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GAMMA SORBITOL AS A DILUENT IN TABLETS

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ABSTRACT

Several crystal structures of Sorbitol may be encountered. Eleven Sorbitol samples from five different manufacturers were studied by X Ray diffraction and differential scanning calorimetry. Three crystalline forms were identified. The γ form is the most stable. One of these samples was constituted by the pure γ form.

Sorbitol is usually considered as a very hygroscopic excipient. We studied this most stable Sorbitol for its technological and biopharmaceutical properties in tablet formulation.

Aspirin and Acid Ascorbic tablets were prepared with γ Sorbitol as a diluent, in high concentration, by direct compression. Three disintegrants were tested : maize starch, Kollidon CL^{R}, Ac Di Sol^{R}. Using either lactose or γ Sorbitol as a diluent, different batches of tablets were prepared with the same proportion of diluent and in the same conditions.

Compression properties, hardness, disintegration time, dissolution rate and stability in moist conditions were studied.

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The tablets containing γ Sorbitol show :

- a better ratio compression force/hardness
- a longer time of disintegration and dissolution
- the very great importance of the choice of the disintegrant : Ac Di Sol was much better than Kollidon CL or Maïze starch in this case of formulation : conserved during one year at 80 % Relative Humidity, tablets with γ Sorbitol and Ac Di Sol kept their aspect and their biopharmaceutical properties very well. A slightly greater acid ascorbic alteration with Sorbitol as a diluent than with lactose can be noticed.

It seems that γ Sorbitol is a stable diluent if the Relative Humidity is lower than 80 %. Then it should be avoided with drugs too sensitive to moisture like ascorbic acid.

In spite of a slower release time, its hardening power and its very good compression properties can be of great interest.

INTRODUCTION

Sorbitol is a polyol used frequently in the industrial manufacture of food ingredients. For example it is used in the sweet-industry as a coating agent and as a directly compressed powder for the production of hard tablets designed for sucking. Similar pharmaceutical applications could be developed. Sicard and Leroy (1) point out that "the suitability of Sorbitol for compression depends on its own physical characteristics which are, in turn, governed by the crystallization method used". Several authors have recently studied the compression properties of different samples of Sorbitol (2) (3).

The standard production method is now usually a catalytic hydrogenation of sucrose or starch derivatives under pressure. Solid D Sorbitol is obtained by evaporation and crystallization from saturated solutions. The crystallization method is particulary important for the physicochemical properties of resulting solid Sorbitol "Thus each manufacturer of Sorbitol supplies powder with specific properties" (1). Indeed, according to the samples, variable properties and disadvantages can be observed : the shape of the particles, the surface state, the stability of crystalline structure,

hygroscopicity, the lumping tendency of the powder, the hardness evolution of resulting tablets during storage (4).

These different characteristics are to be correlated with important variations of melting points found in the litterature (from 75° C to 138° C). In fact, several crystalline forms may exist :

. amorphous glass form melting at 75° C (5)
. "A" or "α form" melting at 85° C (5) (6)
. metastable form, melting at 92-94,5° C, "β form" according to ICI (5) (6)
. stable "γ form", melting at 96-99° C (1) (5) (7)
. anhydrous form melting at 110-112° C (8) which does not appear to exist according Park Jeffrey and Hamilton (6) and Huchette (9)
. a racemate, melting at 136-138° C (6).

Other forms, more or less hydrated, are sometimes reported in the litterature. Their melting points are low and variable.

In the present study, eleven samples of Sorbitol, from different dealers were investigated : they were produced, at least, by six different manufacturers.

After these investigations, a stable γ form was selected for a compression study. In vitro availabilities of resulting tablets were determined in comparison with same tablets produced with lactose replacing Sorbitol. The drugs incorporated in the tablets were Aspirin or Ascorbic Acid. Thus, there are two different parts in our presentation :

I. Crystallographic investigation of the different samples of Sorbitol
II. Study of stable γ form of Sorbitol as diluent in tablets.

MATERIALS

I. Eleven samples of Sorbitol denominated S_1, S_2, S_3... S_{11}, from Belgium, France, Finland, Switzerland, U.S.A.

II. Pure γ Sorbitol "Neosorb 60"^{R} (S_2) (Roquette - Lestrem - France)
Lactose Fast Flo "spray dried" (Mendel Co New York U.S.A.)
Aspirin : crystallized acetyl salicylic acid (Cooper - Melun - France)

Ascorbic Acid (Cooper - Melun - France)

Maïze Starch (Roquette - Lestrem - France)

Kollidon CL^{R} (BASF - Ludwigshaffen West Germany)

Ac Di Sol^{R} (FMC Corporation - Philadelphia - U.S.A.)

Magnesium stearate (Cooper - Melun - France)

Talc (Cooper - Melun - France)

Sterotex (Expandia - Paris - France)

Tablet formulation :

Aspirin and Ascorbic acid tablets were prepared with either γ sorbitol or lactose as diluent. The drug and the diluent were used in equal proportion for this experiment.

Three disintegrants were tested at the concentration corresponding to the continuous network for each product, according to the Ringard and Guyot-Hermann formulation theory (10) (11) (12). These concentrations were :

Maïze starch : 11.6 g for 100 g of powder mixture

Kollidon CL : 3.0 g for 100 g of powder mixture

Ac Di Sol : 1.0 g for 100 g of powder mixture.

The mixtures for compression were respectively lubrificated by magnesium stearate (0.5 %) for Ascorbic Acid tablets, Talc and Sterotex (4 %) for Aspirin tablets.

METHODS

I. Study of the different samples of sorbitol

- X Ray powder diffraction : Philips PW 1720 diffractometer with Guinier Hägg X DC 700 Camera (radiation Cu-$K_{\alpha 1}$, λ = 1.5406 Å)
- Differential scanning calorimetry : DSC 2C Perkin Elmer - Heating rate : 5 or 10° C min^{-1}
- Water intake : the respective water content were determined by the Karl Fisher method in four different characteristic samples. They were put at 20° C in controlled relative humidity atmosphere (22 % - 54 % - 70 % and 80 % R.H.). After one month's storage, the water contents were again determined.

II. Compression and study of tablets prepared with γ Sorbitol

The mixing of powders was performed in a Turbula mixer. The powders were always added according to the following order

Drug + diluent
Disintegrant (in two additions)
Magnesium stearate

For each stage of the mixture preparation, the mixing time is fixed at five minutes.

The resulting mixtures were directly compressed with a Frogerais OA single punch tablet machine using 1 cm^2 area flat punches.

Strain gauges are stuck on the upper and lower punches, connected by means of Wheatstone bridges to a computer. This equipment gives us the possibility of noticing for each batch of tablets the average maximum force of the upper and lower stresses, y_1 and y_2.

We investigated on resulting tablets :

- the hardness (Heberlein Durometer)
- the disintegration time (according to European Pharmacopoiea)
- the dissolution studies were conducted according to the USP method with rotating paddle (50 rpm) in USP artificial gastric juice without enzyme. The liquid was withdrawn in continuous process and tested for drug content using ultraviolet spectrometry at 277 nm after suitable dilution for the aspirin tablets. As for ascorbic acid tablets, the drug content was determined by titrimetry using 2.6 dichlorophenol indophenol as titrating solution.

We studied then the properties preservation of tablets during storage in different relative humidies : 22 % R.H. as reference, 70 and 80 % R.H., theoritical R.H. for saturated Sorbitol solution being 74 % at 20° C according to Bussière and Serpelloni (13).

RESULTS AND DISCUSSION

I. Study of the different samples of Sorbitol

DSC results concerning the eleven samples of Sorbitol were collected in table I.

X Ray powder diffraction patterns are depicted in Figure 1.

DSC curves are collected in Figure 1.

TABLE I : Results of differential scanning calorimetry of 11 samples of Sorbitol

Type of Sorbitol	Number of peaks		Temperature max. peaks
S_1	3	. weak	87.4° C
		. intense	91.7° C
		. weak	97° C
	Second essay : Heating was stopped after the second peak. After cooling at 57° C, a second heating run was performed		
		→ 1 peak alone	97.8° C
S_2	1		99° C
S_3	1		99° C
S_4	2	. weak	87.3° C
		. intense	97.9° C
S_5	1		98° C
S_6	2	. broad and weak	86° C
		. intense	96.7° C
S_7	1		97° C
S_8	2	. intense	87° C
		. peak	96° C
S_9	2	. same	86° C
		. intensity	94° C
S_{10}	2	. weak	86° C
		. intense	95° C
S_{11}	1	very large with small shoulder at	95.5° 87° C

S_2 , S_3, S_5, S_7 are the same crystalline forms
S_4, S_6, S_{10} are the same crystalline forms

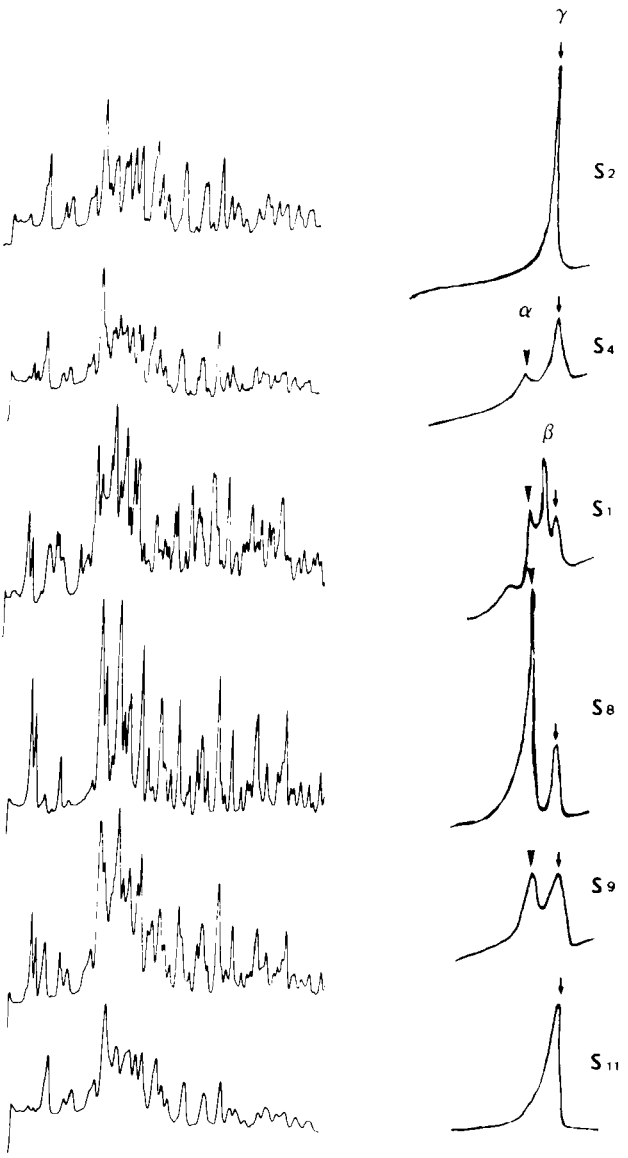

Figure 1. X Ray diffraction and DSC graphs of different samples of Sorbitol. Measures scale being different for each sample, those graphs are only qualifying (position of peaks).

We see that several sorts of crystalline structures of Sorbitol exist on the market.

The study of S_1 sample shows that the 97-99° C melting form (γ form) is the more stable).

According to the above mentioned literature, it could be thought that the 86-87° C melting form is the α form and the 91.7° C melting form, the β form .

Each sort of Sorbitol has its own use in food or pharmaceutical industries. Regarding their use in their solid state as diluents in tablet formulation, it seems that the more stable form is the γ one.

We tested it for hygroscopicity and we compared it with the following :

S_1 (α + β + γ Sorbitol)
S_8 (much α + β)
S_{11} (very impure γ form)

After one month's storage at different relative humidities, we measured the water content increase of these four samples by the Karl Fischer method.

The results are displayed in table II.

Sorbitol / Lactose comparison :

Except for the Ascorbic Acid / Ac Di Sol tablets, the results are nearly the same but for a sound discussion they must be compared with hardness values of resulting tablets.

II.2. Hardness

TABLET IV : Hardness of Sorbitol and Lactose tablets (in N)

			Hardness m	Hardness C.V.	Hardness y_1
Aspirin	Maïze Starch	Sorbitol	124	7.7%	1.19
		Lactose	90	10.8%	0.91
	Kollidon CL	Sorbitol	64	11 %	1.22
		Lactose	60	11.8%	1.07
	Ac Di Sol	Sorbitol	87	11.3%	1.51
		Lactose	50	11.8%	0.92
Ascorbic Acid	Maïze Starch	Sorbitol	54	8.3%	0.51
		Lactose	29	8.3%	0.29
	Kollidon CL	Sorbitol	65	10.7%	0.71
		Lactose	56	11.6%	0.51
	Ac Di Sol	Sorbitol	91	8 %	0.76
		Lactose	52	12.9%	0.44

We can see the more hardening effect of Sorbitol : without demanding more important stresses, Sorbitol give a greater hardness to the tablets.

II.3. Disintegration time

TABLET V : Disintegration time of Sorbitol and Lactose tablets

Drug	Disintegrant	Diluant	Disintegration time
Aspirin	Maïze Starch	Sorbitol	11min 18sec
		Lactose	1min 35sec
	Kollidon CL	Sorbitol	5min 04sec
		Lactose	1min 10sec
	Ac Di Sol	Sorbitol	8min 37sec
		Lactose	52sec
Ascorbic Acid	Maïze Starch	Sorbitol	6min
		Lactose	1min 32sec
	Kollidon CL	Sorbitol	2min 45sec
		Lactose	1min 09sec
	Ac Di Sol	Sorbitol	5min 19sec
		Lactose	37sec

Sorbitol / lactose comparison :

Except for the Ascorbic Acid / Ac Di Sol tablets, the results are nearly the same but for a sound discussion they must be compared with hardness values of resulting tablets.

II.2. Hardness

TABLE IV : Hardness of Sorbitol and Lactose tablets (in KN)

			Hardness $\bar{m}$	C.V.	Hardness $\bar{y}_1$
Aspirin	Maïze Starch	Sorbitol	124	7.7%	1.19
		Lactose	90	10.8%	0.91
	Kollidon CL	Sorbitol	64	11 %	1.22
		Lactose	60	11.8%	1.07
	Ac Di Sol	Sorbitol	87	11.3%	1.51
		Lactose	50	11.8%	0.92
Ascorbic Acid	Maïze Starch	Sorbitol	54	8.3%	0.51
		Lactose	29	8.3%	0.29
	Kollidon CL	Sorbitol	65	10.7%	0.71
		Lactose	56	11.6%	0.51
	Ac Di Sol	Sorbitol	91	8 %	0.76
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	Ac Di Sol	Sorbitol	8min 37sec
		Lactose	52sec
Ascorbic Acid	Maïze Starch	Sorbitol	6min
		Lactose	1min 32sec
	Kollidon CL	Sorbitol	2min 45sec
		Lactose	1min 09sec
	Ac Di Sol	Sorbitol	5min 19sec
		Lactose	37sec

The much slower disintegration time of tablets prepared with Sorbitol as diluent can be clearly noticed. It will be of great interest to see the consequences on the dissolution rate.

II.4. Dissolution rate

TABLE VI : Dissolution rate (in percentage) of Aspirin and Ascorbic Acid from Sorbitol or Lactose tablets

	Maïze Starch		Kollidon CL		Ac Di Sol	
	Sorbitol	Lactose	Sorbitol	Lactose	Sorbitol	Lactose
Aspirin Tablets						
7min 30	1.6	28.8	12.5	34.0	4.0	26.7
15 min	8.3	53.2	37.5	69.6	23.5	74.1
30 min	32.8	66.0	62.2	85.9	78.7	100.0
45 min	52.5	84.9	69.5	89.4	94.0	
60 min	60.3	89.7	75.9	91.2	100.0	
Ascorbic Acid Tablets						
7min 30	98.4	36.0	100.0	100.0	72.8	100.0
15 min	100.0	100.0			100.0	

The dissolution is slower from the tablets containing Sorbitol as diluent, but not as slow as we could imagine considering the disintegration time results.

We can notice the great importance of the choice of the disintegrant : Ac Di Sol is in these formulation case, the best disintegrant. On the other hand, the reproductibility of the measures is the best.

II.5. Evolution of properties during one year storage

This study concerns the most interesting formulations : tablets containing Kollidon CL or Ac Di Sol as disintegrants.

II.5.1. Aspect

With the Kollidon CL as disintegrant, we can notice the deliquescence of tablets containing Sorbitol at 80 % relative humidity. But, with Ac Di Sol, no change of tablets texture is observed whatever may the relative humidity be, for Sorbitol or for Lactose.

In spite of the reputation of Sorbitol for hygroscopicity, the formulation with γ Sorbitol is stable even after one year at 80 % R.H.

II.5.2. Drug conservation

There were few modifications in drug concentration for one year. Yet we can notice a more intense drug alteration in presence of Sorbitol than in presence of Lactose : coloration of Ascorbic Acid tablets, needles of Salicylic Acid on Aspirin tablets. The lower is the relative humidity, the weaker is the alteration. If such unstable drugs like Ascorbic Acid must be incorporated in tablets, then Sorbitol must not be used.

II.5.3. Hardness

After one year storage, the hardness of tablets containing Kollidon CL decreased dramatically when humidity is more important than 22 %, for tablets containing Sorbitol as well as for these containing Lactose as diluent. This phenomenon was previously observed by several authors with the two cross linked PVP, Kollidon CL and Polyplasdone XL (14)

With Ac Di Sol as disintegrant we can notice an increase hardness of the tablets, more important in presence of Sorbitol for the lowest relative humidities (Table VII).

II.5.4. Disintegration time

There are few modifications of the disintegration time of tablets containing Sorbitol and Ac Di Sol, and a decrease of this value in the other cases. In spite of the increase of tablet hardness, we cannot observe any appreciable increase of disintegration time.

TABLE VII : Hardness (in Newtons) and Disintegration time (in seconds) of Aspirin and Ascorbic Acid tablets, after one year of storage in different Relative Humidities (tablets containing Kollidon CL or Ac Di Sol as disintegrant). H = Hardness ; DT = Disintegration Time

Relative Humidity		Sorbitol Time 0	Sorbitol 22%	Sorbitol 70%	Sorbitol 80%	Lactose Time 0	Lactose 22%	Lactose 70%	Lactose 80%
Kollidon CL :									
Aspirin	H	64	64	49	déli-	60	57	33	21
	DT	304	198	92	quescence	70	56	7	6
Ascorbic	H	65	78	déli-		56	70	36	24
Acid	DT	165	185	quescence		69	77	10	7
Ac Di Sol :									
Aspirin	H	87	125	95	81	50	67	56	57
	DT	517	619	775	618	52	23	13	10
Ascorbic	H	91	140	71	152	52	79	66	66
Acid	DT	319	375	312	207	37	28	22	20

II.5.5. Dissolution rate

The evolution of dissolution rate during storage in different relative humidity atmospheres is very weak, when Ac Di Sol is the disintegrant for tablets containing Sorbitol as for these containing Lactose.

When Kollidon CL is the disintegrant, we can notice a more important alteration of tablets containing Sorbitol. We can see

again the very great importance of the choice of the disintegrant when Sorbitol is used. It can be thought that Kollidon CL presenting a tendency for hygroscopicity must not be associated with Sorbitol.

II.5.6. Crystallographic study of Sorbitol in tablets conserved in 70 % Relative Humidity atmosphere

X Ray study of carefully crushed tablets point out that crystal structure of Sorbitol remains in the γ form .

CONCLUSION

Several crystalline forms of Sorbitol can be produced by manufacturers and sold by dealers : for pharmaceutical use, at solid state , as diluent in tablets, the most stable γ form seems to be the most appropriate. In spite of the reputation for hygroscopicity of cristalline "Sorbitol", the γ form can be used for the production of tablets with a good texture preservation, when formulation has been studied carefully : the choice of the disintegrant seems essential. Nevertheless, in presence of too unstable products like Ascorbic Acid, Sorbitol must not be used when contact with high moist conditions.

In spite of a really longer disintegration time of tablets and a slightly longer dissolution time of drug when compared with those obtained with lactose, the very good compression properties and the very hardening effect of Sorbitol can be of great interest in tablet formulation.

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