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Report

Solid Surfactant Solutions of Active Ingredients in Sugar Esters

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This paper describes the preparation of solid solutions of ciclosporin as model solubilizate in water-soluble sugar esters, which are solid, biodegradable, and nontoxic surfactants. Sugar esters were found to be excellent solubilizers for poorly water-soluble drugs such as ciclosporin. Such systems are suitable for the preparation of solid dosage forms for the purpose of oral administration. Addition of water to the solid solutions yields clear solutions of the solubilizate.

KEY WORDS: sugar esters; solubilizers; solid surfactant solution; surfactants, biodegradable; ciclosporin.

INTRODUCTION

The oral bioavailability of poorly water-soluble drugs may be reduced because of slow dissolution in the aqueous medium of the gastrointestinal tract. It is difficult to find water-soluble excipients that completely dissolve active ingredients after addition of water, maintain the solution for long periods even upon dilution, do not impair absorption, and are nontoxic.

Current efforts focus on the preparation of soluble, solid dosage forms of poorly soluble drugs. Thus far, only semisolid or liquid dosage forms are available with the common solubilizers. The sugar esters are surfactants which are solid at room temperature. Experiments were conducted to ascertain whether this class of surfactants could serve as suitable solubilizers, in particular for ciclosporin, and whether combinations with them could be used for production of solid oral dosage forms which would dissolve readily in water.

MATERIALS AND METHODS

Materials

The solubilizers employed were sucrose and raffinose esters of saturated and unsaturated fatty acids (Fig. 1). They are water-soluble at room temperature if they contain at least 90% monoester. The sugar esters investigated (Table I) were synthesized by the ester interchange method of Osipow (1) in our laboratories and were purified by column chromatography. The obtained sugar esters contained at least 95% monoester. The model solubilizate used was ciclosporin (Sandimmun, Sandoz Ltd., Basle, Switzerland). The water solubility of ciclosporin is very low—0.04 mg/ml at 25°C.

Preparation of the Solid Surfactant Solution

When used as solubilizers for active ingredients, polyethylene glycol and polyvinylpyrrolidone are converted to solid dispersions by the melt method or the dissolution method (2). Our solid surfactant solutions were prepared in an analogous manner.

Dissolution of the sugar ester and the active ingredient in ethanol and evaporation of the solvent yielded a loose particulate hygroscopic solid residue; hence this method was preferred to the melt method. In order to obtain clear solutions of the solubilizate on addition of water to the solid surfactant solution, the solubilizing capacity was determined for each sugar ester. Dissolution of 100 parts sucrose monolaurate and 16 parts ciclosporin in ethanol and evaporation of the solvent yielded a solid surfactant solution which dissolved readily in water without being heated. The resultant solution remained clear when diluted with water in any proportion. The active ingredient did not separate from the solution for at least 4 months. The aqueous solution of the solubilizate obtained by dissolution of the solid surfactant solution exhibited newtonian flow properties.

Determining Solubilizing Capacity

Surfactant solutions of a series of concentrations from 1 to 20% were prepared. In each experiment, 10 ml surfactant solution was agitated with a magnetic stirrer during stepwise addition of 10-mg portions of solubilizate; further additions were made only after the previous 10-mg portion had fully dissolved. The solubilizing capacity was defined as the maximum concentration of solubilizate [mg/ml], which would yield a clear solution, remaining clear for at least 3 hr at

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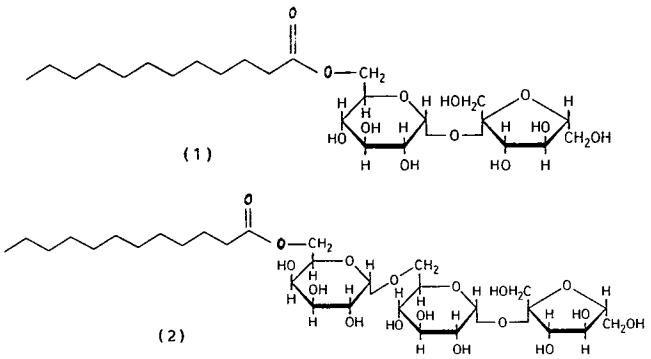

Fig. 1. Structural formulae of sucrose monolaurate (1) and raffinose monolaurate (2).

room temperature. The precision of this method of determining solubilizing capacity at room temperature was ±1 mg/ml. For all the sugar esters investigated the solubilizing capacity was directly proportional to the surfactant concentration. Table II shows the quantities of ciclosporin which could be dissolved in sucrose monolaurate solutions of various concentrations at room temperature. Table I lists the water-soluble sugar esters and their solubilizing capacities for ciclosporin. Table III shows the solubilizing capacities of sucrose monolaurate for other model substances from which solid surfactant solutions could also be prepared.

Whether ciclosporin was added to an aqueous sucrose monolaurate solution or solid surfactant solutions were prepared by the melt or dissolution method, the same solubilizing capacity was found in all three cases: 100 parts sucrose monolaurate solubilize 16 parts ciclosporin.

Proof of Solid Solution

A solid surfactant solution of ciclosporin prepared by the dissolution method in ethanol was investigated by Guinier–de Wolff X-ray structural analysis (3). The X-ray diagram showed that the ciclosporin and the sugar ester were present in a completely amorphous state; no lines were present in the diagram (4).

In the dissolution rate study ciclosporin completely dissolved in water, which again indicates the presence of a solid solution (5).

Conversion to Solid Dosage Forms

Preparation of the solid surfactant solution by the dissolution method yields a free-flowing powder which can be mixed in any required proportion with magnesium stearate as lubricant or with other excipients. Care must be taken to maintain dry working conditions, since the sugar esters are hygroscopic. Solid surfactant solutions prepared from sucrose monolaurate and ciclosporin are suitable for direct tableting; they can also be handled in liquid form as suspensions in liquid paraffin for filling hard gelatine capsules (6).

Table I. Solubilizing Capacity of Water-Soluble Sugar Esters (10% Solution) for Ciclosporin at Room Temperature

Hydrophilic residue	Lipophilic residue	Solubilizing capacity (mg/ml)
Sucrose	Monocaprate C10	12
	Monolaurate C12	16
	Mono-oleate C 18 II	25
Raffinose	Monolaurate C12	13
	Mono-oleate C 18 II	20

Table II. Solubilizing Capacity of Sucrose Monolaurate Solutions of Various Concentrations for Ciclosporin at Room Temperature

Concentration of sucrose monolaurate in water (%)	Solubilizing capacity for ciclosporin (mg/ml)
1	1.5
3.5	5.5
5	8
6.5	10
8	13
10	16
15	24
20	32

RESULTS AND DISCUSSION

Most water-soluble surfactants have a fluid or semisolid consistency at room temperature, and their use is therefore limited to liquid dosage forms. The water-soluble sucrose and raffinose monoesters, on the other hand, have the advantage of being solid at room temperature. Patient compliance is improved by the availability of an oral dosage form employing a solid surfactant solution based on the tasteless sugar esters. Esters of sugars with straight-chain aliphatic monocarboxylic acids are the only known nonionic, 100% biologically degradable surfactants derived from natural products (7). They are nontoxic by the oral route and, in many countries, are permitted food additives (8–10). They are therefore suitable for use as the excipient matrix in solid surfactant solutions of all solid drugs on which they have a solubilizing effect.

Because of the improved solubility of ciclosporin in the solution obtained by addition of water to the solid surfactant solution with sucrose monolaurate, it was hoped that the active ingredient would be completely absorbed *in vivo*, resulting in improved bioavailability. This hypothesis was investigated in rats receiving radioactively labeled ciclosporin by the oral route. The bioavailability of ciclosporin in the form of solid surfactant solution was 26% greater than in the form of Sandimmun, the commercially available oral solution.

Table III. Solubilizing Capacity of Sucrose Monolaurate for Various Model Substances

Model solubilizate	Solubilizing capacity of a 10% aqueous solution of sucrose monolaurate (mg/ml)
Proquazone	3
Progesterone	3
Isradipine	0.5
Methyl *p*-hydroxybenzoate	8

Although the intermolecular bonding between ciclosporin and sugar ester in the solid solution may be increased, the dissolution rate was rapid. The good solubility is attributed to the surfactant as solvent in the solid solution. To emphasize this point, the preparation was labeled a solid surfactant solution. The structural state is that of a solid solution with a surfactant as solvent which forms a real micellar solution after the addition of water.

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