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Sucrose esters with various hydrophilic–lipophilic properties: Novel controlled release agents for oral drug delivery matrix tablets prepared by direct compaction

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ABSTRACT

Sucrose esters (SE) are esters of sucrose and fatty acids with various hydrophilic–lipophilic properties which have attracted interest from being used in pharmaceutical applications. This study aimed to gain insight into the use of SE as controlled release agents for direct compacted matrix tablets. The study focused on the effect of hydrophilic–lipophilic properties on tableting properties and drug release. Sucrose stearate with hydrophilic–lipophilic balance (HLB) values ranging from 0 to 16 was systematically tested. Tablet formulations contained SE, metoprolol tartrate as a highly soluble model drug and dibasic calcium phosphate dihydrate as a tablet formulation filler in the ratio 1:1:2. The compaction behaviour of matrix tablets was compared with the compacts of individual starting materials as reference. SE incorporation improved the plasticity, compressibility and lubricating property of powder mixtures. The hydrophilic–lipophilic properties of SE affected tableting properties, drug release rate and release mechanism. Increasing hydrophilicity corresponding to the increased monoesters in SE composition increased the relative porosity, elastic recovery and tensile strength of the tablets due to the increased hydrogen bonding between the monoesters. This also facilitated the swelling behaviour of SE, which sustained the drug release rate. A sustained release effect prevailed in tablets containing SE with HLB values of 3–16. The ability to improve the tableting properties as well as sustain the drug release rate of the highly soluble model drug via gelation of SE highlights SE as promising controlled release regulators for direct compacted matrix tablets comprising drugs with various solubilities according to the Biopharmaceutics Classification System.

1. Introduction

Matrix-based systems are monolithic systems with an active component homogeneously dispersed in a matrix-forming polymer which controls the drug release rate. The systems can be prepared by methods as simple as direct compaction of powder blends of the drug and polymers or methods involving sophisticated processes, e.g., granulation, spray-drying, solid dispersion. The ease of manufacturing process, the ability to achieve appropriate drug release rates and at the same time to cope with high drug loading have highlighted these systems and attracted attention to controlled release drug delivery systems in recent decades. Success of the formulations is dependent on the selection of an appropriate matrix-forming agent that gives a desirable drug release rate [1].

Sucrose esters (SE) are esters of sucrose and fatty acids derived from edible fats and oils. As sucrose has eight free hydroxyl groups, it can be esterified with up to eight fatty acids to form esters ranging from monoesters to octaesters. Differences in fatty acid type and degree of esterification generate a wide range of material properties. Generally, commercial SE are categorized according to the type of fatty acid substitution, and their mixture compositions of mono- and polysubstituted fatty acid esters provide various hydrophilic–lipophilic properties, with hydrophilic–lipophilic balance (HLB) values ranging from 0 to 16 [2]. The higher the proportion of monoesters, the higher the hydrophilicity of the material. As they comprise both hydrophilic parts from hydroxyl head groups of sucrose and lipophilic parts from fatty acid tails, SE are denoted as non-ionic surfactants, with a unique emulsification property that tolerates any temperature variation [3,4]. SE are also proved to be non-toxic and biodegradable, as they can be enzymatically hydrolysed to sucrose and fatty acids prior to intestinal absorption or excreted in faeces, depending on the degree of esterification [5,6].

Various chemical properties and benefits of SE (tasteless, odourless, non-toxic and biodegradable) lead them to extensive use in the field of food additives [7–9], and they are also attractive for pharmaceutical applications. Many research groups have focused on exploiting the amphiphilic property of SE to improve drug solubility [10], drug stability [11] and drug absorption through mem-

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brane [12–15]. However, studies of SE in the area of commonly used tablet formulations are limited and emphasize using specific types of SE for particular approaches. Ntawukulilyayo et al. [16] reported that slow drug release was observed from microcrystalline cellulose matrix tablets containing SE with a HLB value of either 1 or 15, regardless of two fatty acid types, i.e., stearate and palmitate, whereas tablets containing SE with a HLB value of 7 had a less sustained release effect. Koseki et al. [17] observed a viscous gel layer around the disintegrated particles of microcrystalline cellulose-based tablets using sucrose stearate with a HLB value of 16 as a disintegrant. These findings exemplify the effect of hydrophilic–lipophilic properties of SE on the drug release rate and suggest control of the release rate via gelation of hydrophilic SE. Besides the influence on the controlled release rate, the hydrophilic–lipophilic properties of SE also affect the tableting process and the final characteristics of a tablet. Sucrose stearate with a HLB value of 3 sufficiently reduces the ejection force during the tableting process [18], whereas tablet hardness is increased with this type of SE, but at a HLB value of 16 [17].

From an economical point of view, direct compaction is the process of choice for tablet formulations, owing to its one-step process operation. However, materials that suit this process should be proved to have appropriate compaction behaviour. In the present work, oral drug delivery matrix tablets were prepared by direct compaction. The aim of this study was to investigate systematically the effect of SE on tableting properties and drug release rate over a HLB value range from 0 to 16. Matrix systems composed of sucrose stearate and dibasic calcium phosphate dihydrate (DCP), a practically insoluble tablet filler, are reported to have no interaction with SE that influences the drug release rate [16]. Furthermore, DCP undergoes fragmenting deformation under compaction, and thus the plasticity and compressibility of SE could be verified from the compaction of powder mixtures. Metroprolol tartrate (MTP) was used as a model drug, owing to its high solubility (>1 g ml^{-1}) [19], classified as Class I drug according to the Biopharmaceutics Classification System [20]. The ratio of the drug to SE was set at 1:1 in order to verify the controlled release effect of SE. Matrix tablets were compacted using a tablet press replicator at high compaction speed with a view to simulation of industrial-scale production. Physical properties and compactions of individual starting material as reference compacts were studied in comparison. Release data were examined for profile comparison and release mechanism. Finally, a complete overview of SE (HLB value 0–16) with respect to their compaction behaviour and controlled release effects is presented and discussed.

2. Materials and methods

2.1. Materials

Sucrose stearates (Ryoto®; S070, S170, S370, S570, S970, S1170, S1570 and S1670) were kindly provided by Mitsubishi-Kagaku Foods Co. (Tokyo, Japan). The details of HLB values, composition and melting temperatures of SE are summarized in Table 1 [2]. Metoprolol tartrate (Batch number MT-20/00, Karinco, Milan, Italy) was sieved through a 200-μm standard sieve, and the particle size fraction below 200 μm was used. Dibasic calcium phosphate dihydrate (Emcompress®, Edward Mendell, New York) and magnesium stearate (Novartis Pharmaceuticals, Basel, Switzerland) were used as received.

2.2. Methods

2.2.1. Particle size and apparent density

The particle size of the starting materials, i.e., DCP, MTP and SE, was examined on a laser diffractometer (Mastersizer X, Malvern, UK). Powder was passed through the focused laser beam and scattered light at an angle inversely proportional to their size. A volume mean diameter ($D_{4,3}$) was calculated from at least three measurements.

The apparent density of the starting materials was analysed on a gas displacement pycnometer (AccuPyc 1330, Micromeritics, US). Powder was purged with helium, and the density was reported as an average value of five repetitive purging cycles. The test was performed in triplicate.

Table 1
HLB values, composition and melting temperatures of sucrose stearate.*

Abbreviation	Trade name	HLB value	Monoesters (%)	Melting temperature	
				Start point (°C)	Peak point (°C)
H-0	S070	0	<1	52	61
H-1	S170	1	1	51	61
H-3	S370	3	20	51	58, 69
H-5	S570	5	30	50	57, 65
H-9	S970	9	50	49	56
H-11	S1190	11	55	49	55
H-15	S1570	15	70	49	55
H-16	S1670	16	75	49	56

* Data supplied by the supplier [2].

2.2.2. Compaction of individual starting material

Starting materials of 400 mg were accurately weighed and compacted using a Zwick material tester (Zwick GmbH, Germany) with a 100-mm flat-faced punch at a compaction force of 90 MPa and punch speed 0.003 m s^{-1} by manual feed. The powder was stored in a desiccator containing silica gel overnight and subsequently equilibrated in an ambient condition (24 ± 1 °C, 60 ± 5% RH) for 4 h before compaction. The powder was transferred into the die cavity, and the die holder was lifted up against the stationary upper punch to reach the desirable compaction force. The distance between the die holder and the reference level was detected and plotted against the applied force for the analysis of work of compaction. At least three compactions were performed for each starting material, and the compacts were stored in an airtight container in ambient conditions before analysis.

2.2.3. Compaction of matrix tablets

Powder mixtures of 20 g batch size composed of MTP, SE and DCP in the weight proportion 1:1:2 were prepared. MTP and SE were weighed in a 100-ml amber glass bottle and mixed with a Turbula mixer (Willy A. Bachofen AG, Switzerland) at 50 rpm for 5 min. DCP was added to the powder blend and mixed for a further 5 min. The degree of bottle filling was <50%, achieving good mixing behaviour. Before compaction, 0.5% wt. magnesium stearate was added to the powder blend and mixed for 3 min. A formulation without SE was prepared for comparison, in which the proportion of SE was replaced by DCP to keep the same tablet mass.

Matrix tablets were prepared using a tablet press replicator, Presster® (Metropolitan Computing Co., US), equipped with 10-mm flat-faced punch at the linear speed of 0.408 m s^{-1} without pre-compaction. A powder blend of 400 mg comprising 100 mg MTP was accurately weighed and compacted by manual feed. The punch surface and die wall were cleaned with acetone after each compaction for the accuracy of ejection force and take-off force detection. Twenty tablets were prepared for each formulation and stored in an airtight container in ambient conditions before analysis.