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RESEARCH PAPERS

THE EFFECT OF HYGROSCOPIC FORMULATION INGREDIENTS ON THE SORPTION CHARACTERISTICS OF TABLETS

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ABSTRACT

In order to examine the effect of hygroscopic ingredients on the sorption characteristics of tablets, three hygroscopic additives - citric acid anhydrous (CAA), sorbitol (SI) and maltodextrin (MA) - were added at concentrations of 10% and 20% to a standard tablet granulate formulation prepared with three different initial moisture contents. The additives chosen were intended to be representative of a range of active ingredients with varying hygroscopicity characteristics.

The granulate/additive mixtures, together with the corresponding additive-free mixtures, were then tabletted, and the sorption isotherms of the resulting tablets were determined. The sorption-related changes in hardness, thickness, diameter and disintegration time were also investigated.

Examination of the sorption isotherms showed that the position of the "ansorption point" - the point where the isotherm crosses the x-axis and thus the point at which the tablets start to adsorb water - was much more dependent on the initial

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moisture content of the tablets than on the presence of a hygroscopic additive. The presence of a hygroscopic additive had little or no effect.

The additives did not begin to have any marked effects on the sorption isotherms of the finished tablets until the relative humidity level reached 62%. Above 62%, however, the differences in the hygroscopicity characteristics of the individual additives had a direct impact on the sorption profiles of the tablets.

As increasing amounts of moisture were adsorbed, tablet hardness fell whilst tablet thickness and diameter increased. The increases in thickness were in all cases greater than the increases in diameter. These findings applied to all tablets irrespective of their initial moisture content.

The sorption-related changes in disintegration time did not exhibit any consistent pattern and have therefore not been interpreted.

A comparison of the areas under the adsorption isotherms yielded the following results:

- The three additives adsorbed differently. Their adsorption, however, was always greater than that of any of the tablet variants.

- The areas under the adsorption isotherms of the additive-containing tablets were in all cases greater than the areas under the adsorption isotherms of the corresponding additive-free tablets. However, the differences were not always directly related to the concentration of the additive or to the area under the adsorption isotherm of that additive.

The relevance of these findings for routine pharmaceutical practice is discussed.

1. INTRODUCTION

The role of moisture adsorption and desorption as a cause of physical changes in tablet formulations has been widely studied. The changes which occur are varied in nature, affecting appearance (1), hardness (2, 3), disintegration time (4), dis-

solution rate (5) and thickness and diameter (6). The phenomenon is an important one, and programmed sorption determination techniques have been devised to predict sorption-related changes in the physical properties of tablets (7).

Formulation parameters are also known to affect the sorption characteristics of tablets under certain relative humidity conditions. Sangekar et al. (8), for instance, carried out tests on tablets prepared from various direct compression excipients and found that the sorption characteristics of the tablets were directly dependent on the excipient used.

The long-established practice of adding small quantities of humectants to tab-let granulates to ensure they are moist enough for compression is another example of formulation parameters determining the sorption characteristics of the finished tablet (9).

If the sorption characteristics of a tablet formulation are modified, the sorption-related physical properties of the tablets can also be expected to change. Studies carried out on tablets with different initial moisture contents have shown that increasing the initial moisture content increases both the relative humidity level at which the tablets start to adsorb moisture and, in parallel, the relative humidity level at which they start to lose their hardness.

Further studies on placebo tablets manufactured with different initial moisture contents showed that the initial moisture content affected not only the sorption isotherms and the hardness values but also the disintegration time, the thickness and the diameter (6).

The aim of the present study is to investigate the effect of hygroscopic additives on the sorption characteristics of a standard tablet granulate formulation. The additives have been carefully chosen to represent a range of active ingredients having varying hygroscopicity characteristics.

The tablets examined in the study were manufactured with three different initial moisture contents, so that the effect of initial moisture content on both sorption characteristics and sorption-related physical changes could also be investigated.

2. MATERIALS AND METHODS

2.1. Materials

Lactose, Ph. Eur., 2nd Ed. (Grade D 80; Meggle, Reitmehring, Germany)
Maize starch, DAB 10, dried (Roquette GmbH, Frankfurt am Main, Germany; the starch is dried for 16 h at 45°C in a tray dryer with a fresh air supply)
Soluble maize starch (Snowflake 6598; Cerestar Polyols GmbH, Krefeld, Germany)
Magnesium stearate, DAB 10 (Chem.-Werke Otto Bärlocher GmbH, Munich, Germany)
Water, purified, DAB 10
Citric acid, anhydrous, USP XXII (Jungbunzlauer, Ladenburg, Germany)
Sorbitol, DAB 10 (Sorbitol Instant Pharma; E. Merck, Darmstadt, Germany)
Maltodextrin, NF XVII (Glucidex 19; Roquette GmbH, Frankfurt am Main, Germany)

2.2. Apparatus

As described in (6).

2.3. Composition of Standard Tablet Granulate Formulation

Constituents	*mg/tablet*
Lactose	78.7
Dried maize starch	36.2
Soluble maize starch	4.9
Magnesium stearate	0.2
Water (volatile constituent)	22.0

2.4. Granulation

Batch size: 2 x 5.0 kg

The lactose and the dried maize starch were dry-mixed in a Friko kneader and the resulting mixture was uniformly moistened with an aqueous solution of soluble

starch heated to 45°C. The mass was then wet-screened in a Frewitt granulator (mesh size of screen: 1.6 mm) and dried at 50°C in a tray dryer. The dried granulate was screened again in a Frewitt granulator (mesh size of screen: 1.0 mm) and then divided into three portions, which were subsequently dried until their moisture contents were 3.1%, 2.1% and 1.5% respectively, as determined with an Ul-tra X moisture determination apparatus. The appropriate quantity of magnesium stearate was added to each portion of granulate, with mixing being carried out in a cube mixer.

2.5. Preparation of Final Tabletting Mixtures

Table 1 shows the full range of mixtures prepared for tabletting. Two concentrations of each additive were tested at each moisture content level. One variant at each moisture content level was manufactured without additives.

2.6. Tabletting

The mixtures listed in Table 1 were compressed on an instrumented eccentric tablet press to produce flat, round, bevel-edged tablets weighing 120 mg and having a diameter of 7 mm and a hardness value of 50 N.

Prior to the sorption studies, the tablets were stored for several days at 25°C in airtight bottles with twist-off caps.

2.7. Programmed Sorption Studies

2.7.1. Storage of Samples and Determination of Sorption Isotherms

As described in (6).

2.7.2. Determination of Values for other Physical Parameters

As described in (6).

TABLE 1
Composition of Mixtures Prepared for Tabletting

Moisture content of granulate	Additive	Additive concentration (w/w)
1.5%	-----	----
1.5%	Citric acid	10%
1.5%	Citric acid	20%
1.5%	Sorbitol Instant	10%
1.5%	Sorbitol Instant	20%
1.5%	Maltodextrin	10%
1.5%	Maltodextrin	20%
2.1%	----	----
2.1%	Citric acid	10%
2.1%	Citric acid	20%
2.1%	Sorbitol Instant	10%
2.1%	Sorbitol Instant	20%
2.1%	Maltodextrin	10%
2.1%	Maltodextrin	20%
3.1%	----	----
3.1%	Citric acid	10%
3.1%	Citric acid	20%
3.1%	Sorbitol Instant	10%
3.1%	Sorbitol Instant	20%
3.1%	Maltodextrin	10%
3.1%	Maltodextrin	20%

2.7.3. Determination of Areas under the Adsorption Isotherms (AUC_{ad} Values)

The areas under the adsorption isotherms (AUC_{ad} values) were determined by integration using a computer program developed in-house (11). Integration was carried out between the relative humidity at the ansorption point (the point at which the isotherm intersects with the x-axis) and the highest relative humidity used in the study (84.3% at 25°C). The ansorption points were determined by interpolation, again using the computer program.

3. RESULTS AND DISCUSSION

3.1. Sorption Isotherms of the Additives

Figure 1 shows the sorption isotherms of the three additives used in the study. CAA and SI exchange very little moisture with the atmosphere until comparatively high relative humidity levels are reached. MA starts to adsorb measurable quantities of moisture at lower relative humidities than either CAA or SI but, by contrast, the rate at which it adsorbs moisture does not increase significantly as the relative humidity rises.

CAA and SI do not start to adsorb significant amounts of moisture until the relative humidity reaches 62%. After this point, however, adsorption increases rapidly, although SI and CAA behave slightly differently. Between 62% and 75.5% r.h., the adsorption curve for SI rises very steeply whilst that for CAA rises more gradually. Between 75.5% and 84.3% r.h., however, the curve for CAA rises much more sharply and, at a relative humidity level of 84.3%, CAA has adsorbed more moisture than SI.

In view of the marked differences in the sorption profiles of the three additives, it was expected that the sorption characteristics of the various tablet variants would also show marked differences.

3.2. Effect of the Additives on the Sorption Isotherms of the Finished Tablets

It is known from previous studies that the ansorption point of a formulation - the point at which the sorption isotherm crosses the x-axis - can be altered by varying the initial moisture content of that formulation (2). The differences in initial moisture content lead to parallel shifts in the sorption isotherms, with higher moisture contents causing a rightward shift and lower moisture contents a leftward shift (6). This phenomenon is well illustrated in Figure 2a, which shows that the isotherms of the additive-free tablets are displaced rightwards as the initial moisture content of the granulate increases. Figures 2b and 2c show that

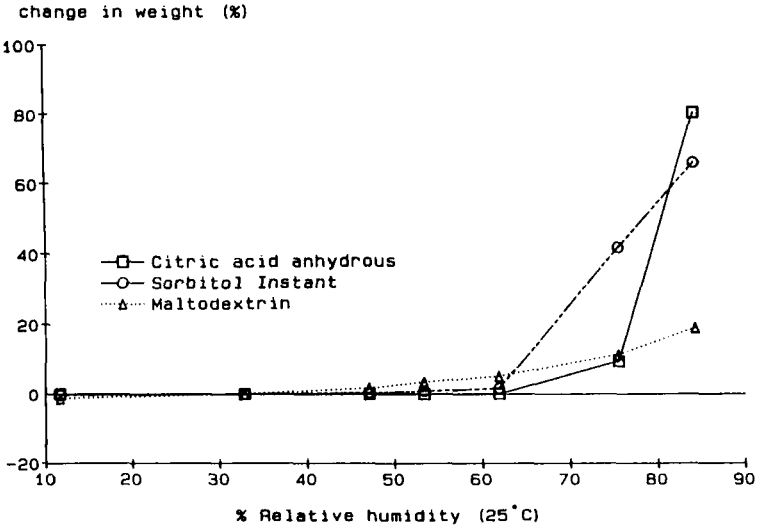

FIGURE 1: Sorption Isotherms (at 25°C) of Citric Acid Anhydrous (CAA), Sorbitol Instant (SI) and Maltodextrin (MA, Glucidex 19)

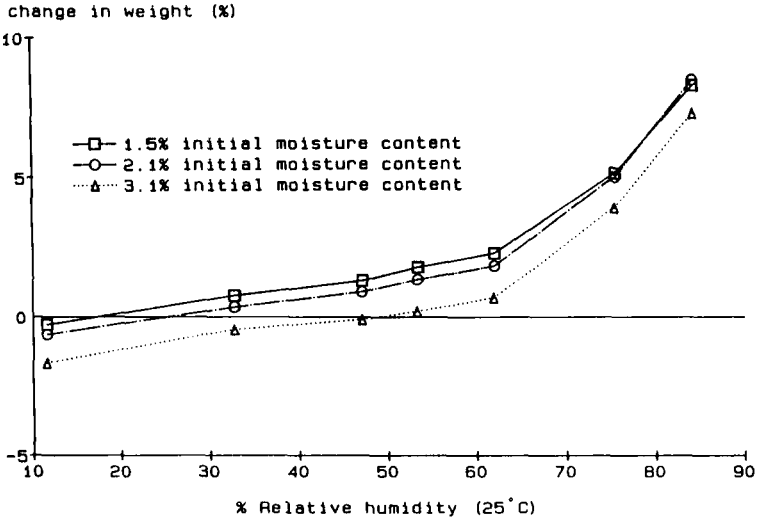

FIGURE 2 a: Sorption Isotherms (at 25°C) of Additive-Free Tablets with Initial Moisture Contents of 1.5%, 2.1% and 3.1%

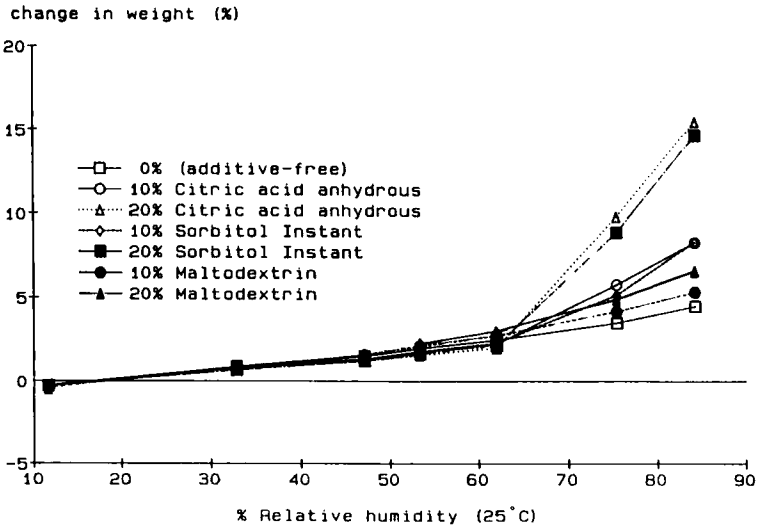

FIGURE 2b: Sorption Isotherms (at 25°C) of Additive-Containing Tablets with an Initial Moisture Content of 1.5%

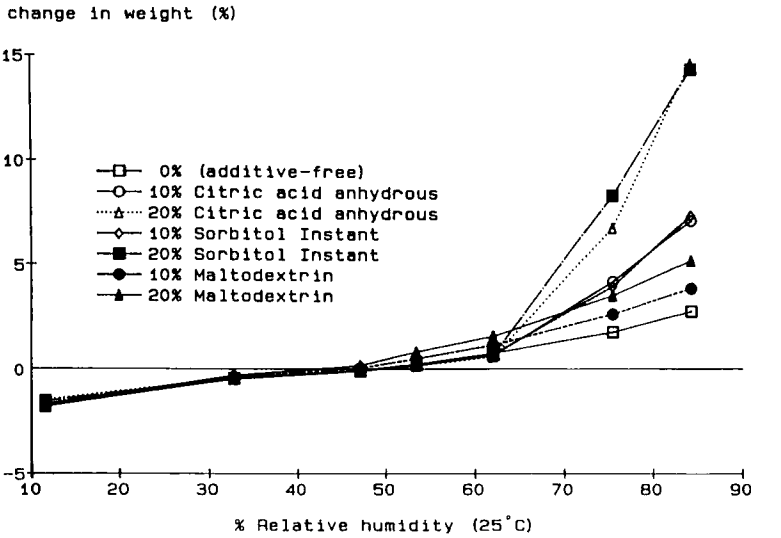

FIGURE 2c: Sorption Isotherms (at 25°C) of Additive-Containing Tablets with an Initial Moisture Content of 3.1%

the isotherms of additive-containing tablets are similarly displaced at relative humidities up to 62% (see also Table 2). The additives themselves adsorb little or no moisture up to this point (see Figure 1) and thus have little effect on the isotherms of the tablets containing them. At relative humidities above 62%, however, the marked differences in the sorption characteristics of the additives start to have a pronounced effect on the sorption characteristics of the tablets containing them, and the isotherms of the tablets are determined by the sorption profiles of the respective additives. Above 62% r.h., all additive-containing tablets adsorb more moisture than additive-free tablets with the same initial moisture content.

The increases in adsorption which occur in the additive-containing tablets at relative humidity levels above 62% differ according to the additive present and, qualitatively speaking, these differences closely reflect the adsorption profiles of the additives on their own.

In order to quantify the differences in adsorption profiles, the areas under the adsorption isotherms (AUC_{ad} values) were determined by integration (11). Integration was carried out between the relative humidity at the ansorption point and the highest relative humidity used in the study (84.3% at 25°C).

Figure 3 is a bar chart which shows the AUC_{ad} values for both the individual additives and the tablet variants listed in Table 1. The AUC_{ad} values represent the amounts of moisture adsorbed by the various materials and formulations. The main points to emerge from the chart are as follows:

- The AUC_{ad} values for the three additives differ widely from one another and are always higher - in some cases many times higher - than the AUC_{ad} values for the additive-free tablets.

- The AUC_{ad} values for additive-containing tablets are always higher than the AUC_{ad} values for additive-free tablets with the same initial moisture content.

- Higher additive concentrations always lead to higher AUC_{ad} values.

- The higher the initial moisture content of the tablet granulate, the lower the

TABLE 2
Interpolated Ansorption Points of Tablets prepared from Mixtures in Table 1

Additives	Initial moisture content of granulate		
	1.5%	2.1%	3.1%
	Relative humidity at ansorption point		
0%	16.9%	23.8%	48.5%
10% citric acid	17.1%	24.9%	49.2%
20% citric acid	17.1%	25.2%	49.3%
10% Sorbitol Instant	17.3%	25.3%	48.9%
20% Sorbitol Instant	17.9%	25.5%	48.9%
10% maltodextrin	18.1%	25.0%	45.5%
20% maltodextrin	19.4%	24.8%	41.8%

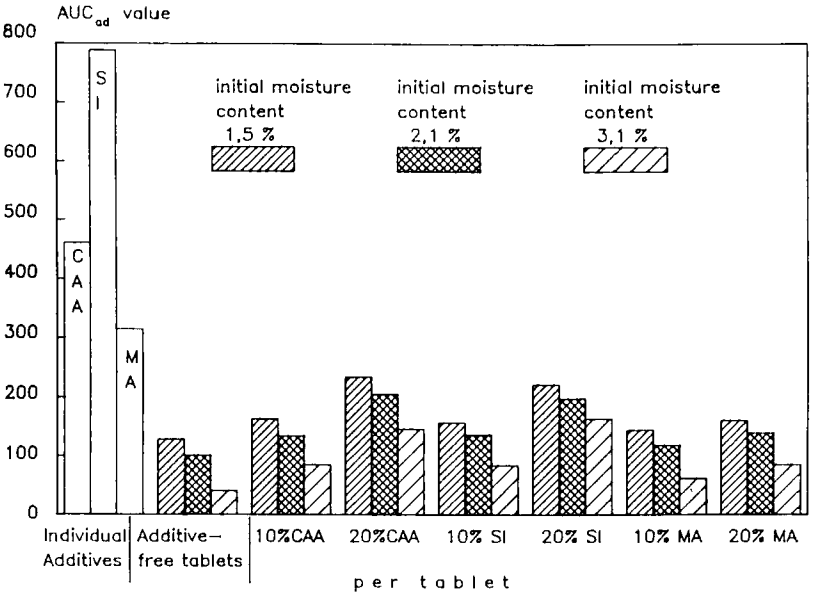

FIGURE 3: AUC_{ad} Values for Individual Additives and All Tablet Variants listed in Table 1

AUC_{ad} value for the finished tablet. Tablets with higher initial moisture contents have less capacity for adsorption.

- The AUC_{ad} values for the additives are not always directly related to the AUC_{ad} values for the tablets containing those additives. For instance, the AUC_{ad} values for tablets containing CAA are sometimes higher than the AUC_{ad} values for tablets containing SI despite the fact that the AUC_{ad} value for SI on its own is higher than the AUC_{ad} value for CAA on its own. No such discrepancy appears to exist with MA, however, at least in qualitative terms. The AUC_{ad} value for MA on its own lies in between the AUC_{ad} values for CAA and SI on their own, and the AUC_{ad} values for tablets containing MA lie in between those of the corresponding tablets containing CAA and SI. The likely explanation for this finding is that there is a difference in adsorption mechanisms between the additives and the tablets and/or between tablets containing different additives.

It would appear from the above results that there is no simple way of making either qualitative or quantitative predictions of the AUC_{ad} values (and hence the adsorption capacities) of mixtures from the AUC_{ad} values of their ingredients. This finding is consistent with the results of studies performed in 1945 by Griffin (12), who investigated softened glue compositions containing varying amounts of sorbitol and/or glycerol and found that the hygroscopicities of the glue and the softeners were not additive. It does not, by contrast, support the conclusions of the early research work done by Scott et al. (13), who suggested that it would be possible to predict the sorption characteristics of tablets from the sorption profiles of their ingredients.

Zografi et al. (19) and Lang and Steinberg (20) have devised equations to describe the sorption behaviour of binary and ternary mixtures, but whether these can easily be adapted to the complexity of a multi-component tablet granulate, if at all, remains in doubt. The issue is in any event outside the scope of this paper.

3.3. Effect of the Additives on Sorption-Related Changes in Tablet Hardness

Figures 4a - c show the differences between the hardness/sorption curves of additive-containing tablets and the hardness/sorption curves of additive-free tab-

lets. Clearly, the addition of any of the additives at either of the concentrations tested leads to changes in these curves. The most marked differences occur, as with the sorption isotherms (cf. Figures 1 - 2), at relative humidity levels above 62%/25°C. Below this level, it appears that the resistance of the tablets to sorption-related changes in hardness is proportional to the initial moisture content of the tablet granulate. This finding is consistent with the results of earlier studies (6, 7).

At relative humidity levels above 62%, additive-free tablets and tablets containing CAA and SI rapidly become less hard as moisture adsorption increases. Many authors have noted this phenomenon, which is presumed to be due to the reduction of binding forces and the dissolution of solid bridges as a result of moisture uptake (4, 14, 15). Moisture uptake also leads to increases in tablet thickness and diameter (see 3.4. and 3.5.), which themselves would promote hardness loss owing to a weakening in the forces of attraction and a destruction of solid bridges.

The results obtained in our study are consistent with the assumption of Young and Nelson (20) that water from a moist atmosphere is initially adsorbed onto the surfaces of a dry material in a unimolecular layer. At this stage, both surface binding and diffusional forces are at work. Further uptake of water at the surface of the material, due to an increase in the relative humidity of the atmosphere, causes diffusional forces to predominate, with the result that moisture penetrates into the material. This is precisely the type of diffusion which appears to take place in both the additive-free tablets and the tablets containing CAA and SI at relative humidities above 62% in our study.

Tablets containing MA behaved rather differently from the other tablet variants in respect of the relationship between sorption and hardness. This was not unexpected in view of the differences in the sorption isotherms noted under 3.2. The sorption/hardness curves show that, as moisture adsorption increases, the tablets rapidly become much harder. This may be due to the fact that maltodextrin has an adhesive effect when exposed to moisture, a property which has been exploited in wet granulation processes, where the substance has been used as a binder (10). As further moisture is adsorbed, however, the diffusional forces mentioned above start to operate and tablet hardness then shows a very marked decrease.

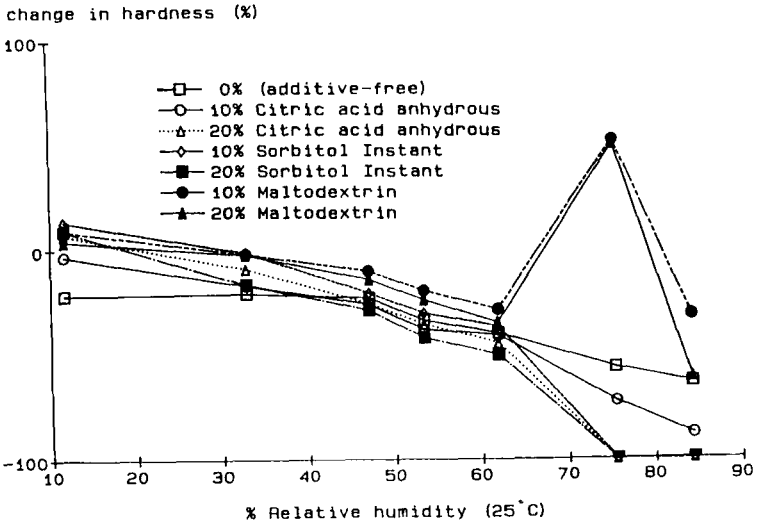

FIGURE 4a: Sorption/Hardness Curves (at 25°C) of Tablets with an Initial Moisture Content of 1.5%

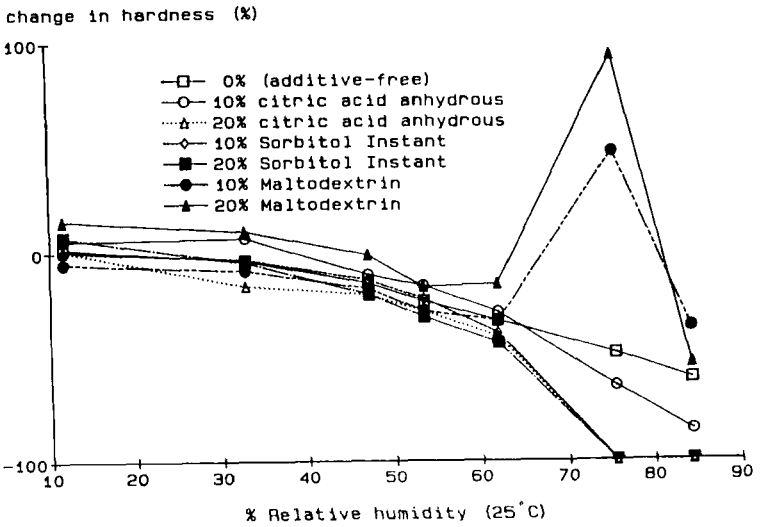

FIGURE 4b: Sorption/Hardness Curves (at 25°C) of Tablets with an Initial Moisture Content of 2.1%

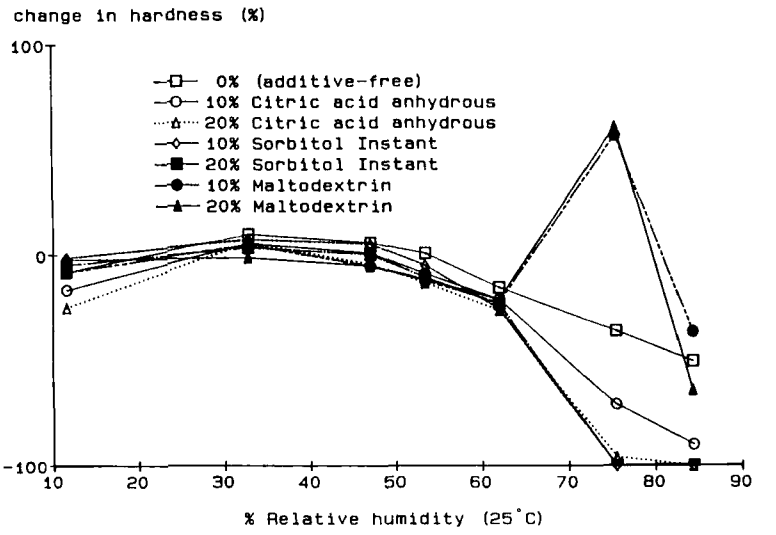

FIGURE 4c: Sorption/Hardness Curves
(at 25°C) of Tablets with an Initial Moisture Content of 3.1%

For each additive-containing tablet variant, two concentrations of additive were tested. The results showed that only in the case of CAA did the concentration alter the effect of the additive on the sorption/hardness curve. It can therefore be assumed that lower concentrations than the ones used in this study will also have a marked effect on the sorption/hardness curves.

3.4. Effect of the Additives on Sorption-Related Changes in Tablet Thickness

The sorption/thickness curves illustrated in Figures 5a - c show clearly that, for all tablet variants tested, tablet thickness increases with increasing moisture adsorption. The findings in detail are as follows:

- Hygroscopic additives accelerate the rate at which thickness increases on adsorption. Even MA causes an increase in the rate of expansion at relative humidities above 62% (cf. 3.3. and Figures 4a - c).

- The highest increases in thickness and the greatest variations between the tablet variants occur at relative humidities above 62%.

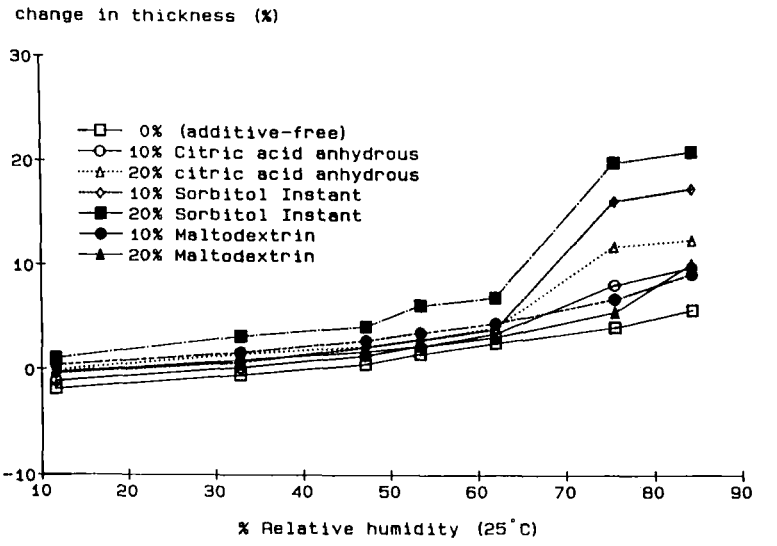

FIGURE 5a: Sorption/Thickness Curves
(at 25°C) of Tablets with an Initial Moisssture Content of 1.5%

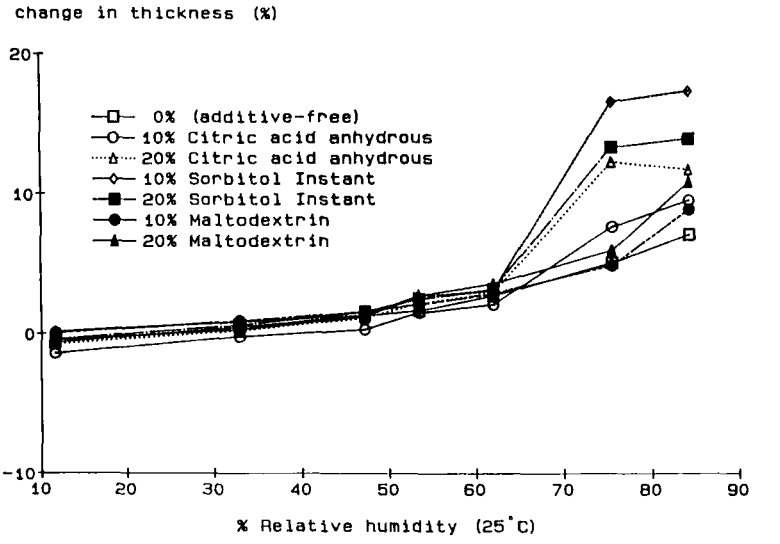

FIGURE 5b: Sorption/Thickness Curves
(at 25°C) of Tablets with an Initial Moisture Content of 2.1%

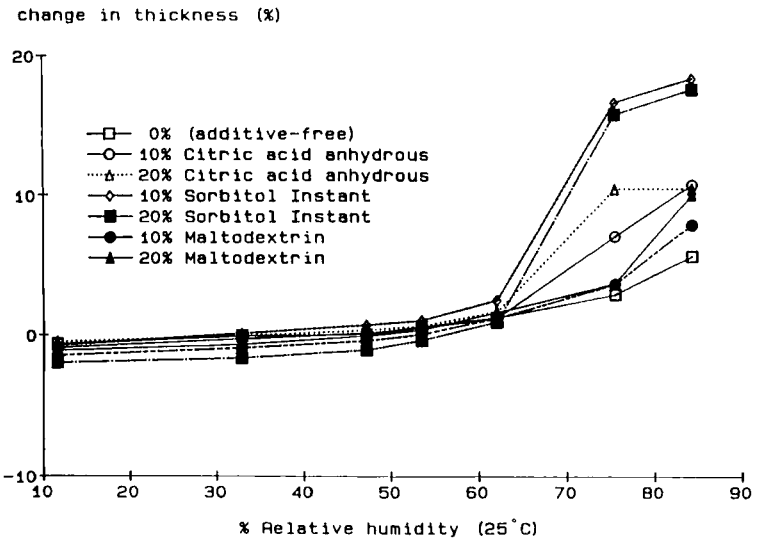

FIGURE 5c: Sorption/Thickness Curves
(25°C) of Tablets with an Initial Moisture Content of 3.1%

- The resistance of the tablets to sorption-related changes in thickness is proportional to the initial moisture content of the tablet granulate, with the wetter granulates providing the greater resistance.

The increases in thickness are most probably due to swelling of the starch caused by penetration of water into the tablet. Similar increases have been observed in earlier studies by ourselves (6) and, among others, Uzunarslan and Akbuga (18). The latter carried out experiments on ranitidine hydrochloride tablets prepared using maize starch and found a marked increase in tablet volume at 75% r.h. but not at 50% or 30% r.h.

3.5. Effect of the Additives on Sorption-Related Changes in Tablet Diameter

The results obtained in respect of tablet diameter, as illustrated in Figures 6a - c, correspond largely to those obtained in respect of tablet thickness. However, the increases in diameter are in all cases smaller than the increases in thickness. This finding is consistent with the results of earlier studies (6).

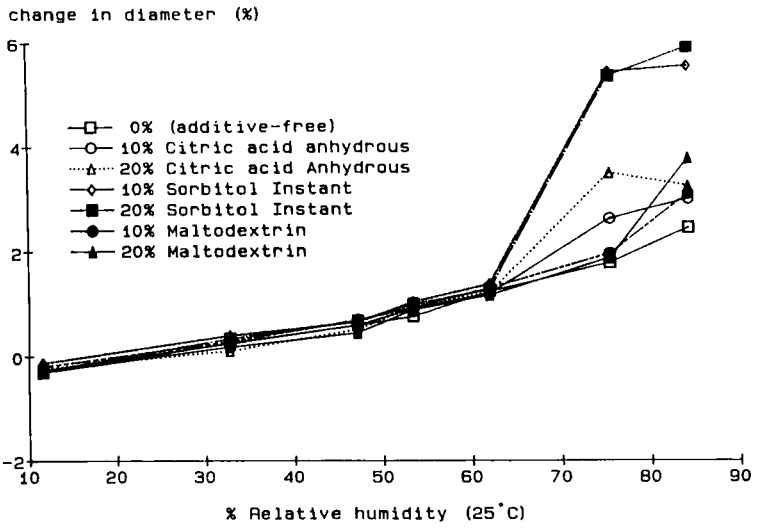

FIGURE 6a: Sorption/Diameter Curves
(at 25°C) of Tablets with an Initial Moisture Content of 1.5%

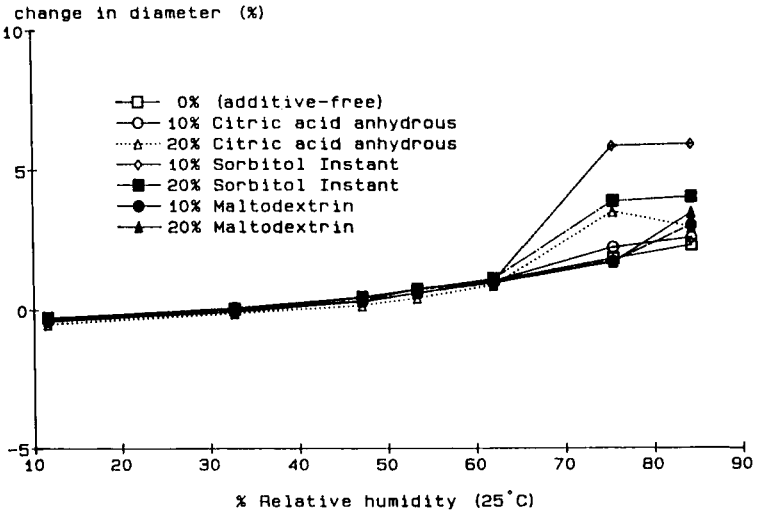

FIGURE 6b: Sorption/Diameter Curves
(at 25°C) of Tablets with an Initial Moisture Content of 2.1%

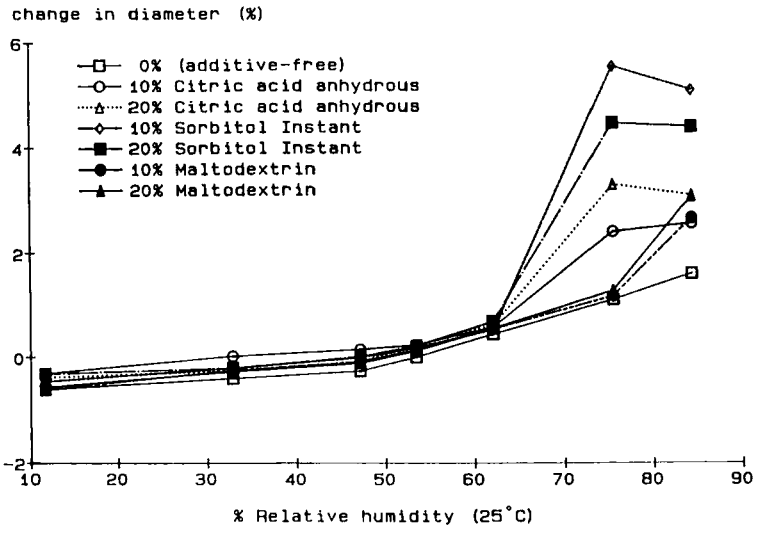

FIGURE 6c: Sorption/Diameter Curves
(at 25°C) of Tablets with an Initial Moisture Content of 3.1%

3.6. Effect of the Additives on Sorption-Related Changes in Disintegration Time

As in a previous study (6), the disintegration times of the various tablet variants differed widely and no clear pattern was detectable. The results have therefore not been plotted or interpreted.

4. CONCLUSION

The standard tablet granulate formulation chosen for this study is identical, at least in qualitative terms, to the excipient composition of a large number of tablet formulations manufactured by wet granulation (17). In addition, CAA, SI, MA and other excipients and active ingredients with similar sorption isotherms are in widespread use. This means that the results obtained in the present study assume a more general importance.

Two main points emerge from this study:

- The moisture-sensitivity of a tablet formulation is highly dependent on its initial

moisture content, and close control of this parameter will ensure optimum stability characteristics on storage.

- Hygroscopic additives do not markedly increase the adsorption of atmospheric moisture by a tablet until comparatively high relative humidity levels are attained. Hence, also, they do not markedly affect sorption-related parameters such as thickness and diameter until these levels are reached. In addition, it is clear that hygroscopic additives have little or no effect on the relative humidity level at which a tablet starts to adsorb water.

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