

EVALUATION OF THE INTERACTION BETWEEN A SUCROSE ESTER AND DICLOFENAC SODIUM

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Abstract

The objective of this study was to investigate the effect of diclofenac sodium on the gelling behavior of sucrose ester P1670. The swelling process of P1670 was determined by means of rheological and microscopic measurements. The rheological studies demonstrated that diclofenac sodium has a significant influence on the swelling of P1670. The results observed by hot-stage microscopy revealed the interaction between the two materials. In the case of diclofenac sodium-containing products, P1670 can not be used to modify the drug release, because this drug destroys the gel structure of P1670.

Rezumat

Scopul acestui studiu a fost investigarea efectului diclofenacului sodic asupra comportamentului de gel a esterului de sucroză, notat P1670. Procesul de gelificare a P1670 a fost evaluat prin măsurători reologice și microscopice. Studiile reologice au demonstrat că diclofenacul sodic are o influență semnificativă asupra acestui proces. Termomicroscopia a relevat interacțiunea dintre cele două substanțe. În cazul produselor cu diclofenac sodic, P1670 nu poate fi utilizat ca agent de modificare a cedării substanței active, deoarece aceasta distruge structura de gel a P1670.

Keywords: sucrose ester, interaction, swelling

Introduction

Sucrose esters (SEs) are tasteless, odourless and non-toxic materials, and are therefore good emulsifiers for alimentary products. They are also suitable for use in medicines and cosmetics, because they are non-irritant to the eyes and skin. They are non-ionic surface-active agents consisting of sucrose as hydrophilic group and fatty acids as lipophilic groups [1]. Through variation of the type or number of the fatty acid groups, a wide range of hydrophilic-lipophilic balance (HLB) values (1-16) can be obtained. Depending on their HLB values, they are available with a broad range of properties: o/w and w/o emulsifying properties, solubilizing properties [2] or bioavailability-modifying properties [3-6]. They have antibacterial effects [7], and can also be used as lubricants [8].

The most common pharmaceutical application of SEs is the modification of bioavailability. The SEs are of great potential as alternative matrices in drug delivery systems [9]. Seiler et al. [6] prepared controlled-release matrix formulations of theophylline with S1670 by hot melt extrusion. Ntawukulilyayo et al. [5] similarly used SEs (S1570 and P1570) as tablet matrix-forming agents in the cases of ibuprofen and theophylline.

We previously investigated the structures of the SEs [10] and the effects of drugs on their structures [11-12]. Dissolution studies were also performed and the effects of the SEs on drug release for meloxicam and diclofenac sodium (DS) were evaluated. It was found that, hydrophilic SEs display swelling behavior in aqueous medium and it has an effect on the meloxicam release. DS is a water-soluble drug, which is often used in various hydrophilic swellable matrices [13]. In our study, the hydrophilic, swellable P1670 does not have any significant effect on the dissolution of DS in artificial enteric juice [11]. We presumed that the reason for this may be the difference in pH (pH of aqueous DS solution: 7.8; pH of aqueous P1670 solution: 5.5) or by the salting-out effect of DS.

In the present study, DS-P1670 samples were prepared by different methods and the effect of P1670 on drug release was studied by *in vitro* drug release measurements. The interaction between DS and P1670 has been investigated by means of rheological and hot-stage microscopic (HSM) measurements. These examinations allow an evaluation of the behavior of P1670 alone and together with DS in artificial enteric juice.

Materials and methods

P1670 was kindly provided by Syntapharm GmbH (Germany), and DS was from Sigma Co. (Hungary).

Sample preparation

For the measurements applied in this study, equal amounts of DS and P1670 were mixed in a mortar. For the *in vitro* drug release studies, 0.1 g of this physical mixture were filled by hand in size No. 0 hard gelatine capsules, or 0.2 g were compressed into tablets at a fixed compression force of 5 kN or 10 kN using a hydraulic press (Specac, Inc., USA).

In the case of rheological and hot-stage microscopy (HSM) measurements, the equal amounts of DS and P1670 were dispersed in artificial enteric juice (pH 7.5).

In vitro drug release study

In vitro drug release studies were performed on DS-P1670 tablets or hard gelatine capsules. The release of the model drug 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 content of the samples was measured spectrophotometrically ($\lambda = 276$ nm) (Unicam UV/Vis spectrophotometer).

Rheological measurements

For these measurements, a PaarPhysica MCR101 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 mm). During the measurements, the temperature of the samples was modulated from 25 °C to 40 °C at a heating rate of 1 °C min⁻¹ while the resulting viscosity changes were recorded. The tested liquid contained 5% P1670 and 5% DS in artificial enteric juice (pH 7.5).

Hot-stage microscopy (HSM)

These observations 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. Data were imported into a computer and captured images were analysed using the Leica Q500MC program.

Results and discussion

It was observed in our previous study [10], that P1670 has a gel forming behavior in aqueous media, but in the case of DS containing melted products, this SE had no effect on the drug release [11]. In the present work, DS-P1670 containing products (tablets with various compression force and capsules) were prepared and the effect of P1670 on the drug release was observed.

Fig. 1 shows the results of the *in vitro* dissolution tests. It can be seen that DS was dissolved in the intestinal juice within a few minutes, and the effect of the hydrophilic P1670 was not manifested. The dissolution of the drug was rapid both from the pressed products (DS-P1670 5kN and DS-P1670 10kN) and from the capsule dosage form. In spite of the gel-forming property of P1670, the dissolution of DS could not be delayed with this SE (Fig. 1). These results show that independent to the preparation way, the interaction between DS and P1670 can occur.

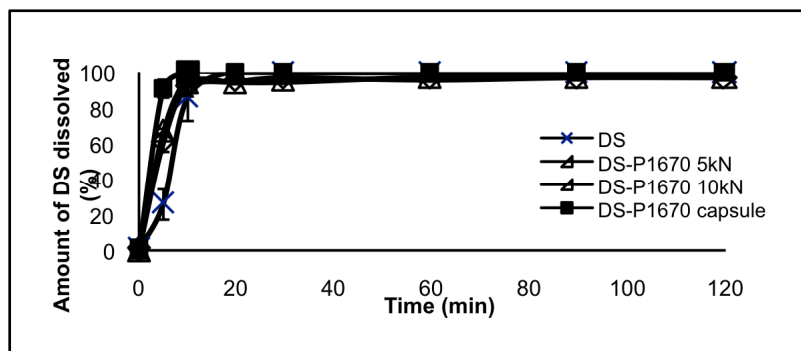


Figure 1

Dissolution of DS and DS-P1670 products

Our previous rheological study showed that the viscosity of P1670 in water increased with the increase of temperature, and this SE gelled over 35 °C [11]. As the dissolution tests were performed in artificial enteric juice, and the pH and the salts contained in the media can have an effect on the gelling of SE, these rheological measurements were also performed in enteric juice (Fig. 2).

It can be clearly seen that P1670 starts to swell above 35 °C in enteric juice, so its gelling can result in a slow drug release at the body temperature. 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 does not change appreciably when increasing the temperature (Fig. 2). These results show that the viscosity decrease of P1670 is caused unambiguously by the presence of DS and not by the pH or the salts contained by the enteric juice.

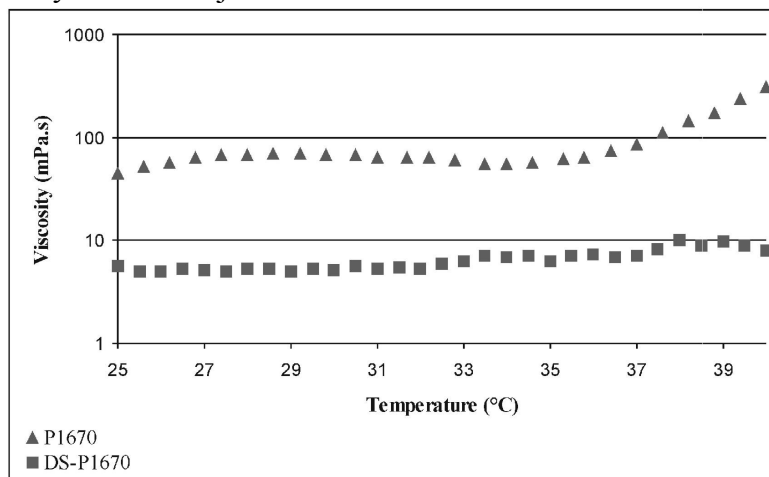


Figure 2

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. 3 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 better expressed at the body temperature.

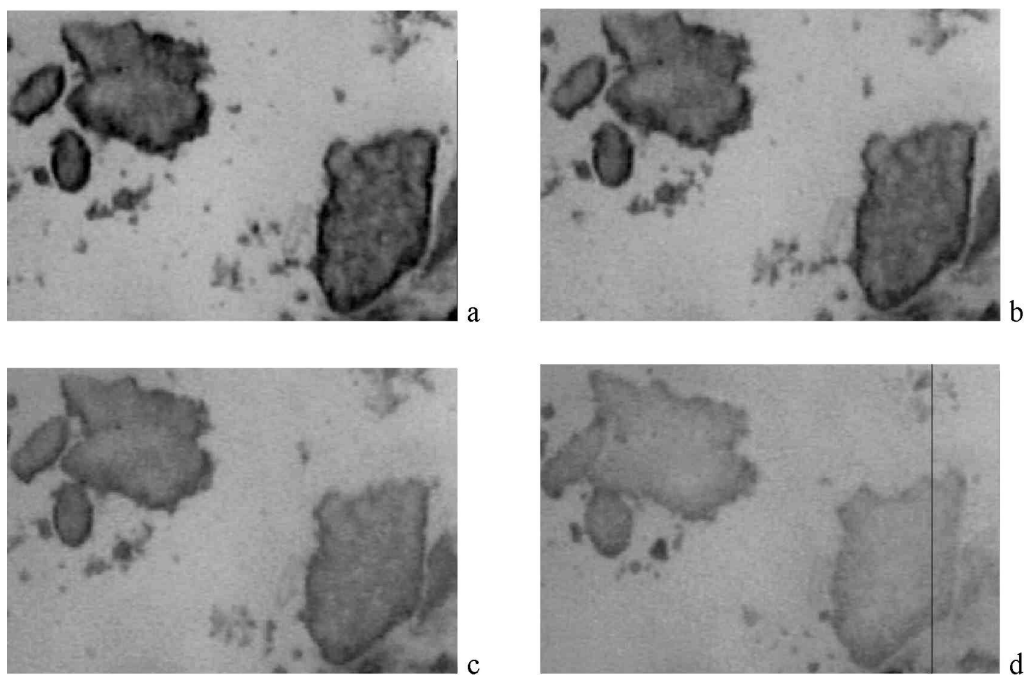


Figure 3

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 a lower temperature, but its structure is destroyed because of the salting-out effect of DS (Fig. 4a,b). It can be seen that, in this case, P1670 is dissolved in the enteric juice at the body temperature (Fig. 4c). This explains why the viscosity of P1670 in enteric juice is constant in the presence of DS (Fig. 2) and why P1670 has no effect on the dissolution of DS (Fig. 1).

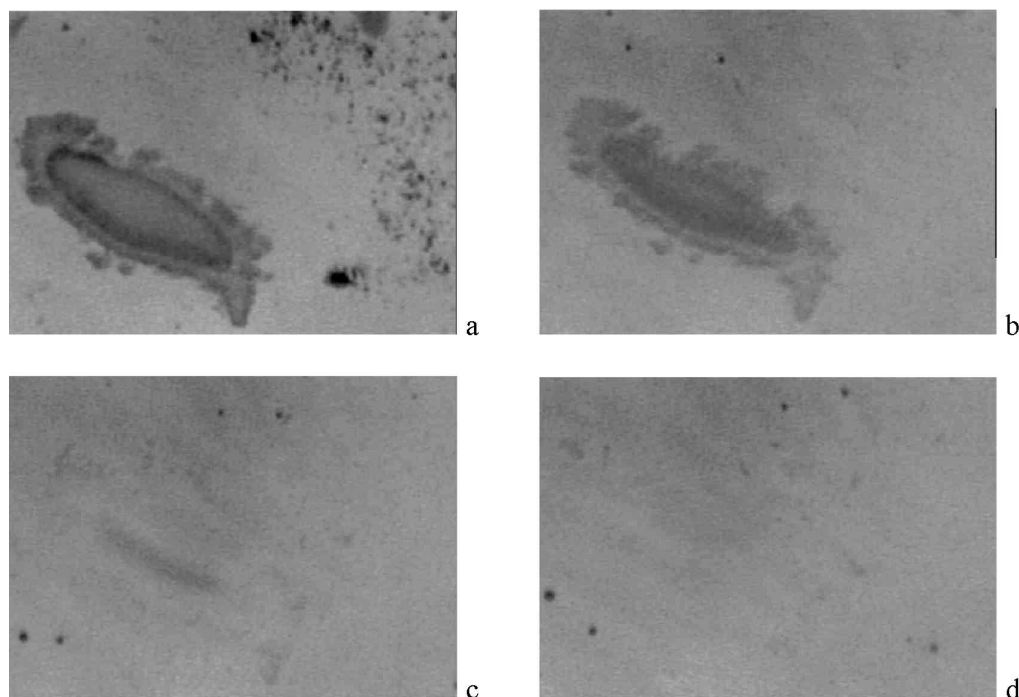


Figure 4

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)

Conclusions

The *in vitro* drug release study showed that independent to the preparation way, the interaction between DS and P1670 can occur. The results of the rheology and HSM studies reveal why the swelling behavior of P1670 is not manifested strongly in the presence of DS, and why SEs can not be used in order to modify the drug release in the case of DS-containing products. DS has a salting-out effect and destroys the gel structure of P1670, after which the SE does not exert any effect on DS release. These results draw attention to the need to consider the properties of the drug during formulation, because they can influence the gel structure of the SEs.

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