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Microcrystalline cellulose-sucrose esters as tablet matrix forming agents

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Abstract

A new tablet matrix system containing microcrystalline cellulose and sucrose esters is described. Theophylline monohydrate and ibuprofen were chosen as model drugs. Theophylline tablets compressed directly using 5% (w/w) sucrose stearate esters (S170, S770, S1570), or sucrose palmitate ester P1570 and microcrystalline cellulose showed a slight retardation of drug release with P1570 and S170, respectively. Increasing the concentration of S170 up to a value of 15% decreased the release to a value of 60% after 3 h. Increasing the concentration of P1570 to 10% showed a dramatic decrease in dissolution as only 30% was released after 3 h. Thermal treatment above the melting temperature range of the palmitate sucrose ester (P1570 5% w/w)-microcrystalline cellulose-theophylline granules decreased the dissolution rate dramatically, demonstrating 80% release after 8 h. The duration of thermal treatment did not have any influence on the drug release profile. Increasing the concentration of palmitate sucrose ester from 5 to 10% decreased the release progressively to a value of about 50% after 8 h. Very similar release patterns were observed when S1570 was used instead of P1570. The sucrose ester S770 performed less well as a matrix forming agent with the microcrystalline cellulose. Dissolution experiments with ibuprofen as model drug indicated the possibility of using the matrix with other drugs. Hydrogen bond formation could be the basic mechanism of matrix formation between microcrystalline cellulose and the sucrose esters. Finally, the pH value, ionic strength and rotational speed seemed to have some influence on the dissolution rate of the theophylline matrix tablet.

Keywords: Matrix forming agent; Microcrystalline cellulose; Sucrose ester; Theophylline monohydrate; Ibuprofen; Sustained release

1. Introduction

The importance and usefulness of sustained release dosage forms are well known and offer several advantages over the conventional dosage forms (Williams et al., 1983). Among the various controlled release methods, a matrix system appears to present an attractive and interesting approach from the economic and process development point of view (Efentakis et al., 1990). Sugar esters are mainly applied in the food industry as emulsifiers, crystallization inhibitors and antibacterial compounds. The application of sucrose esters in pharmaceutical technology remained unknown until recently when Lerk (1991) reported on the use of sucrose laurate and palmi-

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tate in drug formulations. They have the advantage of having low toxicity and being biodegradable (Chester, 1973). Previously, problems due to disintegration and a slow dissolution rate from tablets prepared with nifedipine-sucrose ester coprecipitates in comparison with the pure coprecipitates were reported (Ntawukulilyayo et al., 1993). The objective of the present investigation was to study the dissolution behaviour of tablets containing sucrose esters and microcrystalline cellulose as a filler. Theophylline hydrate and ibuprofen ware used as model drugs.

2. Materials and methods

Theophylline monohydrate was purchased from Flandria (Zwijnaarde, Belgium). Ibuprofen 25 was received from Boots Co. PLC (Nottingham, UK). The following sucrose esters were kindly provided by Ryoto Co. (Mitsubishi-Kasei Food Corp., Tokyo, Japan): sucrose stearate S170 (HLB = 1), sucrose stearate S770 (HLB = 7), sucrose stearate S1570 (HLB = 15) and sucrose palmitate P1570 (HLB = 15). Their characteristics are given in Table 1. Dicalcium phosphate dihydrate (Emcompress, C.N. Schmidt B.V, Amsterdam, The Netherlands), lactose monohydrate 200 M (De Melk Industrie Veghel, Veghel, The Netherlands), microcrystalline cellulose (Avicel PH102; FMC International, Wallingstown, Ireland), and methylcellulose (Methocel A4M Premium E.P., Colcon Ltd, Orpngton, UK) were used as filling agents. Magnesium stearate was purchased from Flandria (Zwijnaarde, Belgium).

2.1. Tablet preparation

Tablets were prepared via direct compression and after wet granulation. The sucrose esters were used in the concentration range between 2 and 15% of the total tablet weight. The amount of drug was kept constant at 100 mg per tablet while the amount of magnesium stearate was 8 mg per tablet and the total tablet weight was set at 500 mg. Unless indicated microcrystalline cellulose (Avicel PH 102) was used as the filling agent. Before use all ingredients were sieved through a 90 μm sieve, and mixed for 10 min in a Turbula mixer (type T2A, W.A. Bachofen, Switzerland). Finally, the magnesium stearate was added and mixing continued for an additional 2 min. Tablets were compressed on a eccentric tabletting machine (Korch type EKO, Frankfurt, Germany) equipped with 13 mm flat punches at pressure ranging from 3.7 to 15.0 kN in order to obtain tablets of hardness 8 kG (Heberlein and Co. AG, Wattwil, Switzerland). When the tablets were prepared via wet granulation, the filler, drug and sucrose ester were mixed in the Turbula mixer for 10 min and next granulated with distilled water. Subsequently, the wet mass was passed through a 1 mm sieve and oven dried at 50° C for 3 h. Batches were then subdivided into three sub-batches and submitted to thermal treatment for 1 h at 50° C, in the melting temperature range of sucrose esters and at 70° C, respectively. The granules were then sieved and the fraction below 90 μm was compressed as described previously. Tablets prepared without sucrose esters were used as reference tablets.

Table 1
Sucrose ester characteristics

Sucrose ester	Nature	Ester composition (%)		HLB value	Melting temperature range (° C)
		Monoester	Di, tri, polyester		
S170	stearate	0	100	1	51–61
S770	stearate	40	60	7	49–60
S1570	stearate	70	30	15	49–55
P1570	palmitate	70	30	15	47–54

2.2. Dissolution testing

Tablet dissolution was performed using the paddle method (USP XXII) and water, simulated gastric (SGF) and intestinal fluid (SIF) (USP XXII) as the dissolution medium and kept at 37° C. In order to study the influence of pH, the ionic strength of the medium was kept constant at a value of 0.165 (with KCl). The drug concentration was monitored spectrophotometrically (Shimadzu 140-02 UV-Visible double-beam spectrophotometer, Kyoto, Japan) at 272 nm for theophylline and 221 nm for ibuprofen. All experiments were run four times. The calibration curve specifications were $y = 0.0623 \times (\text{SD } \pm 0.00987) + 0.00234(\text{SD } \pm 0.00146)$ ($n = 6$) for theophylline monohydrate and $y = 0.045389 \times (\text{SD } \pm 0.00023) + 0.00126(\text{SD } \pm 0.0005)$ ($n = 3$) for ibuprofen.

2.3. DSC determinations

Samples (1.5–4 mg) were weighed and hermetically sealed in flat-bottomed aluminium pans. The samples were heated at a constant rate of 5° C per min and thermograms were obtained with a DSC 2920 system equipped with a Thermal Analyst 2000 programmer (TA Instruments, New Castle, DE, USA). The instrument was calibrated with an indium standard.

The individual substances, as well as physically blended binary and ternary mixtures, were heated over the temperature range of 0–350° C for theophylline and 0–400° C for ibuprofen.

2.4. X-ray diffraction

X-ray diffraction analysis was performed using a Philips X-ray diffractometer (type PW 1051, CuKα (40 kV, 20 mA), Eindhoven, The Netherlands).

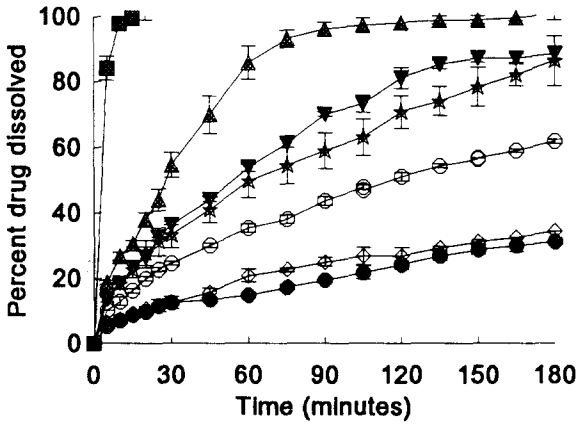

Fig. 1. Mean dissolution profiles in water ($n = 4$; ±SD) of theophylline tablets compressed directly using microcrystalline cellulose (Avicel PH102) and sucrose esters P1570 5% (▲), P1570 10% (◇), P1570 15% (●), S170 5% (▼), S170 10% (★) and S170 15% (○) in comparison with the reference tablet (■).

3. Results and discussion

In a first experiment theophylline monohydrate tablets were compressed directly using microcrystalline cellulose and 5% (w/w) sucrose esters (S170, S770, S1570, P1570) and their dissolution profile in water compared with a reference tablet containing no sucrose ester. The powder mixture prior to tabletting was not subjected to any thermal treatment. Only a slight retardation of drug release was observed for tablets containing P1570 and S170, respectively. Increasing the concentration of S170 up to a value of 10 and 15%, respectively, decreased the dissolution rate progressively, reaching a value of 60% release after 3 h for 15% S170. Increasing the concentration of P1570 up to 10% showed a dramatic decrease in dissolution as only 30% was released after 3 h. A further increase up to a value of 15% did not further influence the dissolution profile (Fig. 1). In the next set of experiments, wet granulation was employed in order to produce tablets. The granules were firstly dried at 50° C for 3 h and then treated thermally at 50, 55 or 70° C for an additional 1 and 4 h for the granules containing P1570 5% and at 62° C (1 and 4 h) in the case of S170 5% granules. Fig. 2 shows that thermal treatment above the melting temperature range of the sucrose ester P1570 (55° C) decreased the dissolution rate dramatically, demonstrating 80% release after 8 h. The duration of thermal treatment (1 and 4 h) did not have any influence on the drug release profile. Increasing the tempera-

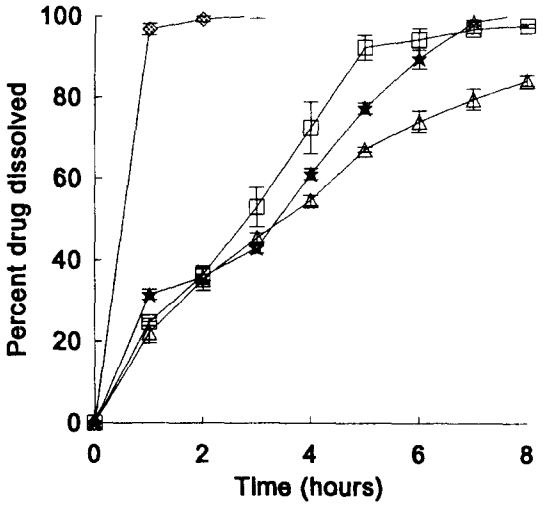

Fig. 2. Mean dissolution profiles in water ($n = 4$; ±SD) of theophylline tablets prepared with a granulated mixture of theophylline hydrate-sucrose ester P1570 5%-Avicel PH102 and thermally treated for 1 h at 50° C (□), 55° C (△), and 70° C (⋆) in comparison with a reference tablet (◆).

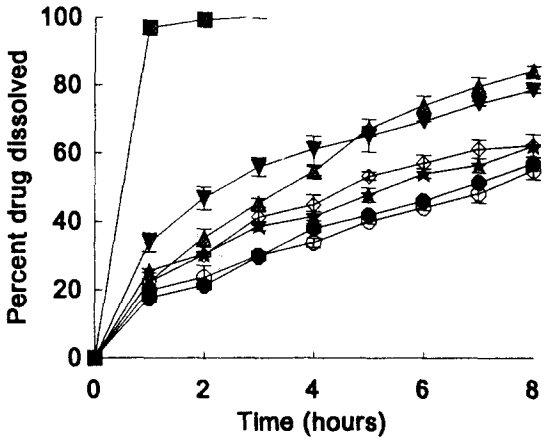

Fig. 3. Mean dissolution profiles in water ($n = 4$; ±SD) of theophylline tablets prepared with a granulated mixture of theophylline hydrate-Avicel PH102-sucrose esters P1570 5% (▲), 7.5% (◆), 10% (●) or S1570 5% (▼), 7.5% (⋆), 10% (○) and thermally treated for 1 h at 55° C in comparison with a reference tablet (■).

ture up to 70° C induced a quite different release pattern and greater release rate in comparison to treatment at 55° C. When 5% sucrose ester S170 was used, a sigmoidal release curve was seen when the granules were treated at 62° C, just above the melting temperature range of this compound. Again the duration of thermal treatment did not have any influence on the drug release profile. When the concentration of P1570 was increased from 5 to 7.5 and 10%, respectively, the release rate decreased progressively to a value of about 50% after 8 h for the granules containing P1570 10% (w/w). Very similar release patterns were observed when S1570 was used instead of P1750 (Fig. 3). The sucrose ester S770 performed less well as a matrix forming agent with the microcrystalline cellulose than P1570 or S1570. In order to identify whether the microcrystalline cellulose-sucrose ester matrix could be used for other drugs except theophylline monohydrate, tablets were made containing 100 mg ibuprofen with increasing concentrations of P1570 (2.5, 5 and 10%). The tablets were made by wet granulation and thermally treated for 1 h at 55° C. Fig. 4 shows the release profiles for ibuprofen. The use of 2.5% P1570 led to drug release of about 55% after 8 h, confirming the use of the matrix forming agents for other drugs. In order to elucidate the unique matrix forming properties of the combination of microcrystalline cellulose-sucrose ester, theophylline monohydrate tablets were prepared with P1570 and dicalcium phosphate dihy-

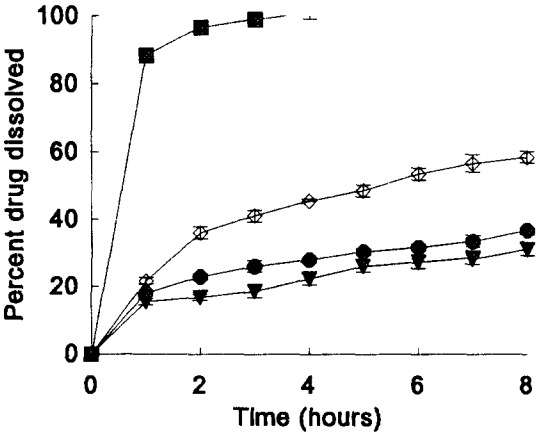

Fig. 4. Mean dissolution profiles in water ($n = 4$; ±SD) of ibuprofen tablets prepared with a granulated mixture of ibuprofen-Avicel PH102-sucrose ester P1570 2.5% (◇), 5% (●) or 10% (▼) and thermally treated at 55° C for 1 h in comparison with a reference tablet (■).

drate, lactose monohydrate or methylcellulose as fillers instead of microcrystalline cellulose. None of these tablets showed any slow release behaviour. In the case of methylcellulose it could be postulated that the etherification of the hydroxyl functions leads to the blockage of the possible hydrogen bond formation between the cellulose molecule and the sucrose ester. This hydrogen bond formation could be the basic mechanism of the matrix forming properties between cellulose and the sucrose ester molecules. Another indirect proof of this interaction is that the use of sucrose stearate with an HLB value of 7 shows no important slow release characteristics, probably due to the fact that a higher degree of esterification of the sucrose molecule partially blocks H-bond formation. The fact that the use of sucrose stearate with an HLB value of 1 again decreased the dissolution rate could be explained by the increasing hydrophobicity of the mixture.

DSC analysis was performed on the granulated mixture of theophylline hydrate-sucrose ester palmitate (P1570 10%) and Avicel PH102, thermally treated and not thermally treated, and on the individual compounds (Fig. 5). The DSC profiles clearly showed a partial disappearance of the dehydration peak of theophylline hydrate (77.01° C), a small shift in the melting endotherm of the sucrose ester and a partial disappearance and shift in the melting endotherm of theophylline. The same observations were noted for ibuprofen mixtures. X-ray diffractometry proved that the partial disappearance of the endotherms was not the consequence of the formation of a partially amorphous product as no change in the crystallinity of the compounds was observed. In one experiment sucrose ester P1570 (5%) was solubilised in water for granulation and used to prepare the matrix tablets. The thermal treatment was kept constant at 55° C for 1 h. No influence was observed on the drug release rate due to the incorporation of the sucrose ester in the granulation liquid. Fig. 6 shows the influence of pH and ionic strength on the dissolution behaviour of theophylline monohydrate-P1570 (10%)-Avicel PH102 mixtures. The dissolution

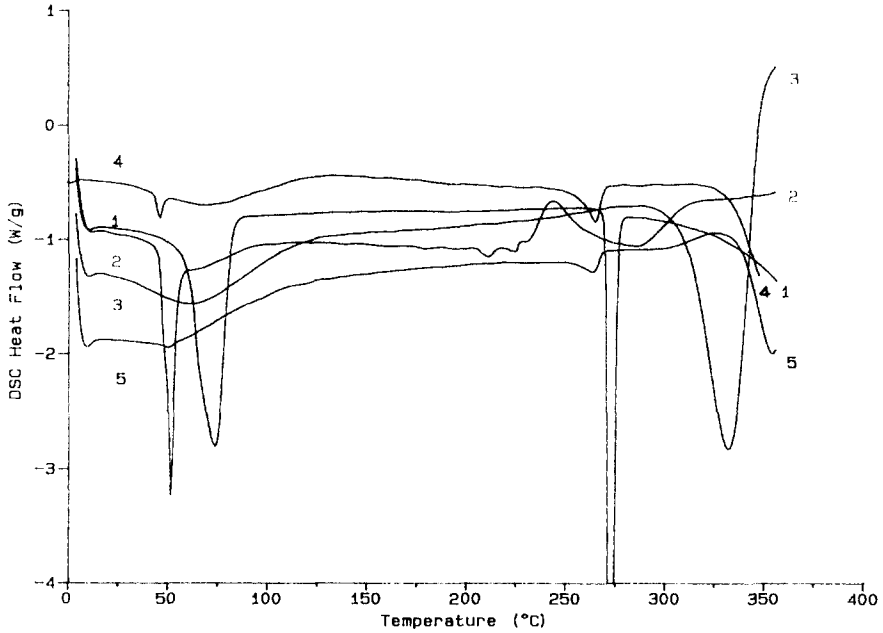

Fig. 5. DSC profiles of theophylline (1), sucrose ester palmitate P1570 (2), Avicel PH102 (3), granulated mixture of theophylline hydrate-sucrose ester palmitate (P1570 10%) and Avicel PH102 without thermal treatment (4) and thermally treated for 1 h at 55° C (5).

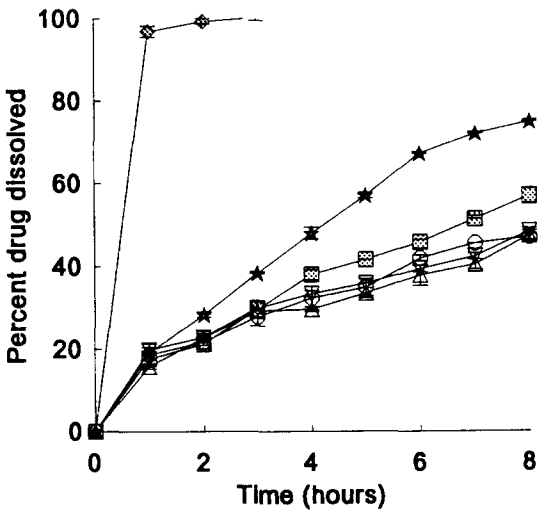

Fig. 6. Mean dissolution profiles ($n = 4$; ± SD) of theophylline tablets prepared with a granulated mixture of theophylline hydrate-Avicel PH102-sucrose ester palmitate (P1570 10%) and thermally treated at 55° C for 1 h. The dissolution media were distilled water (■), simulated intestinal fluid (pH 7.5; $I = 0.094$) (△), simulated gastric fluid (pH 1.2; $I = 0.165$) (★), KCl solution ($I = 0.165$) (○) and simulated intestinal fluid + KCl ($I = 0.165$) (▽) in comparison with a reference tablet (◆).

rate in SGF is greater in comparison to water and SIF, respectively, while it is only slightly influenced by ionic strength. Increasing ionic strength of water up to a value of 0.165 decreased the release rate while no influence was observed when the dissolution was run in SIF. The formulation seemed to be affected by the rotational speed of paddle and stronger erosion was visually observed for a higher rotational speed. It can be concluded that sucrose esters especially palmitate and stearate esters with a high HLB value can form a slow release matrix with microcrystalline cellulose. Further in vivo work should confirm the usefulness of these matrices.

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