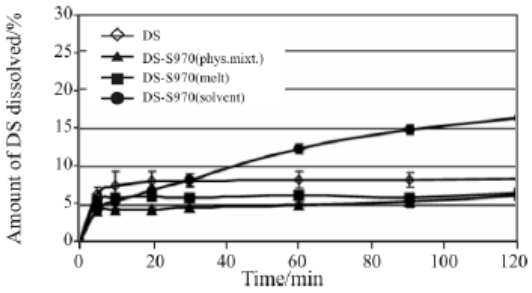

Fig. 6 Dissolution of DS and DS-S970 products

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.

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References

1 Mitsubishi-Kagaku Foods Corporation, Ryoto Sugar Ester Technical Information (1982).
2 F. A. Husband, D. B. Sarney, M. J. Barnard and P. J. Wilde, Food Hydrocoll., 12 (1998) 237.
3 N. Garti, A. Aserin and M. Faunn, Colloids Surf. A., 164 (2000) 27.
4 T. Awad and K. Sato, Colloids Surf. B., 25 (2002) 45.
5 D. Shibata, Y. Shimada, Y. Yonezawa, H. Sunada and K. Kasahara, J. Pharm. Sci. Technol., 62 (2002) 133.
6 L. Hahn and H. Sucker, Pharm. Res., 6 (1989) 958.
7 J. D. Ntawukulilyayo, S. Bouckaert and J. P. Remon, Int. J. Pharm., 93 (1993) 209.
8 J. D. Ntawukulilyayo, C. Demuynck and J. P. Remon, Int. J. Pharm., 121 (1995) 205.
9 M. Otsuka, T. Ofusa and Y. Matsuda, Colloids Surf. B., 10 (1998) 217.

10 S. Marton, A. Anner and G. Csoka, Eur. J. Pharm. Sci., 25 (Suppl. 1) (2005) S155.
11 F. Seiler, J. S. Burton and J. B. Dressman, BPC Science Abstracts, J. Pharm. Pharmacol., 57 (Suppl.) (2005) S28.
12 A. Szűts, E. Pallagi, G. Regdon jr., Z. Aigner and P. Szabó-Révész, Int. J. Pharm., 336 (2007) 199.
13 C. Reitz and P. Kleinebudde, J. Therm. Anal. Cal., 89 (2007) 669.
14 M. Önal and Y. Sankaya, J. Therm. Anal. Cal., 90 (2007) 167.
15 S. C. Mojumdar, M. Sain, R. C. Prasad, L. Sun and J. E. S. Venart, J. Therm. Anal. Cal., 90 (2007) 653.

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