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Stabilisation of suspensions using sucrose esters and low substituted *n*-octenylsuccinate starch-xanthan gum associations.

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Abstract

The crystal growth inhibition capacity of sucrose esters and *n*-octenylsuccinate starch in comparison with Tween 80 and Tween 20 was evaluated in suspensions containing paracetamol as a model drug. The sucrose esters performed slightly better in comparison with the sorbitan derivatives as crystal growth inhibitors. The lowest concentration (0.1% w/v) of *n*-octenylsuccinate starch inhibited crystal growth over a 1 year period and was even as effective as the sucrose esters. Only the suspension prepared with *n*-octenylsuccinate starch at a concentration above 0.2% w/v did not show the presence of large paracetamol crystals sticking to the glass wall. The association of xanthan gum and *n*-octenylsuccinate starch showed specific visco-elastic properties and crystal growth inhibition and offers new perspectives in the preparation of suspension formulations.

Keywords: Suspension stabilisation; Crystal growth inhibition; Sucrose esters; *n*-Octenylsuccinate starch; Xanthan gum

1. Introduction

The formulation of pharmaceutical suspensions is often associated with problems of physical stability such as the difficulty of redispersability of the sediment and crystal growth (Zatz 1985; Akers et al., 1987). The redispersability of suspensions is associated with flocculation-deflocculation behaviour of drugs and the polymer-induced flocculation has been of great interest since most pharmaceutical suspensions contain polymers as suspending agents (Tempio and Zatz, 1980; Duro et al., 1993). Crystal growth in aqueous suspensions may cause a drastic change in the particle size distribution. This change might affect bioavailability and physical stability of suspensions. A number of additives such as polymers and surfactants have been proposed to prevent crystal growth (Simonelli et al., 1970; Motawi et al., 1982). Formulations with drugs showing a certain water solubility particularly cause stability

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problems. This study reports on the use of sucrose esters as crystal growth inhibitors and on the advantages of *n*-octenylsuccinate starch-xanthan gum associations as suspension stabilising agents. Paracetamol was used as the model drug.

2. Materials and methods

2.1. Materials

Paracetamol was purchased from Bufa-Chemie (Frankfurt, Germany), P1570 a palmitate sucrose ester (HLB 15) and S1670 a stearate sucrose ester (HLB 16) were received from Ryoto Co. (Mitsubishi-Kasei Food Corp., Tokyo, Japan). The *n*-octenylsuccinate ester of waxy corn starch with a degree of substitution below 0.03 (CL490) was kindly provided by Cerestar (Vilvoorde, Belgium). Tween 20 (HLB 16.7), Tween 80 (HLB 15) and xanthan gum were purchased from Flandria (Zwijnaarde, Belgium) and Rhône Poulenc (Brussels, Belgium), respectively.

2.2. Methods

All suspensions investigated contained paracetamol 6% (w/v) and 0.5% (w/v) xanthan gum. Methylparaben (0.04% w/v) and propylparaben (0.01% w/v) were used as preservative agents. The tensioactive agents (sucrose esters and Tween) were all used in a concentration of 0.2% (w/v). The *n*-octenylsuccinate starch was used in a concentration range between 0.1% and 6% (w/v). During the suspension preparation the tensioactive agents or the starch derivatives were initially dispersed in water containing the preservative agents. Next, the paracetamol and xanthan gum were added and dispersed using a Silverson Mixer (Waterside, Chesham, UK).

Finally the suspensions were transferred to stoppered 250-ml graduated glass cylinders and stored at room temperature under static conditions and under cyclic temperature conditions (12 h at room temperature, 12 h at 4°C) for 1 year while shaking.

2.3. Evaluation of suspensions

2.3.1. Sedimentation volume

The sedimentation volume was measured in 250-ml graduated glass cylinders. Each suspension was shaken to ensure uniformity prior to the sedimentation study. The sedimentation volume was recorded at 0, 2, 6 and 12 months storage time. The Hu/Ho value (ratio between the total suspension volume and the sediment volume) was calculated.

2.3.2. Resuspendability

The resuspendability of a suspension was evaluated qualitatively. The test consisted of manually shaking the cylinder after the sedimentation experiments were completed. Based on the time and the effort required to convert the sediment to homogeneous suspension, the formulations were evaluated.

2.3.3. Particle size determination

The size of 300 paracetamol crystals was determined at 0, 2, 6 and 12 months (under static conditions and under cyclic conditions) with direct microscopic observation of undiluted suspensions using a Carl Zeiss Microscope (Oberkochen, Germany).

2.3.4. Viscosity determination

Rheological measurements were performed by means of a controlled-stress rheometer (Haake RS 100, Karlsruhe, Germany) using a plate-plate sensor system (PP35). The gap size between the lower and the upper plate was 0.8 mm. A standard oil (Haake 90 200 20, viscosity 14441 mPa·s at 20°C) was used for calibration. In all experiments the measuring temperature was 20°C.

3. Results and discussion

Crystal growth in pharmaceutical suspensions may cause problems in the stability and bioavailability of suspensions. Several authors described the influence of polymers and tensioactive agents on crystal growth inhibition (Motawi et al., 1982; Luhtala 1992; Tanninen et al., 1992). In this

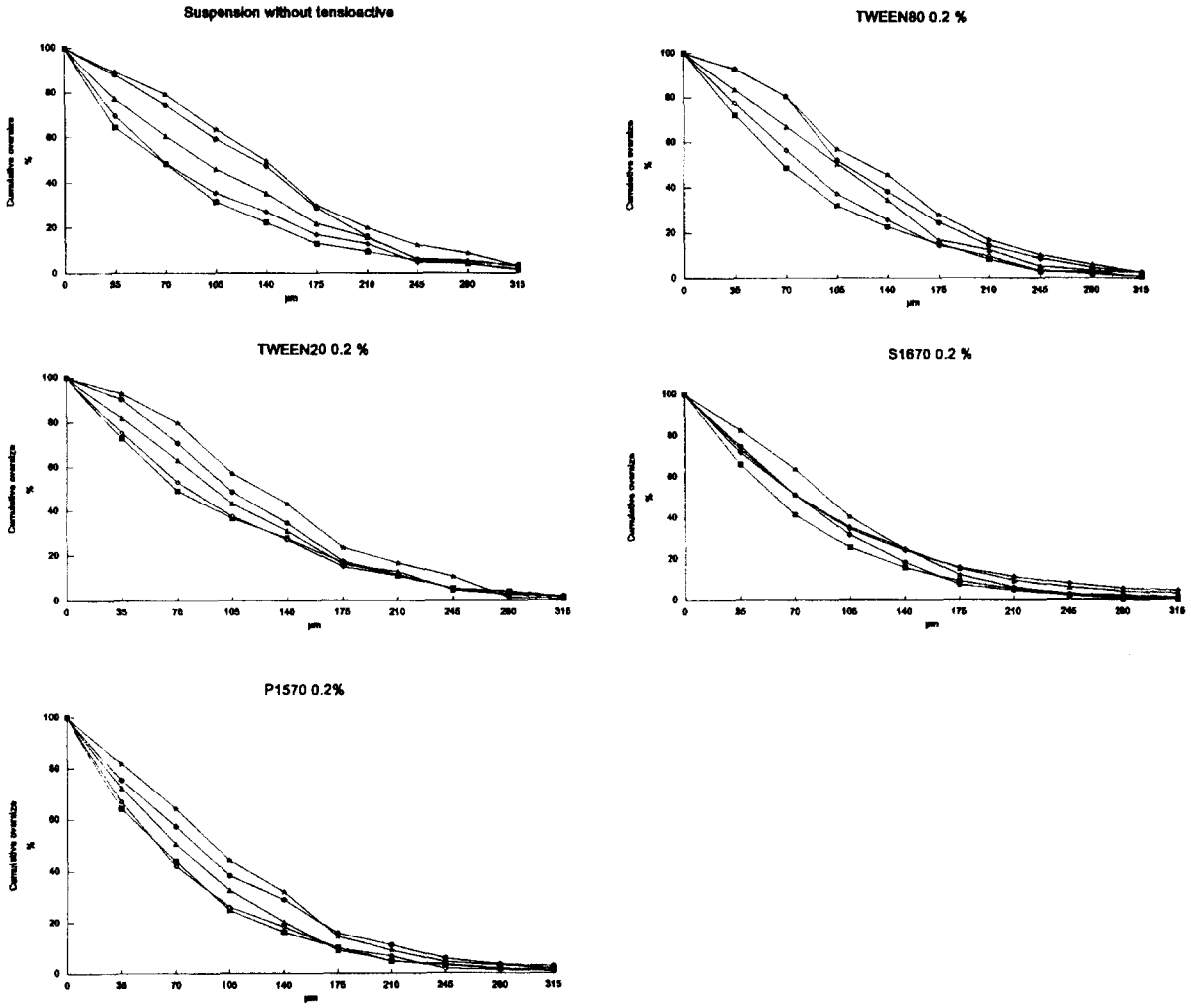

Fig. 1. Evolution of the crystal size distribution of suspensions containing 0.2% w/v of Tween 80, Tween 20, S1670 and P1570, respectively, in comparison with the suspension containing only xanthan gum: at time zero (■); after 2 months (◇); 6 months (▲) and after 12 months without shaking at room temperature (●) or with shaking and cyclic temperature conditions (✱).

study particle size data were built on number bases and are presented as a plot of the cumulative oversize frequency percentage against diameter at various time intervals. Fig. 1 compares the evolution of the crystal size distribution of suspensions containing Tween 80, Tween 20, S1670 and P1570, respectively, in comparison to the suspension containing only xanthan gum. The sucrose esters performed slightly better in comparison to the sorbitan derivatives as crystal growth inhibitors. Because of solubility problems concentrations of sucrose esters above 0.2% w/v in the suspension formulation cannot be used. In the search for non-toxic tensioactive agents pre-

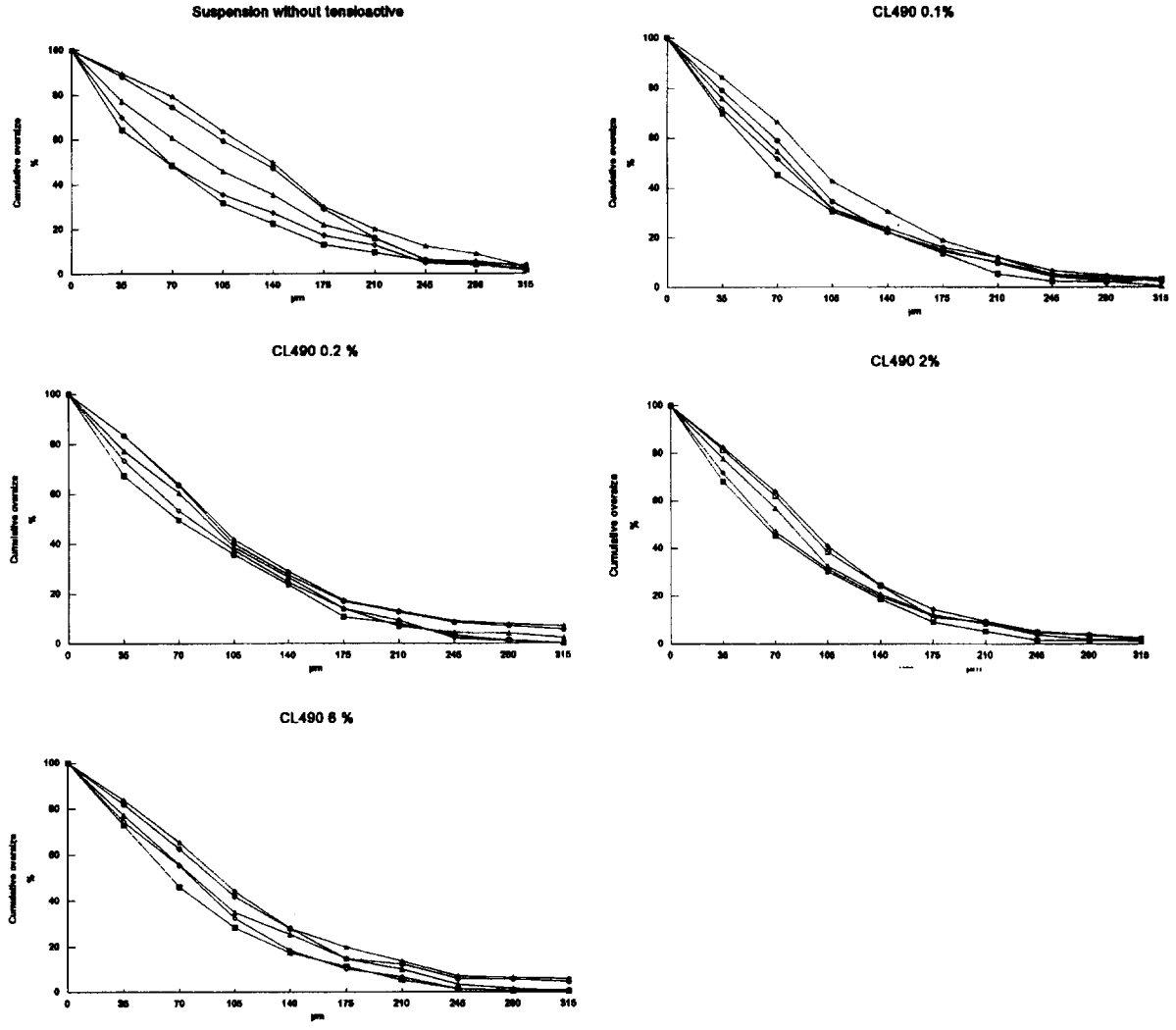

Fig. 2. The crystal size distribution of paracetamol suspensions prepared with increasing concentration of *n*-octenylsuccinate starch: at time zero (■); after 2 months (◇); 6 months (▲) and after 12 months without shaking at room temperature (●) or with shaking and cyclic temperature conditions (✱).

senting viscosity enhancing properties and crystal growth inhibition simultaneously, *n*-octenylsuccinate starch was used in a concentration range between 0.1% and 6% w/v. *n*-Octenylsuccinate starch is a starch derivative with tensioactive properties and is obtained after treatment of a waxy corn starch suspension with a cyclic dicarboxylic acid anhydride containing a hydrophobic substituent group yielding products with tensioactive properties (Be Miller and Paschall, 1984). Such an anhydride is 1-octenylsuccinic anhydride. After chemical modifications the starch ester was pregelatinized making the product cold-water dispersible. The product used has a degree of substi-

tution below 0.03 and is to be considered as a food approved product.

Fig. 2 shows the crystal size distribution of paracetamol suspensions prepared with increasing concentration of *n*-octenylsuccinate starch. The lowest concentration (0.1% w/v) inhibited crystal growth over a 1 year period and was even as effective as the sucrose esters. Increasing concentration up to 6% w/v did not influence these results.

Crystal growth was not influenced when a stability study was performed using a variable temperature program while shaking. Fig. 3 compares the evolution of the Hu/Ho value for suspensions prepared with Tween 80, Tween 20, S1670, P1570 and *n*-octenylsuccinate starch. Only sucrose esters and *n*-octenylsuccinate starch (above 0.2% w/v) were able to stabilize the suspension for 1 year. The use of higher *n*-octenylsuccinate starch concentrations showed a maximal Hu/Ho value beyond 1 year. It should be mentioned that only the suspensions prepared with *n*-octenylsuccinate starch at a concentration above 0.2% w/v did not show the presence of large paracetamol crystals sticking to the wall of the cylinders. Because of the interesting results obtained with the *n*-octenylsuccinate starch it was investigated if the addition of xanthan gum could be omitted, but the presence of the two compounds seemed a prerequisite to formulate a stable suspension. Due to the observation that xanthan gum in combination with *n*-octenylsuccinate starch proved to present excellent stability properties, rheological measurements were performed on suspensions prepared with an increasing concentration of *n*-octenylsuccinate starch with a constant xanthan gum concentration (0.5% w/v). It is well known in food applications that the association of xanthan gum and starch shows a highly pseudoplastic behaviour (Teague et al., 1985). Fig. 4 shows an example of a flow curve of a suspension containing 6% w/v of *n*-octenylsuccinate starch and 0.5% w/v of xanthan gum. Although the shear rate is very low, the viscosity dropped dramatically indicating changes of the structural properties of the suspension. As the sedimentation and the stability of suspensions are more correlated to the rheolog-

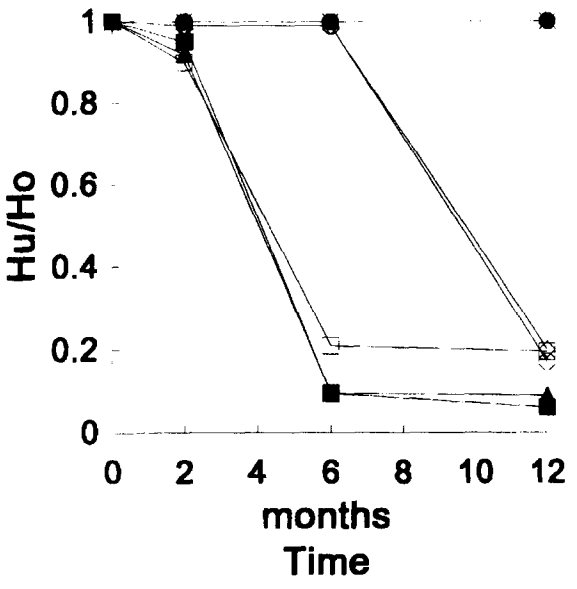

Fig. 3. Evolution of the Hu/Ho values of the suspension containing xanthan gum 0.5% w/v (■); xanthan gum and Tween 20 0.2% w/v (□); xanthan gum and Tween 80 0.2% w/v (▲); xanthan gum and P1570 0.2% w/v (○); xanthan gum and S1670 0.2% w/v (◇); xanthan gum and CL490 4% w/v (×) and xanthan gum and CL490 6% w/v (●).

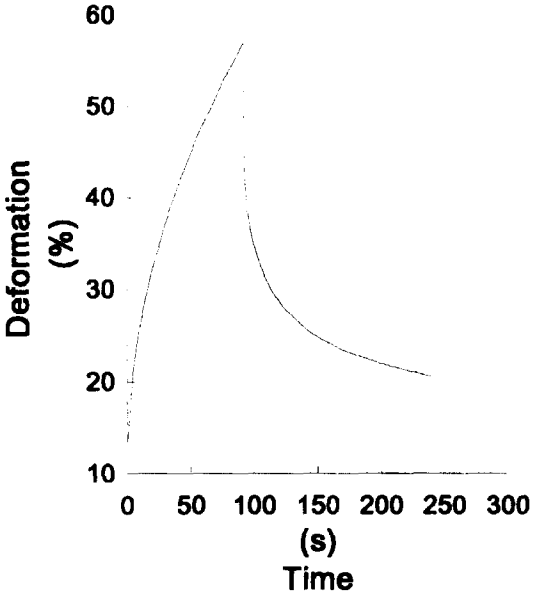

Fig. 4. Viscosity flow curve of a paracetamol suspension containing 6% (w/v) *n*-octenylsuccinate starch and 0.5% (w/v) xanthan gum.

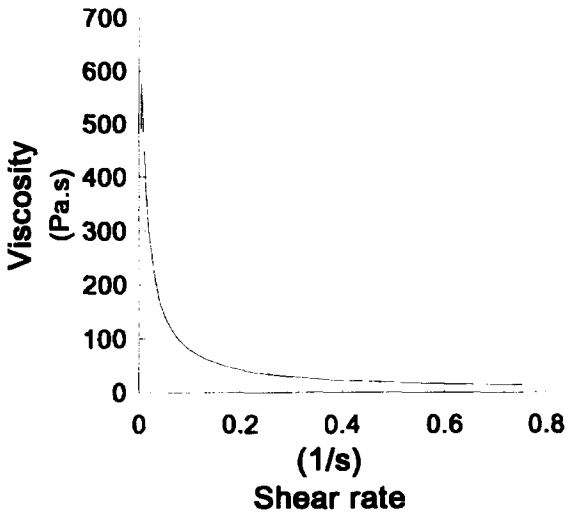

Fig. 5. Creep curve of a paracetamol suspension containing 6% (w/v) *n*-octenylsuccinate starch and 0.5% (w/v) of xanthan gum.

ical properties of the suspension at rest, it was necessary to look for rheological parameters characterizing the "non-destroyed" suspension. By using a controlled-stress rheometer it was experimentally possible to test the formulations at extremely low stress (2 Pa) so that the resulting deformation did not destroy the structure of the suspension. Creep-experiments were performed to analyze the influence of the addition of the starch derivative on the elastic properties of the suspension.

Fig. 5 shows an example of a creep experiment performed on a suspension containing 0.5% w/v xanthan gum and 6% w/v *n*-octenylsuccinate starch. The first part of the curve shows the deformation due to the applied stress, the second part illustrates the recovery of the deformation after stopping the stress and indicates the viscoelastic nature of the suspension. The shear modulus G was calculated and is shown in Table 1. The increase in elasticity of the *n*-octenylsuccinate starch and xanthan gum associations could be explained by an interaction between the non-ionic amylopectine derivative and rod-like xanthan gum molecule. A dramatic increase in G value from 3 to 5.8 Pa was observed when the concentration of *n*-octenylsuccinate starch was increased from 4% w/v to 6% w/v. Interactions between the extended conformation of the xanthan gum molecule and non-ionic amylose has been described in literature (Christianson et al., 1981; Teague et al., 1985). How the interaction occurs between the branched amylopectine molecule and xanthan gum is unclear and requires further investigation.

Table 1
The shear modulus G calculated for a suspension containing paracetamol 6% w/v, xanthan gum 0.5% w/v and increasing concentrations of *n*-octenylsuccinate starch

Suspension with	G (Pa) ± S.D. ($n = 3$)
Xanthan gum	2.11 ± 0.05
Xanthan gum + CL490 0.1%	2.17 ± 0.33
Xanthan gum + CL490 4%	3.35 ± 0.15
Xanthan gum + CL490 6%	5.83 ± 0.29

In conclusion it can be said that sucrose esters are a valuable alternative as crystal growth inhibitors and that the use of the xanthan gum-*n*-octenylsuccinate starch association offers new perspectives in the preparation of suspension formulations.

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