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Research paper

Application of sucrose fatty acid esters in transdermal therapeutic systems

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Abstract

Transdermal therapeutic systems (TTSs) were studied applying different sucrose fatty acid esters (SEs) as drug delivery agents. Matrix and membrane controlled TTSs were prepared and compared. Membrane was made from a methacrylic polymer (Eudragit® NE) of pH independent permeability which can achieve diffusion controlled drug liberation. Model drug was a water soluble β-blocker, metoprolol, which has short biological half-life, so applying it in a TTS, the duration of its action could be prolonged. Sucrose fatty acid esters of different fatty acid chain lengths and consequently different hydrophilic–lipophilic balance (HLB) values were studied considering their effect on the metoprolol release from TTSs. Different mathematical models were applied for the evaluation of the release process. The results of the in vitro studies indicated that SEs of shorter fatty acid chain length and higher HLB value increased the amount of released drug about 10 times. SEs could be promising agents in transdermal therapeutic systems to control the drug release and cutaneous absorption.

Keywords: Sucrose fatty acid esters; Transdermal delivery; Metoprolol; Drug release; Mathematical models

1. Introduction

Sucrose fatty acid esters (SEs) are non-ionic type surfactants having a sugar substituent, sucrose, as the polar head group and fatty acids as apolar groups. Sucrose has eight free hydroxyl groups, which allow the formation of esters from monoesters to octaesters with different fatty acids (stearic, lauric, myristic, oleil acid). Sucrose fatty acid esters contain different fatty acids (stearic (S)-, palmitic (P)-, myristic (M)-, lauric (L) acid) in different ratios, so they have HLB value from 1 to 16 HLB values. Table 1 summarizes the HLB values and type of fatty acid of the examined SEs. Because of this variety, sucrose fatty acid esters can be applied in many areas of pharmaceutical technology in the case of liquid, plastic, semisolid and solid dosage forms as emulsifiers, solubilising agents, lubricants, penetrating enhancers, and pore forming agents [1–3]. They can be applied in cosmetical preparations [4] and as food additives, as well [5]. The type of fatty acid and the degree of esterification determine the HLB value and the melting point of these materials.

In recent years sucrose fatty acid esters (SEs) have been in focus because of their wide range of HLB values and because they damage the barrier less than other surfactants. Although ionic surfactants are more potent enhancers than non-ionic agents, but ionic enhancers can damage the barrier and skin in a reversible manner. Spans and Tweens are well-known non-ionic sorbitane alkanoates and ethoxylated sorbitane alkanoates, they have a narrow range of HLB values [6,7]. According to previous results reported on patch tests of different surfactants concerning

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Table 1
Type of fatty acid and HLB value of different sucrose fatty acid esters

Type of sugar ester	C number of fatty acid chain	Type of fatty acid	HLB
S-370	18	Stearic	3
S-970	18	Stearic	9
S-1670	18	Stearic	16
P-1570	16	Palmitic	15
M-1695	14	Myristic	16
L-1695	12	Lauric	16

dermatological changes, derivatives of sucrose fatty esters cause less dermatological damage (dermatitis) [8].

In the present study, matrix and membrane controlled TTSs with different SEs were prepared. In the case of matrix-type TTSs, drug and SE were incorporated in a water-insoluble but permeable Eudragit® NE polymer matrix [9–11], without controlling membrane. As this polymer cannot be dissolved in the skin wrap; liberation of drug is controlled by diffusion through the matrix. In the case of membrane controlled TTSs, drug and SE were incorporated in a hydroxypropylmethyl cellulose matrix, and this matrix was covered by the previously applied Eudragit® NE membrane, as the liberation rate controlling part of the system.

Most hydrophilic drugs cannot penetrate into the skin (epidermis) from transdermal drug delivery systems without an enhancer, because they have low permeability coefficients, but they show very high permeation with an enhancer or cosolvent. In our work, the model drug was metoprolol tartrate, because of its short biological half-life, which can be sustained using in a TTS. SEs were the liberation and absorption enhancers in TTSs. The primary aim of the present study was to compare the enhancing effect of different SEs on in vitro drug liberation and simulated cutaneous absorption from different types of TTSs.

2. Materials and methods

Ryoto® sugar-esters: Sucrose stearate (S-370, S-970, S-1670), sucrose oleate (O-1570), sucrose palmitate (P-1670), sucrose laurate (L-1695), and sucrose myristate (M-1695) were provided by Mitsubishi Chemical Co. (Japan). Methacrylate ester copolymer (Eudragit® NE 30D) was supplied by Röhm Pharma GmbH (Germany). Metoprolol tartrate USP XXII was purchased from Welding GmbH and Co. (Hamburg, Germany), Hydroxypropylmethyl cellulose (Metolose® 90SH 4000) was provided by Mitsubishi Chemical Co. (Japan).

Shimadzu UV-160A spectrophotometer (Shimadzu Corporation Spectroscopic Instruments, Kyoto, Japan) was used for the analytical determination of the active ingredient. Orion 420A type pH-meter (Orion Research Europa, Switzerland) was used to adjust the required pH value of the media. SM 16753 Sartorius Resorptionsmodell (Sartorius Membranfilter GmbH, Göttingen, Germany) apparatus with suitable accessories was used in liberation and dissolution tests. During the preparation of patch systems an RH 3 T heated magnetic stirrer (Prüfgerät-Werk Medingen GmbH Dresden, Germany) was used. Dissolution studies were performed with a PTW2 dissolution test apparatus (Pharmatest Apparatebau GmbH, Hamburg, Germany).

2.1. Preparation of TTSs

2.1.1. Matrix controlled TTSs

Matrix-type TTS patches containing different SEs were prepared. 0.1 g of metoprolol tartrate and 1% sugar ester were continuously mixed in 5.0 ml distilled water and after that, 5.0 ml of 20% w/w aqueous polymeric dispersion, diluted from Eudragit® NE 30D, was added to this solution. The obtained dispersion was poured into a non-stick round container with a standard diameter of 50 mm to produce the required thickness of the patch. Samples were dried at room temperature (24 h).

2.1.2. Membrane controlled TTS

0.2 g of Metolose® 90SH 4000 was continuously mixed with 5.0 g of water (70 °C) on a heated magnetic stirrer. The required amount of drug (1% metoprolol tartrate) and 1% sugar ester were dissolved in 5.0 g of cold distilled water, and it was added to the opaque Metolose dispersion and stirred until it cleared up. The obtained transparent gel was used as matrix of the patch, which was covered with polymeric film prepared from 20% w/w aqueous dispersion diluted from Eudragit® NE 30D. The Eudragit® NE film was prepared without drug and SE according to Section 2.1.1.

2.2. Study of drug release according to the Ph. Eur. method

This test was performed by PharmaTest apparatus according to Ph. Eur. (Ph. Eur.5.0 Vol 1. 2.9.4). TTSs measured with analytical accuracy were placed into the cell of Ph. Eur. and it was immersed into the temperature-controlled 200 ml acceptor medium (pH 5.5, phosphate buffer solution simulating the acid skin wrap). The acceptor medium kept at 32 ± 0.5 °C was mixed with paddles at 50 rpm, and samples were taken at regular intervals, their volume being replaced with the buffer solution.

2.3. In vitro modelling of cutaneous absorption of metoprolol from TTS

This test was done by Sartorius Resorptionsmodell SM 16750, TTS samples were put into the ointment cell (Type SM 15703) of this apparatus [12]. One hundred milliliters of water was poured into container I to provide the body temperature. The examined TTSs were placed into the cell and the patch was covered by the Sartorius impregnated membrane to simulate skin. One hundred milliliters of phosphate buffer was poured into Container II (pH 7.4).

The temperature was set at 32 ± 1 °C and the surface of the impregnated membrane was 40 cm^2. Samples of 3 ml were taken from container II at predetermined time points,

and they were diluted with appropriate buffer solution before spectrophotometric determination.

2.4. Spectrophotometric assay of metoprolol

The concentration of the active ingredient was determined by spectrophotometric method with Shimadzu UV-160A spectrophotometer (Shimadzu Corporation Spectroscopic Instruments, Kyoto, Japan). The appropriate buffer solution was used as blank and measurements were carried out at 273.4 nm.

2.5. Statistical experimental design

The evaluation of the results was carried out with Statistica 6.1 software (Statsoft, Inc., Tulsa, USA, 2004).

3. Results and discussion

3.1. Drug release

As Fig. 1 shows the use of SEs resulted in significant alteration in drug liberation. Without SEs the drug liberation was about 12% in 6 h. As we expected all types of SEs increased the liberated drug from Eudragit® TTSs, not only the HLB value but also the type of fatty acid in SEs modified this process. All stearate type SEs (S370, S970, S1670) increased the release more than four times, but in case of SEs containing shorter fatty acid chains, for example myristic acid (M1695) and palmitic acid (P1570), the amount of liberated drug increased to 80–90%. Using SE of lauric acid derivative (L1695), the release rate was about 10 times higher than in the case of Eudragit® films without SE.

Results show that along with the HLB value of SEs, the length of fatty acid chains affects drug liberation. SEs of shorter fatty acid increased the release more than SEs of longer fatty acids. In cases of matrix type TTS, the mechanism of liberation showed zero order kinetics. In the first 15 min the liberation was fast and then became slower and showed zero order kinetics. The initial quick release of drug could be explained by the drug diffusion from the matrix surface, while after this drug liberation was regulated by diffusion throughout the swollen matrix. The initial burst time could be advantageous taking the saturation of epidermis with the drug into consideration.

Examining membrane controlled TTS, where the SEs were built into the membrane, the same tendency was observed between the different SEs, but the liberation did not show zero order kinetics (Fig. 2). Since the drug release in membrane controlled TTSs cannot be characterized with

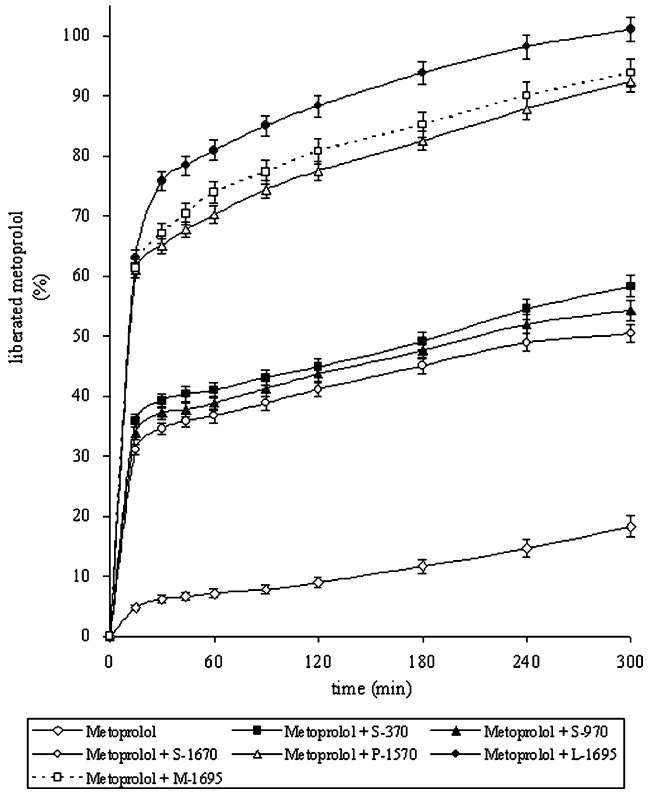

Fig. 1. In vitro release of metoprolol from matrix type TTS containing Eudragit® NE and different SEs (average values ± SD, $n = 3$) [17].

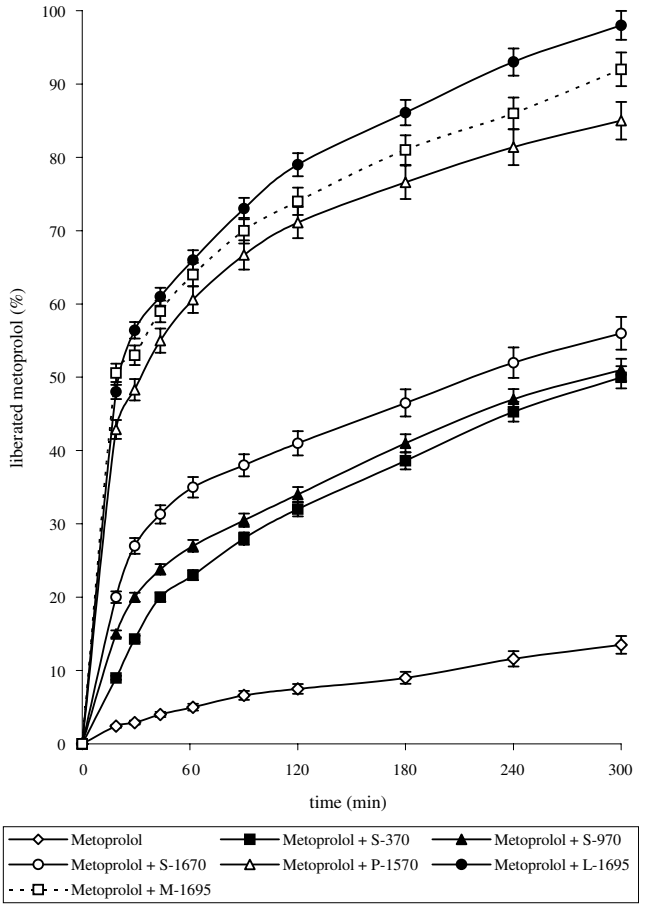

Fig. 2. In vitro release of metoprolol from membrane controlled type TTSs containing Eudragit® NE and different SEs (average values ± SD, $n = 3$).

the zero-order model, the following mathematical models [13,14] were evaluated considering the liberation profiles from membrane controlled TTSs.

1. First-order model

$$M_t/M_{\max} = 1 - \exp(-kt). \quad (1)$$

2. Semiempirical model [15]

$$M_t/M_{\max} = kt^n, \quad (2)$$

where n is the release exponent, k is the liberation rate constant, M_t is amount of drug released at time t, $M_{\max}$ is the maximal amount of drug released.

Table 2 shows the calculated liberation rate constants and correlation values. As it can be seen, application of semiempirical model showed the best correlation coefficients in all cases. These results indicate that the application of matrix controlled TTS is preferred, because it shows zero-order kinetic, consequently constant release rate could be achieved.

Fig. 3 illustrates the effect of C number of fatty acid chains and the HLB value of SEs. The amount of drug released at the 5th hour depends on both HLB value and C numbers of fatty acid chains. In comparison with the sample prepared without SE, the SEs of 18 C number in fatty acid chain increased the amount of drug released by 5–6 times, while it was increased to 8–10 times in the case of SEs of lower C numbers and almost the same HLB values (HLB = 15–16). The possible reason of the obtained phenomena could be that SEs of smaller fatty acid chains (lower C numbers) can be built more completely into the polymeric chains, thus increasing the free volume holes in the polymer resulting in higher permeability. The higher permeability of the polymer enables faster drug release [16].

In the case of SEs it is not sufficient to consider exclusively their HLB value, but the C atom number of fatty acid chains should be taken into account, as well.

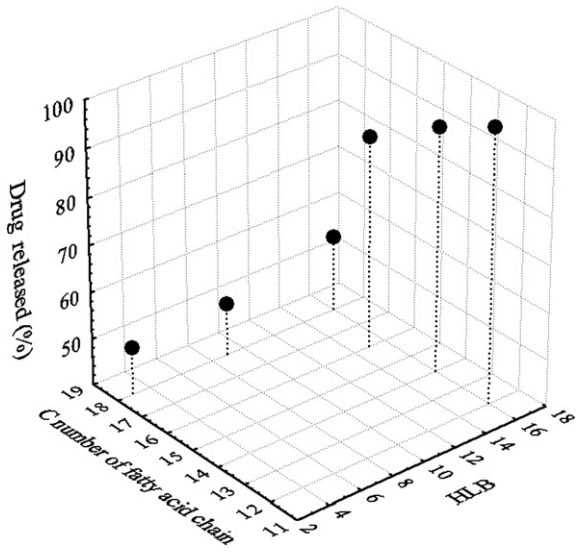

Fig. 3. Drug released at the 5th hour as a function of HLB value and C number of fatty acid chain of the sugar ester.

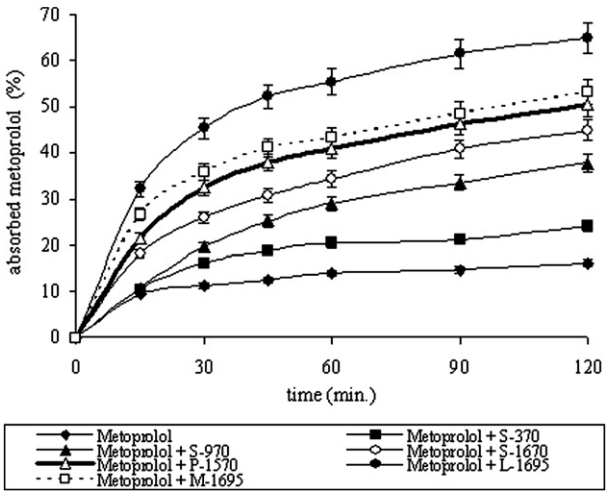

Fig. 4. In vitro percutaneous absorption of metoprolol from matrix controlled TTS of different SEs (average values ± SD, $n = 3$) [14].

3.2. Investigation of in vitro absorption applying Sartorius Resorptionsmodell Apparatus

Matrix controlled TTSs were studied in vitro considering their zero-order drug release. The quantity of SE was varied [17] and the absorbed active ingredient was registered, as the Fig. 4 shows. The highest differences can be observed in the case of SE containing lauric acid (C = 12, HLB = 16); it increases the amount of absorbed drug more than six times. Using SEs of the same HLB values, shorter fatty acid chains increase the absorption better than longer

Table 2
Parameters of the drug release from membrane controlled TTSs containing different SEs

SE type	First order equation		Semiempirical model		
	k_1 (min^{-1})	Correlation coefficient	n	k_2 (min^{-n})	Correlation coefficient
Without	0.005	0.922	0.65	0.003	0.992
S-370	0.027	0.913	0.49	0.030	0.997
S-970	0.049	0.927	0.40	0.056	0.995
S-1670	0.096	0.919	0.30	0.096	0.992
P-1570	0.111	0.885	0.24	0.216	0.997
M-1695	0.150	0.905	0.23	0.244	0.998
L-1695	0.195	0.910	0.27	0.265	0.995

fatty acid chains. The obtained tendency is similar to the results of the drug release study.

4. Conclusion

Although all types of tested SEs increased the drug release, this effect depends on the HLB value and the C atom number of fatty acid chain of SEs. HLB value and the C atomic number of fatty acid chain significantly influenced the in vitro absorption process, too. Result indicates that the matrix controlled TTS demonstrated zero-order kinetics after the initial burst. It could be concluded that various types of SEs are promising agents in transdermal therapeutic systems to control drug release and enhance absorption.

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