University of Szeged
Faculty of Pharmacy
Department of Pharmaceutical Technology
Head: Prof. Dr. habil. Piroska Szabó-Révész DSc

Study of the applicability of sucrose esters in hot-melt technology

Summary of PhD thesis

Angéla Szűts

Supervisor:
Prof. Dr. habil. Piroska Szabó-Révész DSc

Szeged
2009

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.

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). 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 (Mp) and their surfactant properties, so it is useful to evaluate their structural and thermal properties.

2. Aims

SEs are commonly used in food industry, and recently many research work is made to examine their applicability in the pharmaceutics, for example as emulsifiers, solubilizers, or lubricants. The most common pharmaceutical application of SEs is for the modification of bioavailability, often with the hot-melt method. There are only a few information about their structures and thermal behaviour, hence, the aim of my PhD work was to investigate these properties in order to ascertain the applicability of SEs 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. Materials and methods

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. They 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 SEs containing from 1 to 8 fatty acid moieties (Fig. 1).

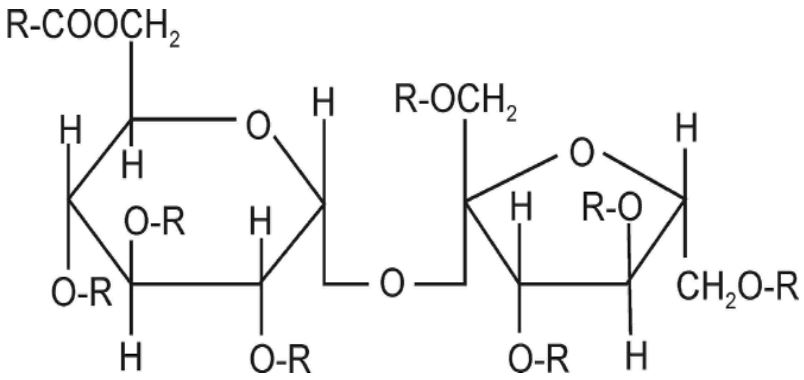

Fig. 1 Chemical structure of sucrose ester

The longer the fatty acid chains in the SEs and the higher the degree of esterification, the lower the HLB value (Table 1). They have many favourable properties, *e.g*. they are tasteless, odourless, non-toxic, non-irritant to the skin, and biodegradable.

Table 1 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

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.

Sample preparation

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

- Untreated samples: SEs without any special treatment (commercial).
- Freshly solidified samples: 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:

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, with heating from 25 °C to 100 °C, and then cooled back to room temperature. After the preparations, the samples were in all cases pulverized in a mortar and sieved to 200 μm.

Hot-stage microscopy

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.

Thermogravimetry

TG studies were performed with a Derivatograph-C apparatus (MOM, Hungary). The samples were heated from 25 to 100 °C at a heating rate of 5 °C min^{-1}.

Differential scanning calorimetry

DSC studies were performed with a DSC 821^e (Mettler-Toledo GmbH, Switzerland). Samples of 10 mg were heated in a sealed aluminium pan. 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 (*CI*) for the freshly solidified sample and the aged sample were calculated from the heats of fusion. For analysis of the drug-containing SEs, samples of 10 mg were heated from 25 ^oC to 300 °C at a heating rate of 10 °C min^{-1}.

Modulated temperature differential scanning calorimetry

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.

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 (λ = 0.15418 nm), 40 kV, 35 mA. The basal spacing (d_L) was calculated from the diffraction peaks by using the Bragg equation.

Rheological analysis

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 (5% SE in water, or 5% SE - 5% drug in enteric juice) 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.

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), and the method of Wu. The liquids used for our contact angle measurement 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}). The polarity percentage was calculated from the γ^p and γ values: (γ^p / γ)*100.

***In vitro* drug release study**

For the dissolution tests, the drug-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 = 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).

4. Results and discussion

A. Characterization of the sucrose esters

Thermal and structural characterization

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.

The DSC measurements revealed that 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. So, this led to an amorphous state. According the MTDSC studies, these SEs undergo glass transitions (*T*g), which coincide with the melting points of the materials (Table 2).

Table 2 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	—

The HSM measurements showed that during heating, hydrophilic SEs merely became soft, but did not flow, while lipophilic SEs melted. 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. 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.

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 2).

The X-ray measurements showed, 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, which are characteristic of the fatty acids contained in the SEs. It can be concluded, that SEs are semicrystalline materials, with crystalline and amorphous regions.

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. After melting and solidification, the structures of the SEs continuously change, probably because polymorphs are undergoing transformation. These results demonstrate that changes in morphology must be considered during research and development. This is especially important as concerns molecularly dispersed materials 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.

Swelling characterization

The different SEs have various swelling properties: the stearate (C18)-containing S1670 and S970 displayed high viscosity at room temperature, which did not change appreciably on increase of the temperature, while 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 be influence the drug release to a great extent.

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

Thermal and structural characterization

The DSC and X-ray results revealed that the drug brought about considerable structural changes in the SEs, to different extents for the various SEs. Comparison of the changes caused by the two drugs demonstrated that, 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 (Table 3).

Table 3 X-ray data on SEs, SE melts and drug-SE melted products

Materials	2θ [°]	Basal spacing [nm]	Counts
P1670	2.2	4.14	10692
P1670(melt)	2.2	4.14	9101
ME-P1670(melt)	2.2	4.14	2852
DS-P1670(melt)	2.2	4	2190
S970	1.6 and 2.1	5.78 and 4.14	4597 and 3648
S970(melt)	1.6	5.51	6939
ME-S970(melt)	1.6	5.51	1739
DS-S970(melt)	2.2	4.14	1640
B370	1.3 and 1,9	6.79 and 4.82	5184 and 2841
B370(melt)	1.4	6.42	6352
ME-B370(melt)	1.3	6.79	1303
DS-B370(melt)	2	4.45	955

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). SEs influenced the wetting behaviour of the drugs according to their HLB values (Table 4), from which is predictable how SEs can change the dissolution of the drugs.

Table 4 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

In vitro drug release

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, 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. (Fig. 2).

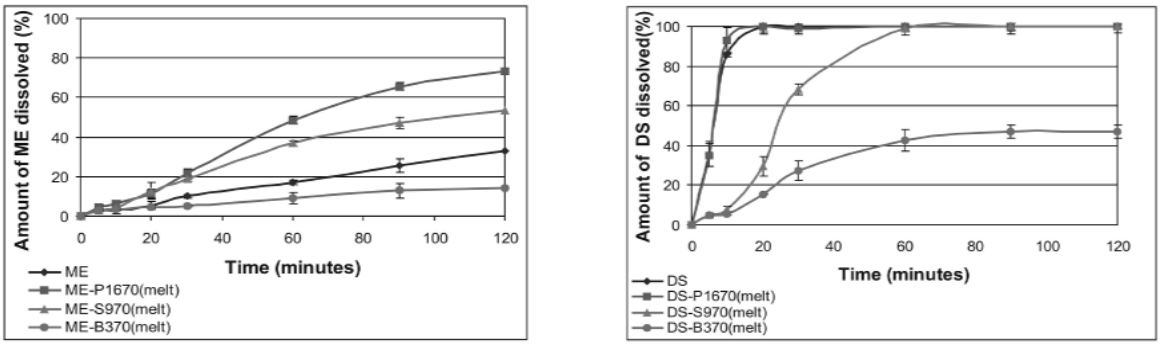

Fig. 2 Dissolution of drugs and drug-SE melted products

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 (Fig. 2).

Study the effects of the drugs on the swelling of 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. 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. 3). In this case, the drug has no an effect on the gelling of P1670.

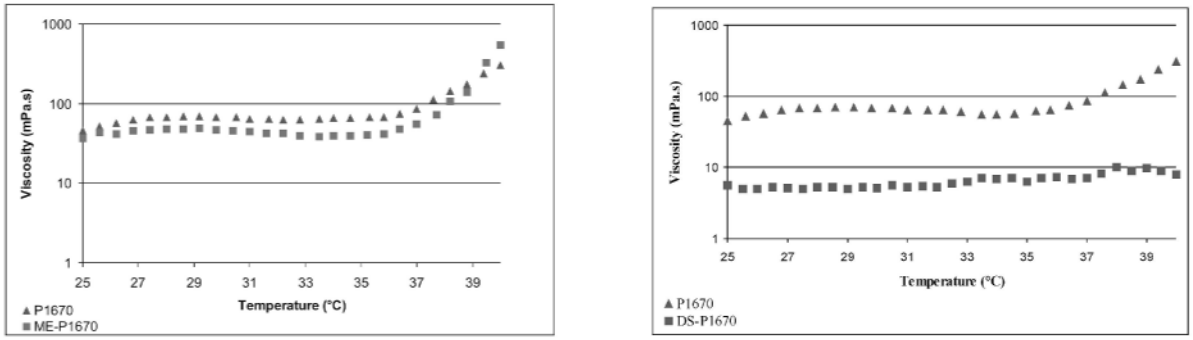

Fig. 3 Viscosity of P1670 and drug-P1670 in enteric juice

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. 3).

The HSM studies showed also that DS has an effect on the swelling of P1670 and destroys the gel structure of the SE. This interaction can be influenced to a large extent by the dissolution of DS.

According these results, 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. 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 experimental results

- 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 dispersion 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 4 summarizes the main results of this thesis, and emphasizes the common and the different properties of the hydrophilic and lipophilic SEs.

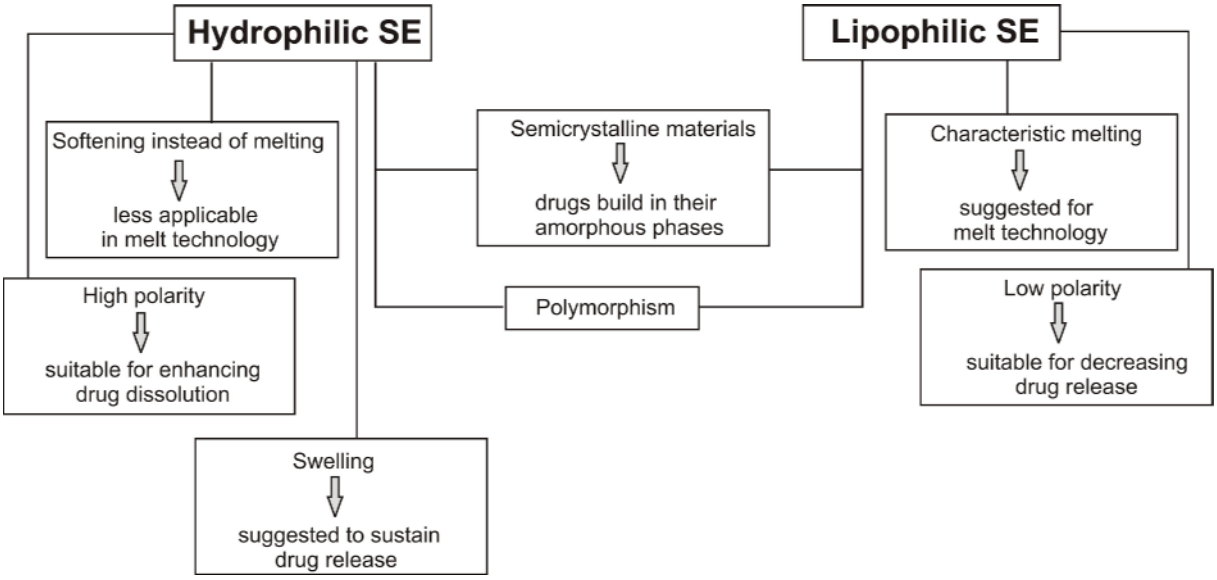

Fig. 4 Common and different behaviour of the SEs

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.

ANNEX

Publications related to the PhD thesis

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

IF: 2.212

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

IF: 2.761

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

IF: 1.483

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