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Mini review

Sucrose esters as natural surfactants in drug delivery systems—A mini-review

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ABSTRACT

Sucrose esters (SEs) are widely used in the food and cosmetic industries and there has recently been great interest in their applicability in different pharmaceutical fields. They are natural and biodegradable excipients with well-known emulsifying and solubilizing behavior. Currently the most common pharmaceutical applications of SEs are for the enhancement of drug dissolution and drug absorption/permeation, and in controlled-release systems. Although the number of articles on SEs is continuously increasing, they have not yet been widely used in the pharmaceutical industry. The aim of this review is to discuss and summarize some of the findings and applications of SEs in different areas of drug delivery. The article highlights the main properties of SEs and focuses on their use in pharmaceutical technology and on their regulatory and toxicological status.

1. Introduction

Increased attention to the environment in recent decades has led to growing interest in the field of natural surfactants (Savić et al., 2010). The sucrose esters (SEs) are formed from natural raw materials: sucrose and fatty acids. As sucrose contains 8 hydroxy groups, compounds ranging from sucrose mono- to octa-fatty acid esters can be produced. The commercial SEs comprise mixtures with various degrees of esterification. The wide range of materials within the SE family results in a similarly wide range of properties. Thanks to their surfactant and other versatile properties, SEs have many applications in different areas of drug delivery, and some of them are already used in the pharmaceutical industry. As surfactants, they may play a role in the solubilization or stabilization of drugs in different preparations, and they can also be included in formulations to modify the bioavailability of drugs. This review will cover the main properties of SEs, and their possible applicability in the pharmaceutical industry.

2. Structure and properties of SEs

SEs are non-ionic surface-active agents consisting of sucrose as hydrophilic group and a maximum of eight fatty acids per molecule as lipophilic groups. The most common fatty acids used in SEs are lauric, myristic, palmitic, stearic, oleic, behenic and erucic acids (Table 1). Through change of the nature or number of the fatty acid groups, a wide range of hydrophilic–lipophilic balance (HLB) values can be obtained.

A number of manufacturers supply SEs, *e.g.* Dai-Ichi-Kogyo Seiyaku and Mitsubishi Kagaku Food Co. in Japan, Croda in the USA, Sisterna and Evonik Goldschmidt in Germany (Godshall, 2005; Hill and Rhode, 1999) and Stearinerie Dubois in France. Most of the SEs are manufactured in different grades, allowing their use in food, cosmetics and pharmaceuticals (Table 2). The commercial SEs are mixtures with various esterification degrees. SEs with high monoester contents are more hydrophilic, whereas a high esterification degree results in lipophilic SEs. Different methods are available for the synthesis of SEs consisting of mono-, di-, tri- and higher esters, and of SEs with high monoester content (Fitremann et al., 2007; Hill and Rhode, 1999; Nagai et al., 2007; Parker et al., 1977; Polat and Linhardt, 2001). SEs with different hydrophilicities can be used in different fields of pharmaceutical technology, *e.g.* for emulsification, solubilization, dissolution modification, absorption enhancement or lubrication. Table 3 shows the recommended HLB of SEs for the different applications.

The properties of SEs are determined by the nature of the esterified fatty acid and by the degree of esterification of the sucrose molecule. Depending on the composition, SEs exist as solids, waxy materials or liquids. The solubility of the monoesters in water is good, while di- and higher esters are not water-soluble. Moreover, the shorter the fatty acid chain, the better the water solubility. Depending on the degree of esterification, SEs decrease the surface tension of water. They also exhibit different solubilizing abilities and foaming properties (Garofalakis et al., 2000; Husband et al., 1998; Soultani et al., 2003). SEs, and especially those with higher HLB values, can form gels in an aqueous environment (Berjano et al.,

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Table 1
Fatty acids commonly used in commercial SEs.

Fatty acid	C-atom number	Degree of unsaturation
Lauric acid	12	0
Myristic acid	14	0
Palmitic acid	16	0
Stearic acid	18	0
Oleic acid	18	1
Behenic acid	22	0
Erucic acid	22	1

Table 2
Different grades and names of SEs according to their manufacturers.

Manufacturer	Grade and *name* of SEs
Dai-Ichi Kogyo Seiyaku Co. (http://www.dks-web.jp/e/)	Food, cosmetic, pharmaceutical (*DK ESTER*)
Mitsubishi Kagaku Food Co. (http://www.mfc.co.jp/english/)	Food (*Ryoto sugar ester*) Cosmetic (*Surfhope SE Cosme*) Pharmaceutical (*Surfhope SE Pharma*)
Croda (www.croda.com)	Personal care, pharmaceutical (*Crodesta*)
Sisterna (www.sisterna.com)	Food, personal care (*Sisterna SE*)
Evonik Goldschmidt (www.evonik.com)	Personal care (*Tegosoft*)
Stearinerie Dubois (www.stearinerie-dubois.fr/)	Food, cosmetic, pharmaceutical (*DUB SE*)

Table 3
Recommended HLB values for different pharmaceutical applications.

Application	Recommended HLB of SEs
Emulsification	Low to high
Solubilization	High
Dissolution improvement	High
Controlled/sustained release	Low to high
Absorption/penetration enhancement	High (especially with C12–C14 fatty acids)
Lubrication	Low to medium
Disintegrant	High

1993; Chansanroj and Betz, 2010; Szűts et al., 2008, 2010a,b; Ullrich et al., 2008).

Depending upon their degree of esterification, SEs melt at low temperatures, usually between 45 and 65 °C. The lipophilic SEs have characteristic melting points, while SEs with higher HLB values merely soften during heating (Heng et al., 2003; Szűts et al., 2007). They can be heated up to 180 °C without harmful effects on their properties. The penta- and heptaacyl esters are markedly less thermally stable than the mono-, di- and triacyl esters at any temperature (Ushikusa et al., 1990).

3. Pharmaceutical applications of SEs

3.1. Emulsification and stabilization

SEs have been manufactured commercially as food emulsifiers since the early 1960s. They are widely used as additives (E473) in the food industry, and have also been noted as good emulsifying and stabilizing agents in the pharmaceutical field. Table 4 summarizes the possible applicability of SEs as emulsifiers and stabilizers in conventional and advanced drug delivery systems.

In 1992, Akoh examined the emulsification properties of polyesters and SEs, and found that they can be used in foods, cosmetics and pharmaceutical products as o/w or w/o emulsifiers. Thevenin et al. (1996) studied SE/cosurfactant microemulsion systems for transdermal delivery. Bolzinger-Thevenin et al. (1999) characterized a SE-containing microemulsion system by means of freeze fracture electron microscopy and small-angle neutron-scattering experiments. In the same year, Garti et al. (1999) reviewed the behavior of SEs in *microemulsion systems*. The applicability of SEs in microemulsions is still widely studied. For example, Fanun, 2008a,b; Fanun (2008a,b, 2009a,b) examined different SE-containing microemulsion systems which can be utilized in foods, cosmetics and pharmaceuticals.

Table 4
Applicability of SEs as emulsifiers in various formulation systems.

Formulation	Reference
Emulsions, suspensions	Akoh (1992), Yokoi et al. (2005)
Microemulsions	Thevenin et al. (1996), Bolzinger-Thevenin et al. (1999), Garti et al. (1999), Fanun (2008a,b, 2009a,b)
Vesicles	Mollee et al. (2000), Honeywell-Nguyen and Bouwstra (2003), Honeywell-Nguyen et al. (2003)
Microspheres, microparticles	Miyazaki et al. (2006), Youan et al. (2003), Youan (2004)
Nanoparticles, lipid nanoparticles	Zimmermann and Müller (2001), Wissing and Müller (2003), Lippacher et al. (2004), Arica et al. (2006), Huang and Moriyoshi (2008)
Nanoemulsions, nanosuspensions, nanodispersions	Tagekami et al. (2008), Piao et al. (2008), Tahara et al. (2008), Klang et al. (2011)

SEs can also be used to form various *vesicles* as drug delivery systems. For instance, Mollee et al. (2000) prepared stable reversed vesicles in oil by using sucrose palmitate as surfactant. These vesicles exhibited high encapsulation efficiencies for *p*-aminobenzoic acid and cholesterol. Honeywell-Nguyen and Bouwstra (2003) and Honeywell-Nguyen et al. (2003) also prepared vesicles by using SEs. They formed elastic vesicles with sucrose laurate and PEG-8-L as surfactants containing pergolide (2003) or rotigotine (2003) for transdermal delivery.

Miyazaki et al. (2006) prepared *microspheres* by an emulsion solvent evaporation process, with DK-F10 (0:5:11:84 Mono:Di:Tri:Polyester, HLB: 1) as emulsifier. Youan et al. (2003) also used the SEs, DK-F50 (34:46:17:3 Mono:Di:Tri:Polyester, HLB: 6), DK-F70 (39:45:12:4 Mono:Di:Tri:Polyester, HLB: 8), DK-F110 (52:36:10:2 Mono:Di:Tri:Polyester, HLB: 11), DK-F140 (61:30:7:2 Mono:Di:Tri:Polyester, HLB: 13) and DK-F160 (72:23:5:0 Mono:Di:Tri:Polyester, HLB: 16) as surfactants in a solvent evaporation method to prepare microparticles. Their results revealed that, at 0.05% (w/v) surfactant concentration, SEs with HLB values of 6–15 furnished discrete and spherical microparticles with higher encapsulation efficiency as compared with the controls, polyvinyl alcohol and Poloxamer 188. The same group also described a spray-drying technique involving the use of SEs to form microparticles (Youan, 2004). With this method superoxide dismutase was efficiently encapsulated into biodegradable microparticles.

SEs can also be used to stabilize aqueous *suspensions*. Yokoi et al. (2005) demonstrated that SEs inhibited the crystal growth and nucleation of amorphous cefditoren pivoxil, which improved the physicochemical stability of the suspension.

There has recently been great interest in the formation of various *nanosystems* in pharmaceutical technology. SEs can be used as emulsifiers, and as stabilizing agents in nanoemulsions, in nanosuspensions, or in solid lipid nanoparticles (SLNs). The electrolyte and pH stabilities of SE-containing SLNs were examined by Zimmermann and Müller (2001). Wissing and Müller (2003) prepared a sucrose stearate-containing SLN and investigated its effects *in vivo*. Lippacher et al. (2004) utilized sucrose stearate as an

emulsifier in SLNs. They developed a semisolid product which provides a new opportunity for topical delivery through use of the SLN system. SE-containing lipid nanoparticles can additionally be prepared by solvent injection or ultrasound emulsification (Arica et al., 2006). Piao et al. (2008) formulated a solid-in-oil nanosuspension for the transdermal delivery of diclofenac sodium, using SEs ER190 (sucrose erucate, 0% monoester, HLB:1) and ER290 (sucrose erucate, 2% monoester, HLB: 2). Tagekami et al. (2008) applied SEs in a lipid nanoemulsion for stability enhancement. The hydrophobic sucrose erucate was used as a surfactant to prepare a solid-in-oil nanodispersion for transcutaneous protein delivery (Tahara et al., 2008). Huang and Moriyoshi (2008) concluded that SEs can be applied as stabilizing agents in supercritical technology. They prepared lidocaine nanoparticles and prevented the fast crystal growth of the drug through the addition of sucrose stearate and pH adjustment. An emulsifier system comprising a mixture of SEs is able to form multilamellar liquid crystalline networks which possess an excellent safety profile and display a broad range of formulation applications (Luu et al., 2010). Klang et al. (2011) developed nanoemulsions with improved structure and long-term stability by employing a natural sucrose stearate (S970, 50% monoester, HLB: 9) as sole surfactant. In their study, a thorough comparison between the novel sucrose stearate-based nanoemulsions and the corresponding lecithin-based nanoemulsions revealed that the SE was superior in terms of emulsifying efficiency, droplet formation and physical and chemical stability.

3.2. Bioavailability modification

Currently, the main field of pharmaceutical application of SEs is the modification of bioavailability. In consequence of their wide HLB spectrum, they can influence drug dissolution or drug absorption/penetration in different ways.

3.2.1. Liberation and dissolution modification

3.2.1.1. Dissolution improvement. In the past 20 years, many research articles have been published in which SEs served as drug-liberation and dissolution-modifying agents. The SEs were usually used to increase the release of poorly water-soluble drugs. For example, Obikili et al. (1988) applied Sucroester 7 (sucrose distearate, HLB: 3) to improve the aqueous solubility of canrenone. With cyclosporine as a model drug, solid solutions were prepared with water-soluble SEs (Hahn and Sucker, 1989). The dissolution of sucrose monolaurate and cyclosporine in ethanol and evaporation of the solvent yielded a solid surfactant solution which dissolved readily in water and remained clear when diluted with water in any proportion. Ntawukulilyayo et al. (1993) later evaluated the dissolution rate-enhancing properties of SEs, preparing coprecipitates of nifedipine with various SEs, and with different drug/SE ratios. In the case of the nifedipine:hydrophilic sucrose palmitate 1:14 coprecipitate, although the dissolution rate was dramatically improved, the product was unstable, and the crystallinity progressively increased during storage.

Otsuka and Matsuda (1995) evaluated the effects of cogrinding with the surfactants sodium laurylsulfate, sodium deoxycholate and sucrose stearate on the dissolution behavior of phenytoin. They used the surfactants at 40%, and examined the structure and the dissolution of the products. In the cases of the ground SE-containing products, the drug was in a crystalline state and the solubility was almost the same as that of the physical mixture. The same authors (1998) also studied these surfactants to increase the dissolution of glybuzole. Besides the ground products and physical mixtures, they produced melted products. Co-melting with sucrose stearate S-1670 (monoester: 75%, HLB:16) and cooling resulted in an amorphous glassy solid, the solubility of which at pH 6.8 was 20% higher than that of the physical mixture. Fumihiko and Yoshiharu (1999) evaluated the effects of SEs on the *in vitro* release and physicochemical properties of a ground halopredone acetate mixture with tamarind gum. They used the DK-ester SS (99% monoester) at 0.01, 0.1 or 1%, and observed the most notable improvement in halopredone acetate dissolution when the SE with the highest HLB value was used at 0.1 and 0.01%.

Modified-release ibuprofen microspheres were prepared by using the emulsion solvent diffusion technique (Perumal et al., 1999). Increasing the concentration of the emulsifier SE F-70 decreased the particle size, which contributed to improved drug-release properties. Horoz et al. (2006) used sucrose stearate as dispersing agent in verapamil hydrochloride-containing microspheres. Crodesta F160 was present in their formulation and, due to the high HLB value (15) of this SE, the drug release was increased.

Hydrophilic Sucroester WE15 (sucrose monopalmitate, HLB: 15) was utilized as additive in melt extrusion to enhance the dissolution of 17β-oestradiol hemihydrate (Hülsmann et al., 2000). Combinations of SE (40%) with polymers (30 or 50% PEG 6000, PVP or PVA 64) resulted in a higher enhancement of drug dissolution than SE (90%) without polymers. Marton et al. (2005) applied different hydrophilic (HLB: 16) SEs (S1670 sucrose stearate, 75% monoester, L1695 sucrose laurate, 80% monoester, and M1695 sucrose myristate, 80% monoester) to improve the solubility of the poorly water-soluble spironolactone. They prepared melted and physical mixtures in drug:SE ratios of 1:0.5, 1:1, 1:3, 1:4 and 1:9. The SEs increased the solubility of spironolactone, but there was no significant difference between the properties of physical mixtures and solid-in-solid solution systems. The highest (11-fold) solubility increase was obtained with M1695 in the case of the solid-in-solid solution system, and the lowest with the S1670 physical mixture and solid dispersion. There was a nearly linear relationship between the amount of spironolactone dissolved and the SE concentration. Szűts et al. (2008) prepared meloxicam and diclofenac sodium-containing melted products with different SEs (P1670 sucrose palmitate, 80% monoester, HLB: 16; S970 sucrose stearate, 50% monoester, HLB: 9; and B370 sucrose behenate, 20% monoester, HLB: 3) in 1:1 weight ratio. They concluded that the drugs were positioned in different structural rearrangements in the crystalline phase of the SEs, and built into the amorphous phase. The dissolution of the examined drugs was influenced in different ways by the SEs. The hydrophilic SEs formed gels in aqueous media, and this increased the release of meloxicam. In the case of diclofenac sodium-containing products, the gel-forming properties of the SEs had no effect, due to interactions between the drug and the hydrophilic SEs (Szűts et al., 2010c). The same group also investigated the effects of the preparation on the structure and dissolution of diclofenac sodium-SE (1:1 ratio) products (Szűts et al., 2009). Physical mixtures and solid dispersions prepared by the melt and the solvent methods were compared. It was found that, in the case of the melted products, the drug recrystallized after solidification, and the drug release was similar to that in the case of the physical mixture. On the other hand, the products prepared by the solvent method contained less crystalline drug. After solvent evaporation, part of the diclofenac sodium was in a molecularly dispersed state, which resulted in faster drug release.

Directly-compressed fast-disintegrating furosemide tablets were developed through the use of sucrose stearate (Koseki et al., 2009). The tablets produced by the addition of S1670 at 0.1% (w/w) had excellent properties as concerns hardness and disintegration rate, and exhibited a faster release of furosemide and a higher plasma concentration than those with the commercial tablet Lasix®.

The applicability of hydrophilic sucrose laurate as surfactant in third-generation solid dispersion systems, together with a polymer, was evaluated in 2011 (Szűts et al.). The presence of 1–15% SE did not appear to affect the solid-state characteristics of the model drug

Table 5
Applicability of SEs as drug-release modifiers.

Drug	Formulation	Reference
Canrenone	Melted product	Obikili et al. (1988)
Cyclosporine	Product formed by solvent evaporation	Hahn and Sucker (1989)
Indomethacin	Suppository	Nakajima et al. (1990)
Nifedipine	Coprecipitated product	Ntawukulilyayo et al. (1993)
Ibuprofen	Tablet	Ntawukulilyayo et al. (1995)
Theophylline monohydrate	Tablet	Ntawukulilyayo et al. (1995)
Phenytoin	Ground product, physical mixture	Otsuka and Matsuda (1995)
Glybuzole	Ground product, physical mixture, melted product	Otsuka et al. (1998)
Ibuprofen	Microsphere	Perumal et al. (1999)
Halopredone acetate	Ground product, physical mixture	Fumihiko and Yoshiharu (1999)
17-β-Oestradiol hemihydrate	Tablet from melt extrudate	Hülsmann et al. (2000)
Theophylline	Matrix tablet from melt extrudate	Seiler et al. (2005)
Spironolactone	Physical mixture, melted product	Marton et al. (2005)
Verapamil hydrochloride	Microsphere	Horoz et al. (2006)
Cromolyn sodium	Proniosome-derived niosome	Abd-Elbary et al. (2008)
Meloxicam	Melted product	Szűts et al. (2008)
Diclofenac sodium	Physical mixture, melted product, product formed by solvent evaporation	Szűts et al. (2008, 2009, 2010c)
Indomethacin	Solid lipid microparticles	Erdal et al. (2009)
Furosemide	Directly-compressed fast-disintegrating tablets	Koseki et al. (2009)
Paracetamol	Physical mixture	Szűts et al. (2010a,b)
Metoprolol tartrate	Directly compacted matrix tablets	Chansanroj and Betz (2010)
Gemfibrozil	Melted product	Szűts et al. (2011)
Vitamins	Granules prepared by wet granulation, melt granulation or compression and grinding	Seidenberger et al. (2011)

gemfibrozil significantly. Sucrose laurate in concentrations below 200 μg/ml resulted in prompt drug release without a toxic effect on human epithelial Caco2 cells.

3.2.1.2. Sustained/controlled release. There has recently been great interest in the use of SEs as controlled-release agents in various drug delivery systems. Table 5 lists the different drugs and dosage forms where SEs were used as liberation and dissolution-modifying agents.

In 1990, Nakajima et al. prepared sustained-release indomethacin suppositories, with SE as additive. They concluded that an appropriate content of SE (*i.e.* 30%) in the suppository base was required to achieve sustained release because it reasonably regulated the infiltration of rectal fluid into the suppository and the mechanical strength of the suppository against disintegration.

Later, SEs were used in matrix tablets to influence drug release by Ntawukulilyayo et al. (1995). Their products contained different SEs (S-170 sucrose stearate, 1% monoester, HLB: 1; S-770 sucrose stearate, 40% monoester, HLB: 7; S-1570 sucrose stearate, 70% monoester, HLB: 15; and P-1570 sucrose palmitate, 70% monoester, HLB: 15) and ibuprofen or theophylline monohydrate as drugs. They observed H-bond formation between the filling agent microcrystalline cellulose and the hydrophilic SEs, and supposed that this can cause the slow release of the drug. Seiler et al. (2005) used a hydrophilic SE, sucrose stearate S-1670, as controlled-release matrix-forming agent in the case of theophylline.

Sucrose stearates D-1811 (HLB: 11) and D-1816 (HLB: 16) were also applied in the formulation of controlled-release proniosome-derived niosomes by Abd-Elbary et al. (2008). They found that the combination D-1811:cholesterol:stearylamine in 7:3:0.3 molar ratio was a promising drug carrier for the nebulizable delivery of cromolyn sodium. Erdal et al. (2009) prepared solid lipid microparticles of indomethacin. Their *in vitro* drug release studies demonstrated that indomethacin release was prolonged when Sucroester® WE15 was present as surfactant in combination with Compritol® 888 ATO as lipid matrix material. They concluded that Sucroester® WE15 may serve as an alternative surfactant in the development of lipid microparticles for the controlled oral delivery of indomethacin.

Szűts et al. (2010a) evaluated the gelling characteristics of two different SEs (P1670 and S970) by rheological measurements, and the effects of the gel-forming SEs on paracetamol release in *in vitro* studies. The results revealed that the gelling of the SEs is temperature- and concentration-dependent. The examined sucrose stearate (S970) had a stronger gel structure than that of sucrose palmitate (P1670) and this exerted a significant effect on the sustained release of the drug. In a later work by the same group, the gelling properties of different hydrophilic sucrose stearates (S970, S1170, S1570 and S1670) were evaluated (Szűts et al., 2010b). It was concluded that 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, undergo more concentration-dependent gelling, and have a greater potential for controlling the rate of release of drugs relative to those with higher HLB values.

Chansanroj and Betz (2010) used different SEs (sucrose stearates with HLB <1, 1, 3, 5, 9, 11, 15 and 16: S070, S170, S370, S570, S970, S1170, S1570 and S1670) as controlled-release agents for direct compacted matrix tablets containing metoprolol tartrate as a highly soluble model drug. Their study focused on the effects of the hydrophilic–lipophilic characteristics on tableting properties and drug release. Larger amounts of monoesters with increasing hydrophilicity resulted in enhanced porosity, elastic recovery and tensile strength of the matrix tablets, and also facilitated swelling behavior that retarded drug release. Several types of SEs were studied as matrix formers in granules prepared by wet granulation, melt granulation or compression and grinding by Seidenberger et al. (2011). They concluded that SE- or triglyceride-based granules can be used for the simultaneous control of the release of multiple vitamins (nicotinamide, pyridoxine hydrochloride, riboflavin 5′-phosphate, thiamine chloride, hydrochloride, thiamine nitrate and riboflavin) that exhibit very different water-solubilities and molecular weights.

3.2.2. Absorption and penetration enhancement

Besides the modification of drug dissolution, other properties of SEs result in interactions with biological barriers, and their effects on absorption and penetration are therefore widely investigated. Table 6 lists model drugs, dosage forms and potential fields of application of SEs as absorption and penetration enhancers.

3.2.2.1. Skin permeability enhancement. The skin permeation behavior of SEs is evaluated mostly in solution dosage forms, microemulsion systems and recently transdermal therapeutic

Table 6
Applicability of SEs as absorption enhancers.

Drug	Formulation	Application field	Reference
Cyclosporine A	Solution	Oral	Lerk and Sucker (1993a)
Cyclosporine A	Hydrogel	Dermal	Lerk and Sucker (1993b)
Oestradiol	Hydrogel	Dermal	Vermeire et al. (1996)
Lidocaine hydrochloride	Solution	Oral	Ganem Quintanar et al. (1998)
Niflumic acid	Microemulsion	Dermal	Bolzinger et al. (1998)
Hydrocortizone	Microemulsion	Dermal	Lehmann et al. (2001)
4-Hydroxybenzonitrile	Solution	Dermal	Ayala-Bravo et al. (2003)
Insulin	Solution	Nasal and ocular	Ahsan et al. (2003)
Calcitonin	Solution	Nasal and ocular	Ahsan et al. (2003)
Lidocaine	Solution	Dermal	Okamoto et al. (2005)
Ketoprofen	Solution	Dermal	Okamoto et al. (2005)
Lidocaine hydrochloride	Solution	Dermal	Cázares-Delgadillo et al. (2005)
Daunomycin	Solution	Oral	Takaishi et al. (2006)
Octyl methoxycinnamate	O/w emulsion, nanoemulsion, nanocapsule	Dermal	Calderilla-Fajardo et al. (2006)
Metoprolol	TTS patch	Dermal	Csóka et al. (2007)
Timolol maleate	TTS patch	Dermal	El-Laithy (2009)
Propofol	Solution	Dermal	Yamato et al. (2009)
Ibuprofen	Hydrogel	Dermal	Csizmazia et al. (2011, 2012)
Vinpocetin	Proniosomal formula	Dermal	El-Laithy et al. (2011)

system as TTS patches. For example, Lerk and Sucker (1993b) reported that sucrose laurate has intermediate skin permeability-enhancing properties and proposed that this SE is a suitable, non-irritating excipient for the dermal formulation of the poorly water-soluble cyclosporine A. Sucrose laurate hydrogels were formulated and investigated as a percutaneous delivery system for oestradiol in rabbits (Vermeire et al., 1996). In that study, sucrose laurate was an effective absorption enhancer for percutaneous drug delivery.

Bolzinger et al. (1998) prepared a bicontinuous SE microemulsion to enhance the bioavailability of niflumic acid. The microemulsion system, which contained 3.2% sucrose monolaurate and 14.8% sucrose dilaurate, was compared with the commercially available Nifluril® ointment. Their results showed that the microemulsion containing 1% niflumic acid was as effective as Nifluril® ointment containing 3% niflumic acid. Lehmann et al. (2001) also studied SE-containing microemulsions. Two SEs were used as surfactant/cosurfactant: sucrose laurate L-595 (HLB: 5) (6%) and L-1695 (HLB:16) (12%). Their microemulsion exhibited an increased transepidermal water loss and significant stratum corneum dehydration. They additionally evaluated the impact of the microemulsion on hydrocortisone (0.5%) penetration and found that their SE-containing product produced a demonstrable drug penetration as compared with Basiscreme (Deutscher Arzneimittel Codex), but caused significant irritative skin redness.

The effects of SEs on the permeability of the human stratum corneum and on the percutaneous penetration of 4-hydroxybenzonitrile were investigated by Ayala-Bravo et al., 2003. They examined the hydrophilic sucrose oleate O-1570 (HLB: 15) and sucrose laurate L-1695 (HLB: 16) in water or in Transcutol®. Treatment of the skin with 2% SE in Transcutol® significantly increased the extent of 4-hydroxybenzonitrile penetration relative to the control. When skin treated with these formulations was examined spectroscopically, the C—H asymmetric and symmetric stretching bands of the lipid methylene groups were characterized by decreased absorbances and frequency shifts to higher wavenumbers. These effects on the stratum corneum lipids and 4-hydroxybenzonitrile penetration were more pronounced for sucrose laureate when it was combined with Transcutol®. These results showed that the combination of SEs and Transcutol® can temporarily alter the stratum corneum barrier properties, thereby promoting drug penetration.

Okamoto et al. (2005) examined the effects of different SEs on the transdermal permeation of lidocaine and ketoprofen. They found that sucrose laurate with an HLB value of 16 increased the permeation of ionized lidocaine from an aqueous vehicle. On the other hand, sucrose laurate with an HLB value of 5, which was not reported earlier as an absorption enhancer, increased the permeation of lidocaine and ketoprofen from propylene glycol. Sucrose laurate and sucrose oleate in Transcutol® were evaluated as permeation enhancers for the percutaneous penetration of lidocaine hydrochloride, a charged molecule, as a function of ionization (Cázares-Delgadillo et al., 2005). The results suggested that sucrose laurate enhanced the penetration of the ionized form of the drug, causing a 12-fold greater flux relative to the control, whereas sucrose oleate was more effective in promoting permeation of the unionized species. The structural properties of the SEs and the degree of ionization of the drug are important characteristics affecting the transdermal flux of lidocaine.

The influence of sucrose laurate and sucrose oleate on the *in vivo* percutaneous penetration of octyl methoxycinnamate formulated in colloidal suspensions (nanoemulsions and nanocapsules), and conventional o/w emulsions were studied by Calderilla-Fajardo et al. (2006). The results indicated that nanoemulsions formulated with sucrose laurate exhibited higher penetration than that of other formulations in the stratum corneum. The total amount of octyl methoxycinnamate detected in the stratum corneum and the penetration depth were strongly dependent upon the nature of the formulation, the particle size and the type of enhancer.

Transdermal therapeutical systems containing different SEs (S-370, S-970, S-1670, P-1670, M-1695 and L-1695) were prepared and investigated by Csóka et al. (2007). Their results revealed that all types of tested SEs enhanced drug release. SEs with shorter fatty acid chain lengths and higher HLB values increased the amount of metoprolol released ~10-fold. The HLB value and the length of the fatty acid chain significantly influenced the *in vitro* drug release and also the absorption process. El-Laithy (2009) examined SEs as transdermal delivery agents. On the basis of *in vitro*, skin permeation and clinical results, a timolol maleate–sucrose laurate (1.5%) TTS patch was successfully used for controlled transdermal timolol maleate delivery, where the steady-state plasma drug level was achieved with improved bioavailability and negligible skin irritation. To increase the transdermal delivery of propofol, several penetration enhancers were studied by Yamato et al. (2009), who investigated four kinds of SEs (L595, L1695, O1570 and S1570), both alone and in combination with other enhancers, such as propylene glycol, isopropyl myristate, macrogol, L-menthol, D-limonene, oleic acid and stearic acid. SEs combined with propylene glycol were more effective in increasing permeation than SEs alone.

The proniosomal-controlled transdermal delivery of vinpocetin was examined by El-Laithy et al. (2011). Different SEs (S-1670, S-970, S-370, P-1670, M-1695 and L-1695) were incorporated as permeation and absorption enhancers in the systems. Sucrose laurate proniosomes could be considered very promising candidates as absorption and penetration enhancers for the delivery of vinpocetin transdermally. One patch containing the same drug load as one commercial tablet preserved a plasma concentration in excess of the minimum effective concentration for 48 h and would be able to replace 6 commercial tablets, thereby improving patient compliance and ensuring a better clinical outcome.

The enhancer effect of sucrose laurate (S-1670) was compared with that of Transcutol® on ibuprofen penetration by Csizmazia et al. (2011). They concluded that SE can increase the skin penetration and permeation of ibuprofen efficiently, and Transcutol® leads to ibuprofen accumulation in the stratum corneum, thereby ensuring sustained drug release. The same group investigated the skin penetration-enhancing effect of sucrose laurate in an ibuprofen-containing hydrogel and examined its influence on the special lipid bilayer of the stratum corneum (Csizmazia et al., 2012). The degree of moisturization and penetration was more intense in the case of the ibuprofen-SE gel treatment as compared with an ibuprofen gel without SE. The sucrose laurate-containing gel did not cause greater alterations in the stratum corneum structure than the ibuprofen gel without sucrose laurate. It has been proven that SE acts as an effective hydration enhancer and increases the penetration of ibuprofen through the skin.

3.2.2.2. Oral absorption enhancement. Sucrose laurate enhanced the absorption of cyclosporine A in an *ex vivo* experiment involving the use of normal gut epithelial tissue and Peyer's patch tissue of guinea pigs (Lerk and Sucker, 1993a). The absorption of cyclosporine A was superior to that of the commercially available drinking solution. Two different regions of the oral mucosa, the pig palate (keratinized) and cheek (non-keratinized), were used for the study of *ex vivo* permeation of lidocaine hydrochloride (Ganem Quintanar et al., 1998). Four hydrophilic SEs (S-1670, O-1570, P-1670 and L-1695) were compared with other enhancers, such as ethanol, oleic acid and Transcutol®. Among the SEs tested, only sucrose laurate (L-1695, 1.5%) was able to increase the passage of lidocaine through the buccal and palatal mucosae, with an enhancement ratio of 22 for the buccal and 14 for the palatal mucosa.

The effects of SEs are also investigated in cell culture models. Food emulsifiers including SEs were studied on the activity of the P-glycoprotein drug efflux pump of human intestinal Caco-2 cells (Takaishi et al., 2006). The cellular accumulation of daunomycin, a P-glycoprotein substrate, was markedly enhanced by SEs. The results showed that this enhanced accumulation was not due to P-glycoprotein inhibition, but rather to the increased daunomycin permeability of the cell membranes that was induced by the emulsifiers. In the evaluation of the potential of the use of SEs as oral absorption enhancers (Kis et al., 2010), water-soluble SEs (L-1695 sucrose laurate; M-1695 sucrose myristate; and P-1695 sucrose palmitate; HLB: 16) were tested for toxicity and paracellular permeability with the Caco-2 cell line model. In agreement with our previous findings (Szűts et al., 2011), L-1695 at a concentration of 200 μg/ml significantly reduced the transepithelial electrical resistance and increased the paracellular transport of the marker molecule fluorescein in Caco-2 cell layers without changing the immunostaining of tight junctions, indicating its possible use as an absorption enhancer in oral formulations.

3.2.2.3. Nasal and ocular absorption enhancement. Sucrose cocoate SL-40 (HLB: 15), which contains a mixture of SEs of coconut fatty acids in aqueous ethanol solution, was examined for nasal and ocular adsorption (Ahsan et al., 2003). In order to determine its potential utility in enhancing nasal and ocular drug delivery, absorption studies were performed on anaesthetized male Sprague–Dawley rats with calcitonin and insulin, two distinct therapeutic peptides. Administration of a nasal and ocular insulin formulation containing 0.5% sucrose cocoate caused a significant increase in plasma insulin levels, with a concomitant decrease in blood glucose levels. Administration of a nasal calcitonin formulation containing 0.5% sucrose cocoate caused a rapid increase in plasma calcitonin levels and a concomitant decrease in plasma calcium levels, while ocular administration of 2.2 U calcitonin formulated with 0.5% sucrose cocoate led to smaller changes in plasma calcitonin and calcium levels, which did not reach statistical significance. The most abundant SE in sucrose cocoate was sucrose monododecanoate, with smaller amounts of sucrose monotetradecanoate. *In vivo* experiments confirmed that SEs containing acyl chains of 12–14 carbons were the most effective enhancers of nasal peptide drug absorption.

The effects of SEs were also studied on a cell culture model of the nasal barrier (Kürti et al., 2012). Laurate (D-1216) and myristate (M-1695) SEs and reference non-ionic surfactants Tween 80 and Cremophor RH40 were investigated on RPMI 2650 human nasal epithelial cells for the first time. The results indicated that laurate and myristate SEs can be potentially used as permeability enhancers in nasal formulations to augment drug delivery to the systemic circulation.

4. Regulatory and toxicological status of SEs

SEs are approved as food additives (E473) and are widely used in the food industry. In 1992, the Scientific Committee for Food established an acceptable daily intake (ADI) of 0–20 mg/kg bw/day for SEs of fatty acids and sucroglycerides derived from palm oil, lard and tallow fatty acids. In 2004, in the light of new studies, the European Food Safety Authority (EFSA) re-examined the safety of these food additives and established a group ADI of 40 mg/kg bw/day for SEs of fatty acids. Sucrose laurate was not considered in that evaluation, but the EFSA (2010) recently pointed out that the current specifications should be changed to include sucrose laurate.

As SEs are often used in various food products, their absorption, distribution and metabolism have been thoroughly evaluated (Daniel et al., 1979; Shigeoka et al., 1984; Noker et al., 1997). The results showed that the SEs are hydrolysed to sucrose and fatty acids prior to intestinal absorption, the extent of the hydrolysis depending on the degree of esterification of the SE. The higher fatty acid esters of sucrose, such as the octa- and hepta-esters (*e.g. Olestra*), are not absorbed by humans and are excreted unchanged, while the lower esters are partially hydrolysed and absorbed as sucrose and individual fatty acids.

Daniel et al. (1979) studied the metabolism of sucrose mono- and diesters of beef tallow in rats and showed that these esters were hydrolysed to sucrose and fatty acids before absorption and did not accumulate in the tissues following repeated exposure. The metabolism of sucrose stearate and sucrose palmitate was examined in rats by using SEs labeled with ^{14}C in the sucrose or fatty acid moiety (Shigeoka et al., 1984). This study also confirmed that the SEs must be hydrolysed to free fatty acids and sucrose prior to absorption. Radio-labeled sucrose stearates with different esterification degrees (sucrose tetra-, hexa- and octastearates) were evaluated for absorption in rats (Noker et al., 1997). The amount of radioactivity absorbed was greatest for the tetraester, and the extent of absorption and the metabolism of the radioactivity were inversely related to the degree of esterification.

The tolerability of SEs has been confirmed in animal tests. The oral toxicity and carcinogenicity of sucrose stearate S-570 were evaluated by Takeda and Flood (2002). A 13-week and a 2-year

Table 7
SEs in pharmaceutical products according to the FDA Inactive Ingredients Database.

Sucrose ester	Route; dosage form	Maximum potency[a]
Sucrose palmitate	Oral: powder, for suspension	1%
Sucrose polyesters	Topical: powder, for solution	0.125%
Sucrose stearate	Oral: capsule, extended release	31.835 mg
Sucrose stearate	Oral: capsule, sustained action	44.569 mg
Sucrose stearate	Oral: tablet, extended release	44.56 mg
Sucrose distearate	Topical: emulsion, cream	5%

[a] The maximum amount of inactive ingredient for each route/dosage form.

feeding study were conducted on Fischer 344/DuCrj rats, during which S-570 was fed at 0, 1, 3 or 5% (w/w) of the diet. There were no SE-related effects on survival, tumor incidence, ophthalmological or hematological findings, clinical chemistry, organ weights or histopathology. Sucrose stearate S-170 was also studied in F344 rats (Yoshida et al., 2004). Dietary S-170 was given *ad libitum* at levels of 0, 1.25, 2.5 or 5% to rats to determine chronic toxicity, and at 0, 2.5 or 5% in the carcinogenicity study. Their results clearly demonstrated that these SEs display neither toxic nor carcinogenic activity in F344 rats under the conditions of the study.

The toxicity data on SEs in animal models and in humans were recently surveyed by Drummond et al. (2005). The results of acute toxicity studies in animals demonstrated that no significant toxic events were associated with the oral ingestion of SEs, except when lard and tallow SEs were administered in a high dose (10 g/kg) to rats. Attention was drawn to the positive haemolytic results when sucrose monopalmitate was administered intravenously to the rat. Conversely, the palm oil SEs did not exhibit haemolytic activity. The various data collected by Drummond et al. did not reveal any effects on the reproduction of the animals in long-term oral ingestion studies, and there was no evidence of increased levels of tumors or other abnormalities. Human data were also collected in the review and the authors concluded that the ADI level of SEs (which was adjusted by the WHO to 0–30 mg/kg in 1998) indicates the general safety of SEs.

SEs based on palmitic/stearic acid or on lauric acid are registered in the Japanese Standards of Cosmetic Ingredients. Most of the SEs (*e.g.* sucrose stearate, palmitate, oleate, cocoate and myristate) are also registered in the Cosmetics Directive of the European Union, and can therefore be used in cosmetics and personal care products marketed in Europe.

In the pharmaceutical field, commercial products may contain SEs for different reasons. Besides their emulsifying, solubilizing and bioavailability-modifying behavior, SEs with low or medium HLB values are applicable excipients for lubrication (Shibata et al., 2002; Surfhope SE Pharma, 2002). In Japan and the US SEs are often applied in oral, external and dental use. In Europe, SE-containing products are available mainly on the German and French markets. Some SEs have a Drug Master File, and sucrose stearate and sucrose palmitate are featured in the European Pharmacopoeia (Ph. Eur.) and in the United States Pharmacopeia/National Formulary (USP NF), confirming their human applicability. As sucrose stearate and sucrose palmitate are registered in Pharmacopoeias, these SEs are increasingly used in pharmaceutical products. The FDA Inactive Ingredients Database lists sucrose stearate and sucrose palmitate in oral dosage forms, and sucrose distearate and sucrose polyesters for administration by the topical route (Table 7).

5. Conclusions

SEs have a wide range of applications in different areas of drug delivery and in the pharmaceutical industry because of their surfactant and other versatile properties. This article has given an overview of the use of SEs as excipients in pharmaceutical technology for emulsification, as lubricants, for the production of controlled-release solid dosage forms, for the improvement of drug dissolution, and for the enhancement of absorption. These properties make SEs exciting and promising excipients in the development of dosage forms for different applications, in spite of the fact that their applicability largely depends on their regulatory and toxicological status.

It is important to note that the ADI of SEs has been re-examined several times and increased during the years from 0 to 20 mg/kg bw/day in 1992 to 40 mg/kg in 2004. This trend may be related to the available data on the metabolism, toxic and carcinogenic activity of SEs. These esters are hydrolysed to sucrose and fatty acids before absorption, and the extent of their absorption and metabolism are inversely related to the degree of esterification. Animal studies have demonstrated that the SEs display neither toxic nor carcinogenic activity and can be considered safe excipients in topical and oral formulations. However, the positive haemolytic result observed for intravenously injected sucrose monopalmitate indicates that further *in vivo* and cell culture studies are needed to establish the safety and applicability of SEs as concerns other formulations and administration routes.

Some SEs have a Drug Master File, and sucrose stearate and sucrose palmitate are registered in Pharmacopoeias both in the European Union and in the United States. The FDA Inactive Ingredients Database lists different SEs, with the maximum potency for each route/dosage form. This collection includes the sucrose stearate and sucrose palmitate, which are suggested for oral dosage forms, and sucrose distearate and sucrose polyesters, for administration by the topical route.

The use of SEs as innovative excipients in pharmaceutical technology is expected to increase further. Although SEs are of great potential as pharmaceutical ingredients, additional investigations are needed to extend their applicability in novel formulations and in new delivery routes.

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