Study of thermo-sensitive gel-forming properties of sucrose stearates.

Angéla Szűts[a], Mária Budai-Szűcs[a], István Erős[a], Rita Ambrus [a], Naoya Otomo[b], Piroska Szabó-Révész[a,*]

[a]Department of Pharmaceutical Technology, University of Szeged, H-6720, Szeged, Eötvös u. 6, Hungary
[b]Mitsubishi-Kagaku Foods Corporation, Sumitomo Fudosan Shibakoen Tower, 2-11-1 Shibakouen, Minato-Ku, Tokyo, Japan

Received: 9 April 2010; Accepted: 1 July 2010

ABSTRACT

Sucrose esters (SEs) are biodegradable surfactants that can be manufactured in various hydrophilic-lipophilic balances (HLB) through the use of different fatty acids. They are used in food and in industries, such as the cosmetics, detergents and pharmaceutical industries. In aqueous media they can form gels, which can affect various industrial processes. The pharmaceutical industry is currently showing an increasing preference for biomaterials and environmentally sensitive gels, and in particular thermo-sensitive gels. By virtue of the non-toxic, biodegradable and gel-forming properties of SEs, they are promising materials with which to form thermo-sensitive delivery systems.

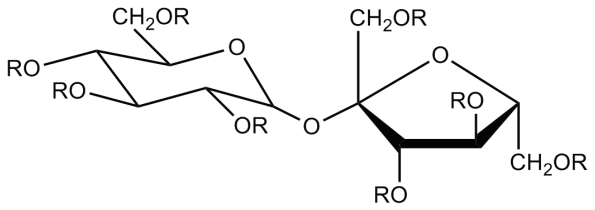
In this study, the gelling properties of some sucrose stearates were investigated by rheological measurements, and compared with each other. The effects of the release of gel-forming SEs on a model drug (paracetamol) were evaluated through *in vitro* drug release studies. The rheological results indicated that the sucrose stearates with lower HLB values have higher gel strengths than those of the more hydrophilic sucrose stearates. The gelling of the SEs is concentration- and temperature-dependent, and this gelling behaviour is responsible for the great effect of sucrose stearates on drug release.

KEY WORDS: Sucrose stearates, thermo-sensitive, gelling properties, rheological measurements, drug release

INTRODUCTION

Sucrose esters (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 shown in Figure 1. By changing the nature or number of the fatty acid groups, a wide range of hydrophilic-lipophilic balances (HLB) values can be obtained. Described as very mild with regard to their dermatological properties and approved as food additives in many countries, they are raw materials for personal care products, cosmetic applications and emulsifiers for food. There has recently been great interest in their use in the pharmaceutical industry (1, 2). They have attracted considerable interest as

* Corresponding author: Department of Pharmaceutical Technology, University of Szeged, H-6720 Szeged, Eötvös u.6, Hungary, Tel: (36-62)-545572, Fax: (36-62)-545571
E-mail: revesz@pharm.u-szeged.hu



R = fatty acid ester moiety or H

Figure 1 Chemical structures of sucrose esters.

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 (3-18).

The most common pharmaceutical application of SEs is for the modification of bioavailability. When SEs are used as dissolution-modifying agents, it is important to consider that the hydrophilic SEs form gels in aqueous media. We have shown previously that sucrose stearate S970 and sucrose palmitate P1670 formed gels in aqueous media and affected drug release (17). Accordingly we investigated the gel-forming behaviour of these two SEs, and demonstrated the applicability of gel-forming SEs to sustain drug release (18). Our results showed that sucrose stearate S970 had a stronger gel structure than that of sucrose palmitate P1670, and it had a greater effect on drug release. There are other types of sucrose stearates, with different degrees of hydrophilicity on the market, and there has recently been great interest in using them as releasing agents in controlled drug delivery systems. For example, Seiler *et al.* (14) examined the possibility of preparing controlled-release matrix formulations of theophylline by using sucrose stearate S1670 with hot-melt extrusion. Abd-Elbary *et al.* (15) developed controlled-release proniosome-derived niosomes, using sucrose stearates S1170 and S1670 as non-ionic surfactants for the nebulizable delivery of cromolyn sodium. Ullrich *et al.* (16) recently investigated the rheological behaviour of aqueous sucrose stearate S1170F dispersions, and concluded that SEs are applicable as alternative new matrices in lipid-based drug-delivery systems.

In recent decades, the use of environmentally sensitive gels, and in particular thermo-sensitive gels, has led to important improvements in drug delivery. Rheological studies of temperature-dependent gelling characteristics have already been described for different types of polymers, such as gelatine, agar-agar, poloxamers (19-23), starch (24) and curdlan (25-27). The most common thermo-sensitive polymers are the poloxamers, the gelation of which depends strongly on temperature and the concentrations of the polymer and other additives, such as other polymers and salts (28-32). However, as the modern pharmaceutical industry is exhibiting an increasing preference for biomaterials and green technology, it is reasonable to seek new types of thermo-sensitive non-toxic biomacromolecules. Because of the non-toxic, biodegradable and gel-forming properties of SEs, they are promising materials with which to form thermo-sensitive delivery systems.

Since sucrose stearate was found to possess a stronger gel structure and greater effect on drug release in our previous study (17, 18), it was decided to evaluate hydrophilic sucrose stearates of different HLB values. The aim of this work was to evaluate the gelling properties of different hydrophilic sucrose stearates (S970, S1170, S1570 and S1670), and to compare their gel strengths, and the temperature and concentration dependences of their gelling. The effects of the different sucrose stearates on drug release were also investigated.

MATERIALS AND METHODS

Materials

Four sucrose stearates with different HLB values were investigated. The hydrophilic SEs

studied, shown in Table 1, were kindly provided by Syntapharm GmbH (Germany). Paracetamol (PAR) was supplied by Hungaropharma Ltd. (Hungary).

Table 1 Data on the studied sucrose stearates (33)

	HLB	Monoester content (%)
S970	9	50
S1170	11	55
S1570	15	70
S1670	16	75

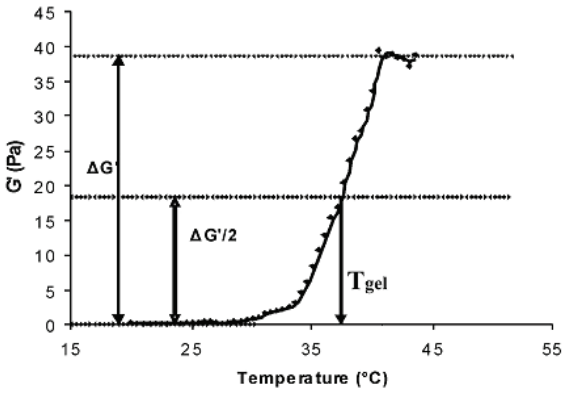


Figure 2 Determination of gelling temperatures of SE/water dispersions.

Rheological measurements

The rheological properties were studied using a Physica MCR101 rheometer (Anton Paar, Austria). The measuring system was of plate and plate type (diameter 50 mm, gap 0.1 mm).

Dynamic frequency sweeps

Dynamic frequency sweep tests were carried out at 37 °C, at 1.0 Pa, within the linear viscoelastic region. From these measurements, the storage modulus (*G'*) and loss modulus (*G"*) were determined for frequencies between 0.1 and 100 Hz.

Gelling characteristics

The gelling characteristics were measured at a constant frequency of 1.0 Hz at a constant strain of 1.5% (this value of the strain was within the linear viscoelastic range of the SE gels). The heating rate was 2 °C/min. The gelling temperature (T_{gel}) of an SE was defined as the temperature where the storage modulus was half-way between *G'* for the SE dispersion and *G'* for the SE gel shown in Figure 2 (28).

The SEs were dispersed with water in a mortar, at room temperature and after the preparation the SE/water dispersions were immediately measured. Each measurement was carried out on a freshly-made sample and was repeated three times.

Dissolution studies

For the dissolution tests, PAR-SE physical mixtures were filled into hard gelatine capsules (size 0). The capsules contained 50 mg of paracetamol 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 artificial gastric juice with a pH of 1.2 (±0.05) at 37 °C (±0.5 °C) was used. The drug contents of the samples were measured spectrophotometrically (λ = 244 nm) (Unicam UV/Vis spectrophotometer). The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Rheological measurements

Dynamic frequency sweeps

The rheological properties of SE/water dispersions were investigated with oscillation tests at body temperature (37°C). With the dynamic frequency (*f*) sweep tests, the dependence of the elastic and viscous moduli (also known as storage and loss moduli) on *f*

were determined. In rheological terms, for a gel the storage (*G'*) and the loss (*G"*) modulus are independent of *f* and *G'>G"*. Gels can usually be classified into one or other of two categories (24, 34): weak gels where the moduli (*G'* and *G"*) depend slightly on *f* and strong gels where the moduli are relatively independent of *f*. Under increased deformation or continuous flow conditions, strong gels rupture into small gel regions rather than flow, while the weak gel network breaks down into smaller flow units, which may flow homogeneously (24, 34).

The dependences of the moduli on *f* were determined at different concentrations of the sucrose stearates. Figure 3 shows the log *G'* versus log *f* plots of S1570/water dispersions; it can be seen that higher SE concentrations resulted in higher moduli and lower dependences on *f*. Consequently at higher concentration, the gel structure is stronger.

Via *f* sweep tests, the gel strengths of the various sucrose stearates were also compared. For 5% sucrose stearate dispersions, at all values of *f*, the sequence of both the *G'* and the *G"* values was: S970>S1170>S1570>S1670 shown in Figures 4 and 5.

Comparison of the slopes of the log *G'* versus log *f*, and the log *G"* versus log *f* plots demonstrated that the higher the HLB value, the higher the slope, which means that the sucrose stearates with lower HLB values have greater gel strengths (lower slopes of the plots) shown in Figure 6.

On the basis of the *f* sweeps, it can be expected that the sucrose stearates with lower HLB values can influence drug release more markedly, while the more hydrophilic SEs (*e.g.* S1670) sustain drug release to a lesser extent.

SEs are often used also to increase drug release (11-13), but the gel-forming properties demand care during formulation. As higher SE concentrations can cause stronger gel structures (Figure 3), SEs can be used only in low amounts to improve drug release.

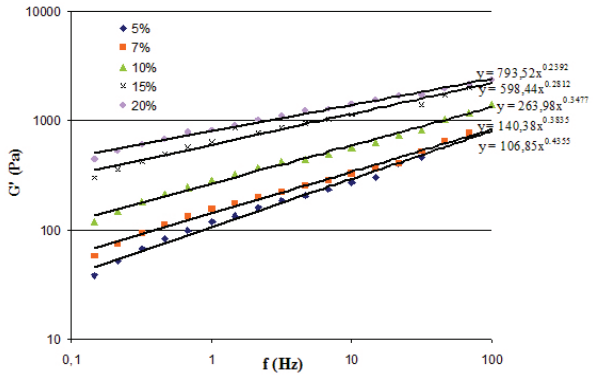


Figure 3 Frequency dependencies of S1570/water dispersions.

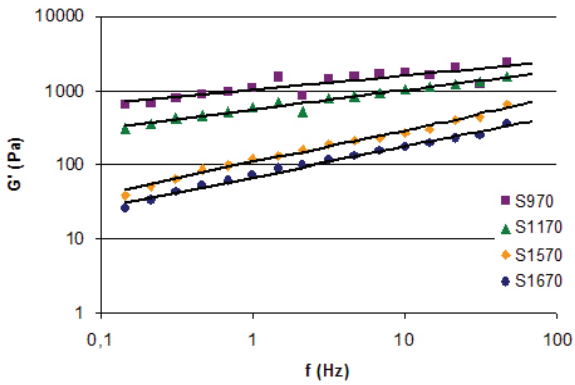


Figure 4 Frequency dependences of 5% SE/water dispersions (log G' vs log f).

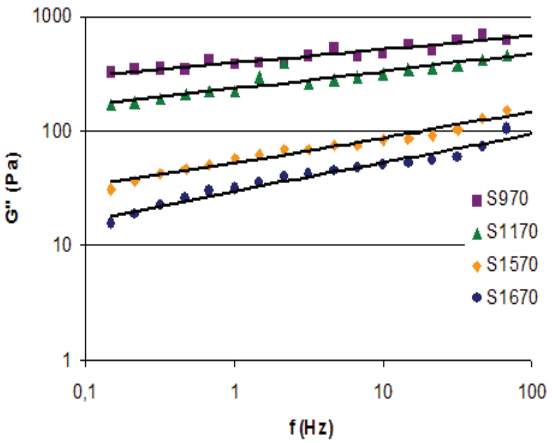


Figure 5 Frequency dependences of 5% SE/water dispersions (log G" vs log f).

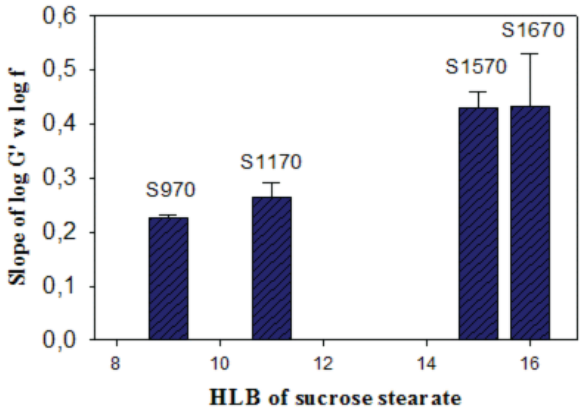


Figure 6 Relationship between HLB and gel strengths of sucrose stearates.

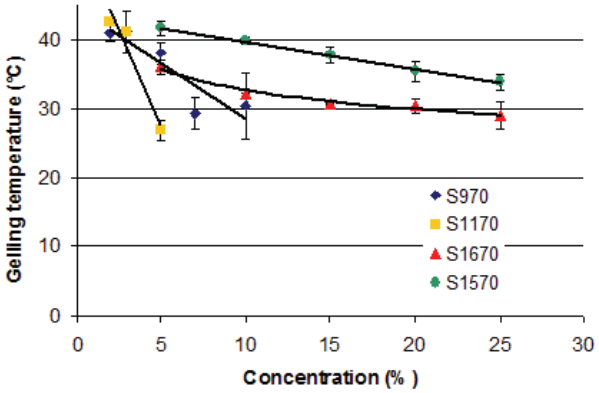


Figure 7 Concentration dependencies of gelling temperatures of SE/water dispersions.

Gelling characteristics

We have previously shown (17, 18) that the gelling of the SEs depends on temperature. Thus, the gelling temperatures of the various sucrose stearates at different concentrations were determined and compared in this study.

The basis of the changes in their viscoelastic properties is micelle formation, which can involve spherical or worm-like micelles, with a hexagonal or lamellar liquid crystal structure. It has been established that increased temperature progressively breaks down the H-bonds between the SEs and the water, which favours the growing of the micelles (35). This increased micellar size or the transition from spherical to worm-like micelles can improve the viscosity of the systems. Besides temperature, other factors can also influence the rheological behaviour of SEs, e.g., the SE concentration, the presence of co-surfactants or oil, and the mode of preparation (36, 37, 16).

The concentration dependencies of the gelling temperatures in this study showed that, the higher the concentration, the lower the gelling temperature, and throughout the whole concentration range, S1570 has the highest gelling temperature shown in Figure 7.

The slopes reveal that the gelling of the SEs with lower HLB values (S970 and S1170) is more concentration-dependent, and they already start to gel at low concentration (5-10%) below 30 °C, which can not be left out of consideration during formulation.

No relationship was found between the gelling temperatures and the HLB values of sucrose stearates. Figure 8 shows the gelling temperatures of 5% SE dispersions, from which it can be seen that S1170 start to gel at the lowest temperature (26.9 °C), while S1570 has the highest gelling temperature (41.63 °C).

Dissolution studies

Paracetamol (PAR) is rapidly released from the capsules containing PAR alone (no SEs) in gastric juice: most of the drug was dissolved

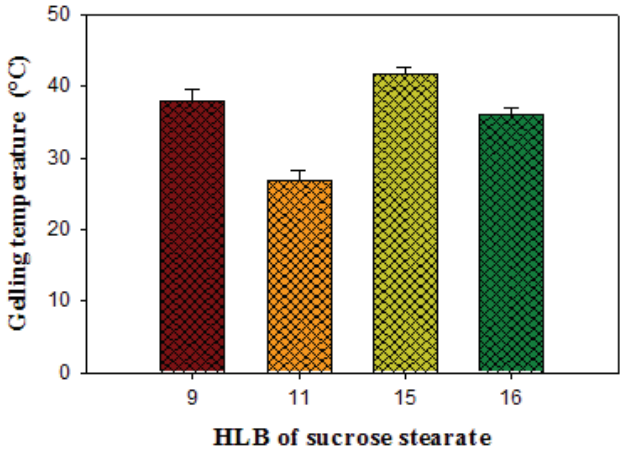


Figure 8 Gelling temperatures of 5% sucrose stearate/water dispersions.

after 10 minutes. The results of the *in vitro* dissolution studies showed that all the examined sucrose stearates sustained the release of paracetamol when used in a 1:1 ratio shown in Figure 9. The release profile of PAR can be further modified as required by using different proportions of these SEs.

The sequence of drug release from the SE-containing products was PAR-S970 < PAR-S1170 < PAR-S1570 < PAR-S1670, which is also the sequence of polarity and the gel strength of the SEs. As S970 has the lowest HLB value and the strongest gel structure, the drug release was the slowest from the S970-containing capsules (16% after 2 hours).

In the cases of the S1170 and S1570-containing products, the amounts of paracetamol dissolved were the same (83%) after 2 hours, but the rate of dissolution was higher for PAR-S1570. Among the studied sucrose stearates, the fastest drug release was achieved with S1670, which has the higher HLB value (16) and the lowest gel strength.

The results of the *in vitro* dissolution study indicate that, besides the SEs with lower HLB values, the most hydrophilic sucrose stearate (S1670) can also be used for sustained drug release. As the gel-forming behaviour is temperature-dependent, sucrose stearates are promising alternative excipients with which to achieve thermo-sensitive drug delivery.

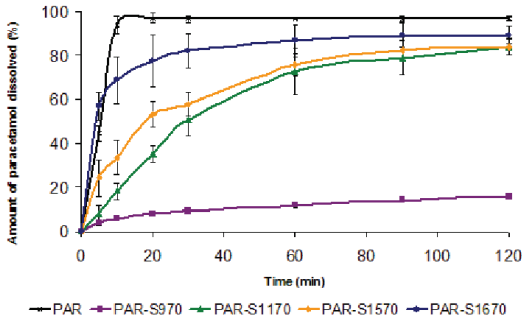


Figure 9 Dissolution profiles of paracetamol and paracetamol-SE samples.

CONCLUSION

The results of this study demonstrate that SEs are appropriate excipients to provide sustained drug release. The gelling temperatures of SE dispersions depend on the concentration and the type of the SE. Sucrose stearates with lower HLB values have greater gel strengths, more concentration-dependent gelling, and greater potential for controlling the release rate of drugs as compared to those with higher HLB values. Because of their temperature-dependent viscoelastic properties, the SEs are appropriate for the formulation of thermo-sensitive controlled drug delivery systems.

ACKNOWLEDGEMENTS

This work was supported by TÁMOP-Hungary research project: *Development of teranostics in cardiovascular, metabolic, and inflammatory diseases* (TÁMOP-4.2.2-08/1-2008-0013).

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