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RESEARCH PAPER

Investigation on a New Modified USP Xanthan with Tablet-Disintegrating Properties

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ABSTRACT

The disintegrating efficiency of a new USP xanthan derivative, Xanthan SM®, was evaluated. First, the physical parameters of Xanthan SM were compared to USP xanthan, a highly gelifying excipient, and AcDiSol®, a powerful and well-known disintegrant. Tablets were prepared by direct compression using acetylsalicylic acid as the drug. The effective amount of each disintegrant was determined. The influence on compression behavior, disintegration time, and drug dissolution rate was considered. This study makes it clear that the characteristics of Xanthan SM are totally different from those of USP xanthan. Xanthan SM proved to be as good as AcDiSol.

INTRODUCTION

In spite of extensive research in the field of disintegrating agents, native starches remain the most widely used. Unfortunately, high starch concentrations are sometimes necessary for fast disintegration, and these products do not always have good compression properties. This is the reason why more sophisticated disintegrants are sometimes more suitable. The smaller amount required of the latter for fast disintegration, can sometimes compensate for the added cost.

Many theories relating to the mechanism of tablet disintegration have been proposed. The common factor among these different theories remains the necessity of water to enter the whole tablet structure. According to Guyot-Hermann (1), the amount of disintegrant in a tablet corresponds to setting up a continuous hydrophilic network, allowing for a fast progression of water

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throughout the entire tablet. This critical concentration also depends on the particle size of the associated drug and diluent. Strong hydrophilic properties consequently appear to be an essential criterion for an ideal disintegrating agent. Low viscosity in situ is a condition for fast progression of water: consequently weak solubility in water and weak mucilaginous behavior in contact with water are desirable properties. These three properties should thus be studied first when a new disintegrant is developed. Compressability is then evaluated. Finally the right concentration of the disintegrating agent must be introduced into the tablet formulation. The dissolution rate of the associated drug is then tested. The purpose of this study is to evaluate the disintegrating efficiency of a new USP xanthan derivative still not marketed, Xanthan SM®.

In previous studies, water uptake of Scleroglucan, USP xanthan, and Xanthan SM in powder form were compared. Different behaviors were seen; Xanthan SM exhibited less gelifying and higher hydrophilic properties, whereas the two other polysaccharides showed a lower water intake over a period of time due to their gelifying properties (2).

In other works, Xanthan SM was compared under the same conditions to Primogel®, a carboxymethylstarch well known for its powerful disintegrating properties. Xanthan SM proved to be an excellent disintegrating agent: 1.5% of Xanthan SM in an Emcompress® tablet of 12 daN hardness, is sufficient to obtain total tablet disintegration in less than 30 sec (3).

In the present work, more fundamental physical parameters of Xanthan SM were evaluated to obtain an insight into its potential disintegrating efficiency and compressability. The results were compared with those obtained simultaneously with USP xanthan in order to establish the difference between its characteristics, and with AcDiSol in order to evaluate its disintegrating ability in comparison with this powerful disintegrating agent.

MATERIALS

- Xanthan CX® USP grade: Sanofi Bio Industries, France.
- Xanthan SM: new derivative of Xanthan CX®, Sanofi Bio Industries, France.
- AcDiSol® USP grade croscarmellose sodium: FMC Corp. SEPPIC, France.
- Crystallized acetylsalicylic acid, aspirin: Cooper–Melun, France.
- Magnesium stearate: Cooper–Melun, France.

METHODS

Powder Properties

Optical Microscopy

Samples in dry state and in water were observed under an optical microscope (Wild Leitz M20) using a micrometric scale to measure particle length and width.

Content of Water-Soluble Material

A 0.5-g sample of disintegrant was dispersed in a tube and shaken vigorously to suspend the sample in 200 ml of water (50 ml for AcDiSol). The suspension was allowed to stand overnight. After filtration, drying (105°C for 3 hr) and weighing of the dry residue, the content of water-soluble material was determined.

Settling Volume

For each product, 0.5 g was weighed and then dispersed in 100 ml of distilled water in a graduated cylinder. The volume of the settled mass was noted after 12 hr.

Particle Compressability

The compression capacity was estimated by the 1 CP method (4) (20% relative humidity at 20°C) on an OA Frogerais (Frogerais, France) instrumented (5) single-punch press (punch diameter = 11.28 mm). Tablets were produced in standardized conditions by introducing preweighed powder samples, manually, into the prelubricated die. The upper punch displacement (X), the force measured on the upper punch ($Y1$) and the force on the lower punch ($Y2$) were noted. Different adjustments of the upper punch displacements X were made to obtain different compression forces ($Y1$). $Y1$ values corresponding to a defined hardness were determined from the linear regression between tablet crushing strength and upper punch force $Y1$ (6). The $Y2/Y1$ ratio, indicative of transmission forces through the powder in the die, was calculated. Tablet crushing strength was measured using a Schleuniger 6D hardness tester. As an indication of the ability of particles to cohere during the compression process, the cohesion index was

calculated (CI: crushing strength/*YI* ratio multiplied by 10^5): the higher this cohesion index, the better the compressability (7).

Formulation Study

Tablet Preparation

Following Ringard's theory (1) to find the best amount of Xanthan SM for fast tablet disintegration, several mixtures of aspirin with disintegrant were prepared at increasing percentages: 1%, 3%, 5%, and 7.5%. Mixtures of aspirin, 200g, with AcDiSol (ACD) or Xanthan SM (XSM) were prepared and coded:

ACD 1, ACD 3, ACD 5, and ACD 7.5, respectively, for formulas with AcDiSol at 1%, 3%, 5%, and 7.5%

XSM 1, XSM 3, XSM 5, and XSM 7.5, respectively, for formulas with Xanthan SM at 1%, 3%, 5%, and 7.5%

Mixing was carried out in a Turbula mixer (W. A. Bachafen, Switzerland) at 90 rpm for 5 min. Just before compression, 0.5% of magnesium stearate was added and mixing was continued for 5 min.

Powder Bed Hydrophilicity

This method is detailed by Ringard (1): 3 g of binary mixtures (aspirin/disintegrant) were placed on a sintered glass disk forming the bottom of a glass tube. The whole device was brought into contact with water and adjusted at 1 mm under the surface of the water. Some methylene blue crystals were put on the surface of powder mixture. The time taken for the capillary rise of water to the surface was noted. This time corresponds to the dissolution of methylene blue crystals due to contact with water rising to the surface.

Ringard and colleagues (1) found that the most hydrophilic mixture (i.e.: with water rising the fastest) corresponds to the critical amount of disintegrant that will establish a "hydrophilic continuous network" inside the tablet. This critical amount will lead to a remarkable improvement in tablet disintegration.

Compressability

Materials used and parameters determined were the same as described previously. Tablets of 800 ± 50 mg were made by direct compression, with a compression chamber of constant volume (depth = 1 cm).

Disintegration Test

Disintegration time was determined according to the European Pharmacopoeia (2nd ed., V.5.1.), in water at 37°C. The data given are the mean of six tablets.

Dissolution Test

The dissolution rates of aspirin from tablets were measured using the paddle device of the European Pharmacopoeia (75 rpm/37 ± 0.5°C).

The dissolution medium was 800 ml of 0.1 N HCl. After 7.5, 15, 30, 45, and 60 min, samples were taken. Drug concentration in each filtered sample was determined by measuring the absorbance at 277 nm using a Shimadzu UV 1205 Spectrophotometer. Dissolution tests were carried out on six tablets and only mean values were retained.

RESULTS AND DISCUSSION

Powder Study

Microscopic Appearance and Size Determination

The shape of Xanthan SM particles was generally isometric and rounded, rarely elongated. The Ferret mean diameter was 95 μm, with 60% of the particles being under 100 μm diameter. In water, the particles swelled considerably. The mean diameter became approximately 250 μm: they appeared as large gelatinous particles more or less agglomerated. It was difficult to observe these particles because they were impregnated with a considerable volume of water; consequently their refraction index became nearly 1.

The shape of Xanthan CX particles was not homogeneous: 18% of elongated fibrous particles can be observed. The remaining particles were similar to those of Xanthan SM but smaller; their mean diameter was 21 μm. The mean length of the fibrous particles was 40 μm, with a mean width of 6 μm. In water, the particles disappeared completely owing to the dissolution phenomenon.

The shape of 75% of the AcDiSol particles was fibrous. These were longer (×2) than those of Xanthan CX. In water, the diameter of the fibers swelled, but the length remained nearly the same.

The microscopic results are summarized in Fig. 1 and Table 1.

Xanthan CX cannot be considered as a disintegrating agent due to its solubility in water. On the other hand,

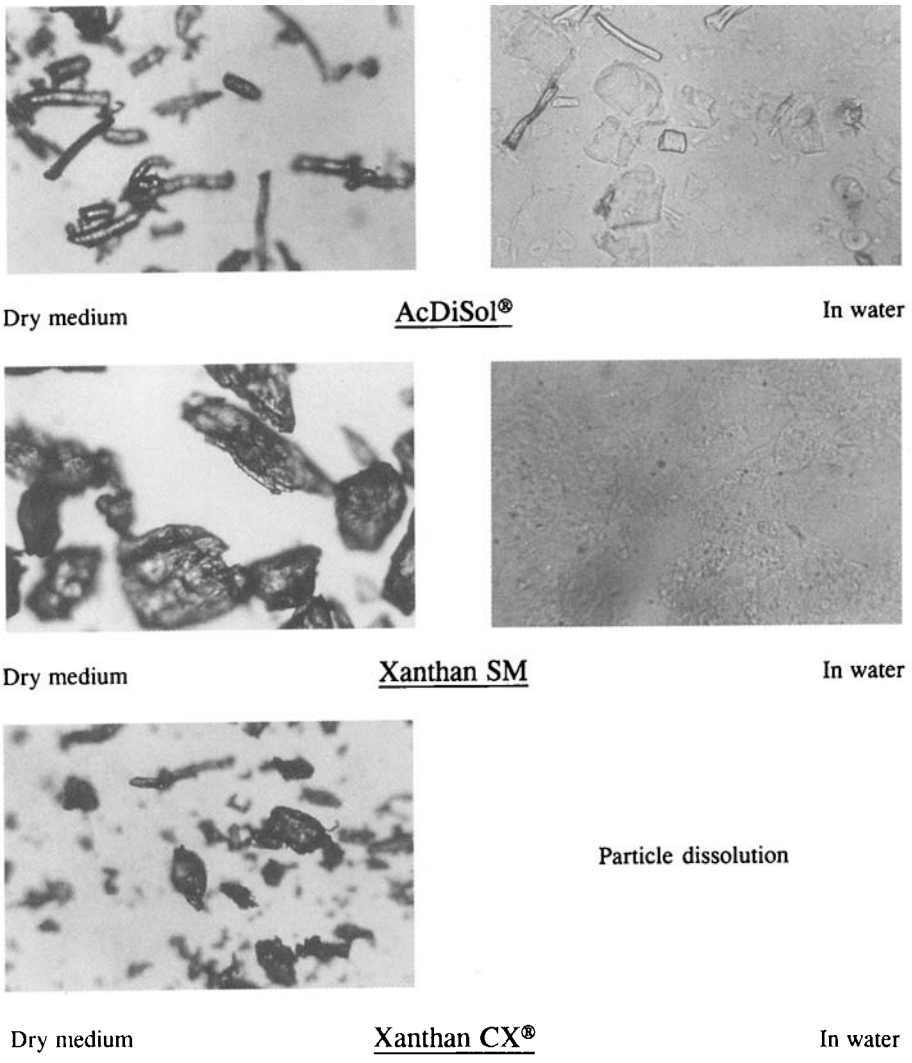

Figure 1. Microscopic appearance in dry medium and in water of AcDiSol, Xanthan SM, and Xanthan CX powder samples.

Table 1

Particle Size of Xanthan SM, Xanthan CX, and AcDiSol in Dry Medium and in Water

Powder Batch	Dry Medium	In Water
AcDiSol	25% isometric particles (mean diameter: 20 μm) 75% fibrous particles (L/w = 80/18 μm)	33% isometric particles (mean diameter: 38 μm) 67% fibrous particles (L/w = 99/43 μm)
Xanthan SM	Isometric particles (mean diameter: 95 μm)	Nearly 250 μm
Xanthan CX	82% isometric particles (mean diameter: 21 μm) 18% fibrous particles (L/w = 40/60 μm)	Particle dissolution

the swelling of Xanthan SM was much higher than that of AcDiSol.

Content of Water-Soluble Material

Sample solubility rates are presented in Table 2. The water-soluble contents were lower for AcDiSol than for Xanthan SM. This solubility rate is an important factor in their use as disintegrating agents.

The water solubility of Xanthan CX was not determined in our experimental conditions due to the absence of supernatant and to the total gelification of the medium.

Powder Bed Swelling in Water

Great differences were observed in swelling behavior (Table 3). The volume of settled particles corresponded to an opaque layer of about 6.5 ml for AcDiSol, that is, a fivefold increase in volume after swelling. With Xanthan SM, a translucent layer of much greater height was observed: 97 ml of highly gelatinous mass. This mass always settled at the same height after shaking and consisted of swelled insoluble particles. With Xanthan CX, no settling mass was observed, which corresponds with the solubility observed under the microscope.

It is obvious that these three products tested would behave differently as disintegrating agents in a tablet formulation.

Table 2

Content of Water-Soluble Material

Powder Batch	Solubility (mg/g)
AcDiSol	1.6
Xanthan SM	1.9
Xanthan CX	Impossible: total gelification

Table 3

Volume of Settled Mass in Water of Dry Powder (0.5 g)

Powder Batches	Sample Mass (ml)	Volume of Settled Mass (ml)
AcDiSol	0.5	2.5
Xanthan SM	0.5	72
Xanthan CX	0.5	No settling

Compressability

The crushing strength variation versus the upper compression force (*YI*) is presented in Fig. 2. From the linear regression relation established between the two parameters, *YI* corresponding to a 12 daN crushing strength value and the relative cohesion index were calculated (Table 4).

As the cohesion index values of Xanthan SM and AcDiSol are not very different, their compressability can be considered as similar. High cohesion index values indicate that they exhibit good compression properties. For the same reason, Xanthan CX can be evaluated as an excipient with very good compressability.

Formulation Study

Selection of Optimal Disintegrant Concentration

Mixtures of aspirin with 1%, 3%, 5%, and 7.5% of AcDiSol and Xanthan SM were submitted to the powder bed hydrophilicity test. Times needed for water to rise to the powder surface are presented in Table 5.

The optimal concentration needed to establish a hydrophilic continuous network was 3% for Xanthan SM and 5% for AcDiSol. The lower amount of Xanthan SM required is due to its higher swelling property.

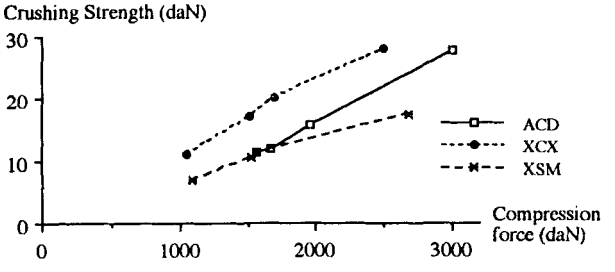

Figure 2. Crushing strength versus compression force using the 1 CP method for AcDiSol, Xanthan SM, and Xanthan CX compacts.

Table 4

Powder Compressability of AcDiSol, Xanthan SM, and Xanthan CX (Crushing Strength = 12 daN)

Powder Batch	*YI* (daN)	Cohesion Index
AcDiSol	1651	727
Xanthan SM	1806	664
Xanthan CX	1103	1088

Table 5

Time (min) Needed for Water to Rise to the Powder Bed Surface for Mixtures of Aspirin with 1%, 3%, 5% and 7.5% Concentrations of AcDiSol, Xanthan SM, or Xanthan CX

Powder Batch[a]	1%	3%	5%	7.5%
ACD	>120	9.83	3.83	5.33
XSM	25.20	9.33	11.00	17.50
XCX	>120	>120	>120	>120

[a]ACD: aspirin/AcDiSol, XSM: aspirin Xanthan SM, XCX: aspirin/Xanthan CX.

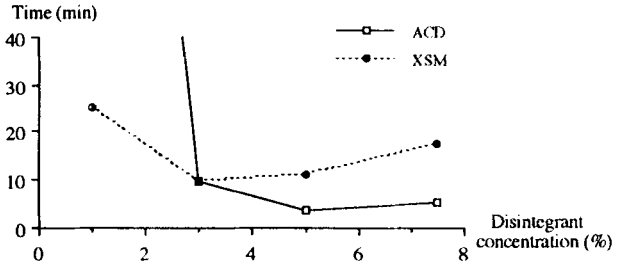

Figure 3. Influence of AcDiSol and Xanthan SM concentrations on aspirin powder bed hydrophilicity.

No water rise was observed with Xanthan CX mixtures due to a gelatinous mass that formed in contact with the sintered glass, blocking the progression of water. Xanthan CX cannot be used as a disintegrant but as an excipient for slow drug release.

The times needed to rise the powder bed surface versus disintegrant concentration are presented in Fig. 3.

Compressability

Mixtures were prepared with disintegrant at the critical concentration and at two close concentrations: just above and just below. An evaluation was made of the influence of Xanthan SM and AcDiSol on the compression behavior of aspirin tablets. Compression parameters were registered for a constant compression chamber depth (1 cm) and for a tablet hardness value of 5 ± 1 daN. Corresponding data are presented in Table 6.

The *Y2/Y1* ratio was satisfactory for all formulations tested and improved the transmission of compression energy through the powder.

The cohesion index values increased along with AcDiSol concentration. The presence of AcDiSol at a higher concentration than the hydrophilic continuous network's critical concentration of 5%, improved the compressability of aspirin. With Xanthan SM, increasing the concentration above the critical amount of 3% influenced the compression behavior of aspirin negatively. Therefore, the critical concentration of Xanthan SM is a limit not to be exceeded.

Disintegration time

Tablets were then submitted to a disintegration test. The disintegration times are presented in Table 7. With AcDiSol formulas, the most rapid disintegration occurred at a concentration of 5%, related to establishment of the hydrophilic continuous network inside the tablet. With Xanthan SM formulas, disintegration took place more rapidly. A concentration increase above 3% has little influence on tablet disintegration, and a 1% concentration was effective. It can be noted that formulas containing AcDiSol and Xanthan SM at the hydrophilic continuous network critical concentration of 5% and 3%, respectively, showed very similar behavior, confirming the theory of the hydrophilic continuous network.

Table 6

Compression Parameters of Aspirin Mixed with Different Concentrations of AcDiSol (ACD) at 3%, 5%, and 7.5% or Xanthan SM (XSM) at 1%, 3%, and 5%

	X (10^{-2} mm)	*Y1* (daN)	*Y2/Y1*	Weight (*SD*) (mg)	Hardness (*SD*) (daN)	CI
ACD 3%	467.3	2716	0.888	783.8 (1.21)	5.34 (0.30)	196
5%	474.6	1358	0.852	782.6 (0.94)	4.24 (0.33)	312
7.5%	473.1	1171	0.852	781.5 (1.23)	4.40 (0.31)	376
XSM 1%	477.2	3454	0.880	802.7 (0.12)	4.56 (0.34)	132
3%	476.6	3747	0.892	800.9 (0.02)	5.00 (0.25)	133
5%	470.8	4000	0.955	810.7 (0.22)	4.70 (0.29)	118

Table 7

Disintegration Time of Aspirin Tablets Containing Different Concentrations of AcDiSol (ACD) and Xanthan SM (XSM)

Formula	Disintegration Time (sec)
ACD	
3%	116
5%	43
7.5%	74
XSM	
1%	65
3%	45
5%	41

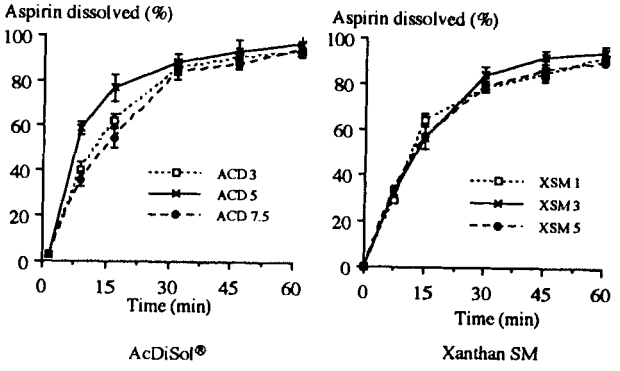

Figure 4. Percent aspirin dissolved at selected time points from aspirin tablets containing different concentrations of AcDiSol (3%, 5%, and 7.5%) and Xanthan SM (1%, 3%, and 5%).

Dissolution Study

Aspirin dissolution rates versus time are presented in Table 8. Aspirin dissolved most rapidly from tablets containing AcDiSol at a 5% level (ACD 5) and from Xanthan SM tablets at a 3% level (XSM 3), with an initial more rapid dissolution in the case of the AcDiSol. Dissolution was essentially complete in both cases at 45 min.

Figure 4 show the dissolution profile for AcDiSol and Xanthan SM formulas, respectively. A similar dissolution profile can be observed.

No significant difference are observable between the dissolution curves of Xanthan SM at 1%, 3%, or 5%. However, the dissolution rate of both formulas containing AcDiSol and Xanthan SM at the hydrophilic continuous network critical concentration of 5% and 3%, respectively, is slightly more important than in the other tablets batches.

CONCLUSION

This study confirms the applicability of the theory of a hydrophilic continuous network in finding the critical

Table 8

Percent Aspirin Dissolved at Selected Time Points from Aspirin Tablets Containing Different Concentrations of AcDiSol (3%, 5%, and 7.5%) and Xanthan SM (1%, 3%, and 5%)

	ACD			XSM		
Time (min)	ACD 3	ACD 5	ACD 7.5	XSM 1	XSM 3	XSM 5
7.5						
%	36.8	55.8	33.2	28.9	32.2	34.0
SD	4.0	2.8	3.1	0.4	1.5	0.4
15						
%	59.2	74.0	51.7	64.0	56.4	57.0
SD	2.7	6.1	4.2	2.6	5.1	0.2
30						
%	83.1	85.5	81.3	79.1	84.7	78.9
SD	3.2	4.1	3.7	2.2	3.1	1.2
45						
%	87.7	90.6	85.3	84.7	92.2	86.7
SD	2.3	5.3	2.8	3.1	2.7	2.6
60						
%	90.5	94.5	91.8	92.3	94.5	90.2
SD	2.0	5.0	3.3	1.6	2.5	0.5

concentration of disintegrant in a tablet to ensure the fast progression of water throughout the whole tablet.

It also confirms that good hydrophilicity and associated weak solubility are the essential characteristics for the activity of a disintegrating agent. Xanthan SM is a good disintegrating agent: its disintegrating properties are similar to those of AcDiSol. The considerable swelling of its particles means that lower amounts are required in tablet formulations, which may compensate any higher cost.

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