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Effervescent Tablets of Ascorbic Acid. I. Physical Study of the Possible Components to Be Used

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ABSTRACT

The stability of ascorbic acid effervescent tablets is substantially affected by moisture. Therefore the choice of suitable excipients is a very important step in the formulation study of this type of tablets. This work reviews the most common excipients used in effervescent preparations. They are characterized by microscopical observation and determination of particle size distribution, density, moisture, hygroscopicity, and electrostatics. Hygroscopicity is the most important property when choosing an excipient for an effervescent preparation. Therefore, two different methods for its determination have been used.

INTRODUCTION

Ascorbic acid, or vitamin C, appears in several oral preparations as an active drug. Among them, effervescent tablets are outstanding because they offer an attractive administration and also improve the absorption of the active drug by previous dissolution in a buffered medium.

The stability of ascorbic acid is affected by high temperatures, oxygen, light, alkalinity, and moisture. This last factor is very important in the case of effervescent tablets, since moisture catalyzes the reaction between acid and basic components even in its sealed packet. From the reaction, more water is produced and the reaction proceeds spontaneously until the complete disintegration of the tablet has occurred (Fig. 1). Furthermore, when moisture is present, ascorbic acid darkens to a brown color with an intensity not proportional to its chemical degradation (1-5).

The aim of this work consisted in obtaining stable effervescent tablets of ascorbic acid. The direct compression technique was used, which apart from being advantageous because water is not used, it is also easier and takes less time than production by wet granulation. However, direct compression of ascorbic acid has many technological problems, such as sticking to punches and matrices, and capping of tablets.

In the first part of this work a systematic study was carried out of the most common raw materials in the composition of effervescent tablets.

$$\text{R-COOH} + \text{XCO}_3 \xrightarrow{\text{H}_2\text{O}} \text{R-COOX} + \text{CO}_2 + \text{H}_2\text{O}$$

Figure 1. Reaction between acid components and basic components of an effervescent tablet.

MATERIALS AND METHODS

Materials

The excipients listed in Table 1, which are possible components of our effervescent tablet, were studied.

The modified sodium bicarbonate was obtained by heating sodium bicarbonate in order to convert the surface of its particles to sodium carbonate. According to several authors (6–12), a conversion of 5% to 10% gives better compression characteristics and becomes less hygroscopic than the common bicarbonate. In our case, a study was carried out to plot a graph showing the conversion of bicarbonate to carbonate at 100°C (Fig. 2). The modified sodium bicarbonate used in our study was obtained by heating common sodium bicarbonate for 45 min. This corresponds to a conversion of about 9%.

Table 1

Components Used in the Study

Component	Supplier
Active drug: ascorbic acid	Merck
Acids	
Citric acid anhydrous	Quimidroga
Tartaric acid	Panreac
Malic acid	Panreac
Monosodium citrate anhydrous	Panreac
Carbonates	
Sodium bicarbonate	Merck
Modified sodium bicarbonate	Merck
Glycine and sodium carbonate	Tessendero Chemie
Sodium carbonate anhydrous	Merck
Binding agents	
Glycine	Merck
Kollidon 25	BASF
PVP 40	Claudio Barcia
Diluents	
Sorbitol Instant	Merck
Mannitol FG	Roquette
Lactose Fast Flo	Foremost
Pharmatose DCL 21	Melkindustrie
Tablettose	Meggle
Sucrose 227-A.2	Fine Foods
Dextrose 070-A.14	Fine Foods
Emdex	Mendell
Lubricants	
Sodium benzoate	Merck
PEG 6000	Claudio Barcia
Fumaric acid	Merck
Adipic acid	Panreac
Sweetening agent: sacharin sodium	Química Massó

The most common lubricants, talc and magnesium stearate, cannot be used, due to the fact that excipients for effervescent tablets must be soluble. Lubricants studied in this work have worse lubricant properties than the above two but they comply with the condition of solubility.

Methods

Excipients were characterized by determining physical parameters of pharmaceutical interest, comparing them with ascorbic acid. All raw materials were passed through a sieve of 1 mm mesh.

Microscopical Observation

A stereomicroscope Zeiss SVD equipped with a Polaroid camera was used. The microphotograph obtained provides information about shape and size of particles. Figure 3 corresponds to a microphotograph of the ascorbic acid employed in the study.

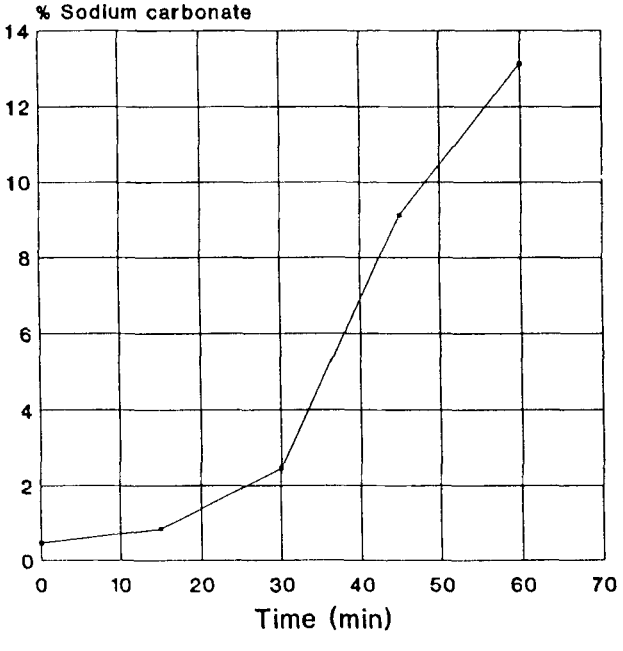

Figure 2. Conversion of bicarbonate into carbonate at 100°C.

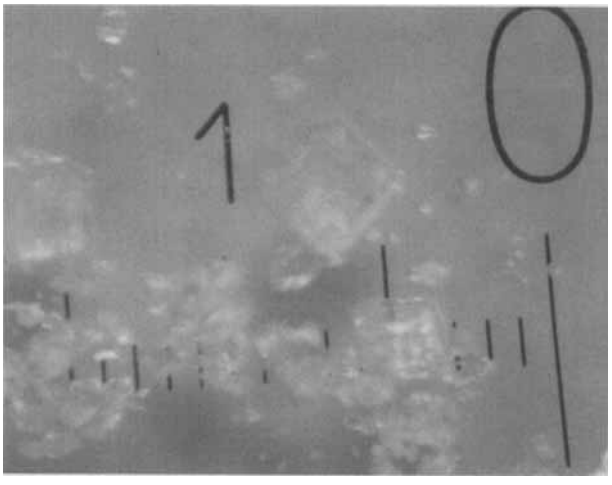

Figure 3. Microphotograph of the ascorbic acid used. Each division corresponds to 10 μm.

Particle Size Distribution

According to the particle size of products, a different apparatus was used: an electromagnetic shaker sieving C.I.S.A. machine and a jet air sieving Alpine A-200 LS machine. From the results, the mean particule diameter for each product was calculated.

Densities

Bulk density (d_0) and tapped density (d_{500}) of acids, carbonates, and diluents were determined by a volumenometer Engelsmann STAV 2003. Compressibility index or Carr index (13) was calculated in order to give an idea of product flow properties.

Moisture

Loss on drying and water content were determined by the Karl Fischer method. For sodium bicarbonate, the method used consisted in drying the product on silica gel for 4 hr, as recommended by USP.

Loss on drying was determined employing an Arizona Instruments machine Max 50. This equipment utilizes a computerized system which reduces the trial time and increases the accuracy in comparison to traditional methods with ovens.

Hygroscopicity

Hygroscopicity is an essential property to take into account when choosing a raw material for an effervescent tablet. The sorption isotherms were drawn determining the equilibrium moisture content at different relative humidities and at a determined temperature. Two methods were used, one with desiccators and the other with a Mahler apparatus.

The desiccators method determines the weight difference of the sample when it reaches equilibrium after being stored in the desiccator at a determined relative humidity. The relative humidity in the desiccator is achieved thanks to a saturated salt solution (14–19). The Callahan and Colls method (14), adopted afterwards by the *Handbook of Pharmaceutical Excipients* (20), was used.

The Mahler machine (21) (Fig. 4) consists of a microbalance connected to a thermostatized water bath. By changing the temperature of the bath, the vapor pressure can be modified inside the apparatus and, consequently, the relative humidity is changed. As low pressure is employed, equilibrium moisture content of the sample is reached rapidly.

According to Callahan et al. (14), products must be classified into four types depending on their hygroscopicity:

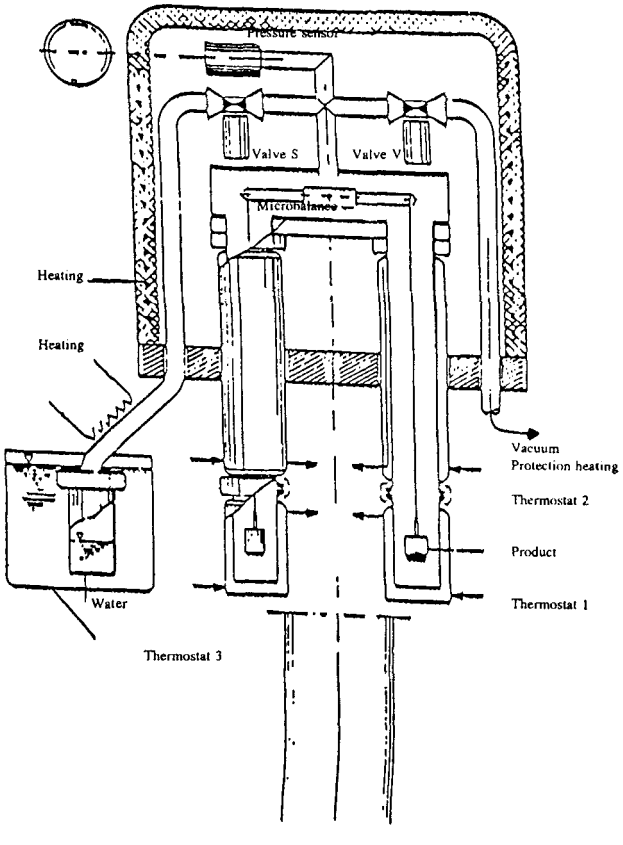

Figure 4. Mahler apparatus.

Type I Nonhygroscopic. Almost no increase in water content under 90% relative humidity. The increase after 1 week of storage over 90% RH is less than 20%.

Type II: Slightly hygroscopic. Almost no moisture increase is produced under 80% relative humidity. After 1 week of storage at 80% relative humidity, moisture is less than 40%.

Type III: Moderately hygroscopic. Moisture content is not over 5% after storage at relative humidities below 60%. After 1 week's storage over 80% RH, less than 50% moisture.

Type IV: Very hygroscopic. Water content can increase with relative humidities as low as 40–50%. Moisture after 1 week's storage over 90% RH can exceed 30%.

Electrostatics

The method by Guyot et al. (22) was followed. The product is poured into a beaker and it is vigorously stirred with a glass stick and with a hard rubber stick; making circular movements along the inside wall. The powder, which is charged easily, will adhere to the stick wall. The glass stick attracts the powder charged negatively. The rubber stick attracts the powder with positive charge.

RESULTS AND DISCUSSION

The microscopical observation revealed that most of the raw materials studied are crystalline (Table 2).

Table 3 summarizes the rest of the pharmacotechnical properties determined. The mean particle size of most products is relatively large. Among them, the small particle size of sodium bicarbonate and Lactose Fast Flo must be emphasized. Apparent densities are high, except for the monosodium citrate and Sorbitol Instant. This suggests that problems in homogeneity of mixtures or separations in the hopper during tabletting will not occur.

Carr tests are good (under 20%) except for monosodium citrate anhydrous, sodium bicarbonate, and glycine and sodium carbonate, which slightly exceed the limit value. Therefore, it can be considered that acids, carbonates, and diluents have good flow.

Moisture of some products is over 0.50%, the maximum limit indicated by Chafai (23) and Barnerias (24) for raw materials of effervescent preparations. It is very

Table 2

Characterization of the Components by Microscopical Observation

Structure	Shape: Prismatic	Shape: Irregular
Crystalline anhydrous	Ascorbic acid	Monosodium citrate
	Citric acid anhydrous	Glycine and sodium carbonate
	Tartaric acid	Sodium carbonate anhydrous
	Malic acid	Sorbitol Instant
	Sodium bicarbonate	Mannitol FG
	Glycine	Lactose Fast Flo
	Fumaric acid	Pharmatose DCL 21
	Adipic acid	Tablettose
	Saccharine sodium	Sucrose 227-A·2
		Emdex
		Dextrose 070-A·14
		Sodium benzoate
Amorphous		Kollidon 25
		PVP 40
		PEG 6000

Table 3

Results Obtained for the Different Raw Materials Studied

Product	D_m (μm)	d_0	d_{500}	*CI* (%)	Moisture (%) Max 50	Moisture (%) *KF*	Hygroscopicity Type	*E*
Ascorbic acid	301.9	0.95	1.07	9.84	0.30		I	+
Citric acid anhydrous	421.7	0.93	1.00	6.54	0.33	0.23	IV	+
Tartaric acid	652.6	0.89	0.94	5.41	0.28		I	+
Malic acid	652.6	0.83	0.93	10.81	0.88		IV	+
Monosodium citrate anhydrous	147.8	0.49	0.64	23.42	0.44		II	+
Sodium carbonate	88.0	0.96	1.25	23.12	0.18[a]	0.11[a]	I	+
Sodium bicarbonate treated	87.2	0.97	1.26	23.32		0.00[a]	IV	+
Glycine and sodium carbonate	216.0	0.88	1.16	24.50	0.70		I	+
Sodium carbonate anhydrous	286.0	1.09	1.25	13.12	0.28		IV	+
Sorbitol Instant	453.0	0.42	0.48	11.45	0.22	1.11	IV	+
Mannitol FG	278.0	0.69	0.75	6.97	0.31		I	+
Lactose Fast Flo	99.0	0.58	0.67	12.76	0.88	4.09	I	+
Pharmatose DCL 21	155.6	0.67	0.78	14.08	0.30	0.27	I	+
Tablettose	188.8	0.57	0.70	18.89	0.38		I	+
Sucrose 227-A·2	256.6	0.69	0.77	10.40	0.76		IV	+
Emdex	239.4	0.64	0.69	7.06	8.95		IV	+
Dextrose 070-A·14	249.7	0.63	0.73	14.55	0.76		I	+
Glycine	516.6				0.22		I	+
Kollidon 25	91.4				2.47	4.09	IV	0
PVP 40	83.6				4.75		IV	+
Sodium benzoate	326.3				0.60		I	+
PEG 6000	440.6				0.31	0.79	I	+
Fumaric acid	76.8				0.34	0.28	I	0
Adipic acid	211.4				0.28		I	0
Saccharine sodium	432.3				3.86		I	+

Note. D_m = mean diameter, d_0 = bulk density, d_{500} = tapped density, *CI* = Carr index, *KF* = Karl Fischer, *E* = electrostatics.
[a]LOD Max50 at 60°C and weight loss on silica gel after 4 hr.

high in Emdex, Kollidon 25, PVP 40, and saccharine sodium. Regarding their high proportion in the composition, acids and diluents should be dried under 0.50% before being used.

The methods employed to determine hygroscopicity (desiccators method and Mahler apparatus method) provide very similar results, as can be seen in Fig. 5, corresponding to sorption isotherms of ascorbic acid obtained by both methods. This makes us conclude that the method of the Mahler apparatus is advantageous, since it is as accurate as the desiccators method and requires only a few hours to reach the equilibrium moisture content, as compared with the 1 week required for the second method.

Figures 6–17 show sorption isotherms of the excipients studied. According to the Callahan et al. classification (14) citric acid anhydrous, malic acid, sodium carbonate anhydrous, Kollidon 25, Emdex, Sorbitol Instant, sucrose 227-A·2, and PVP 40 are very hygroscopic. Monosodium citrate anhydrous is slightly hygroscopic, according to this classification; and the rest are nonhygroscopic. However, citric acid anhydrous, malic acid, and sucrose 227-A·2 increase moisture only significantly over 80% relative humidity. It must be emphasized that when sodium bicarbonate is modified, it becomes very hygroscopic, which contradicts several authors who say exactly the opposite (6–12).

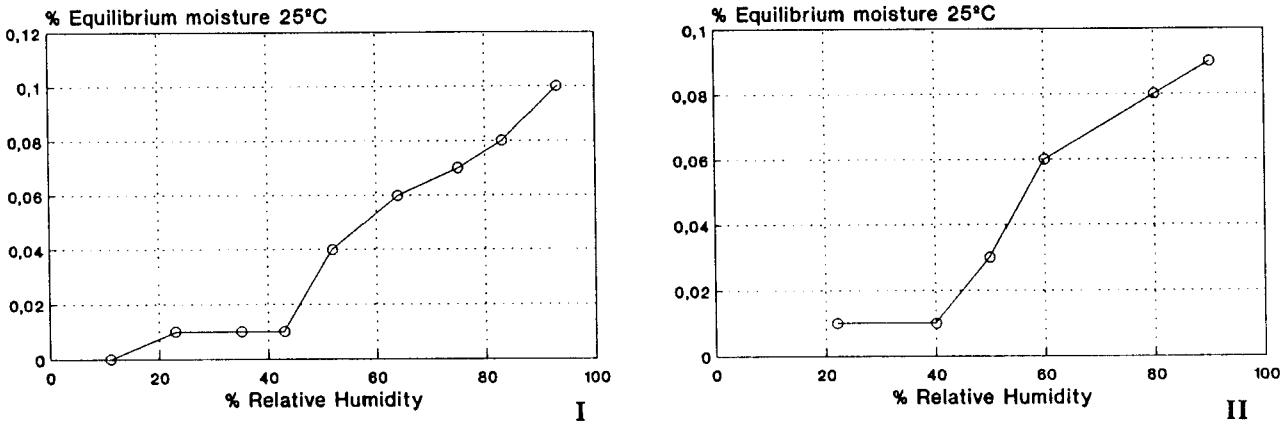

Figure 5. Sorption isotherms of ascorbic acid obtained by the desiccators method (I) and by the Mahler apparatus (II).

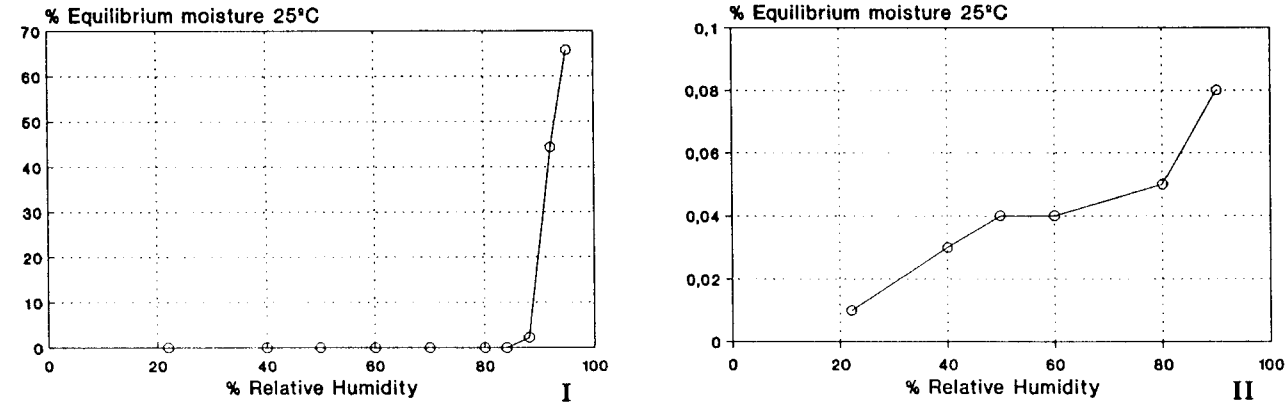

Figure 6. Sorption isotherms of citric acid anhydrous (I) and tartaric acid (II).

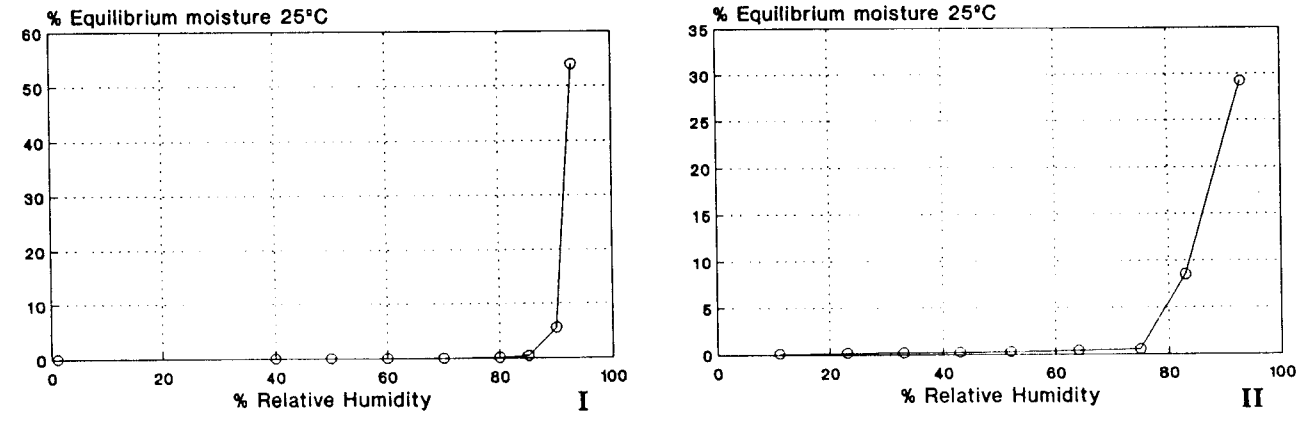

Figure 7. Sorption isotherms of malic acid (I) and monosodium citrate anhydrous (II).

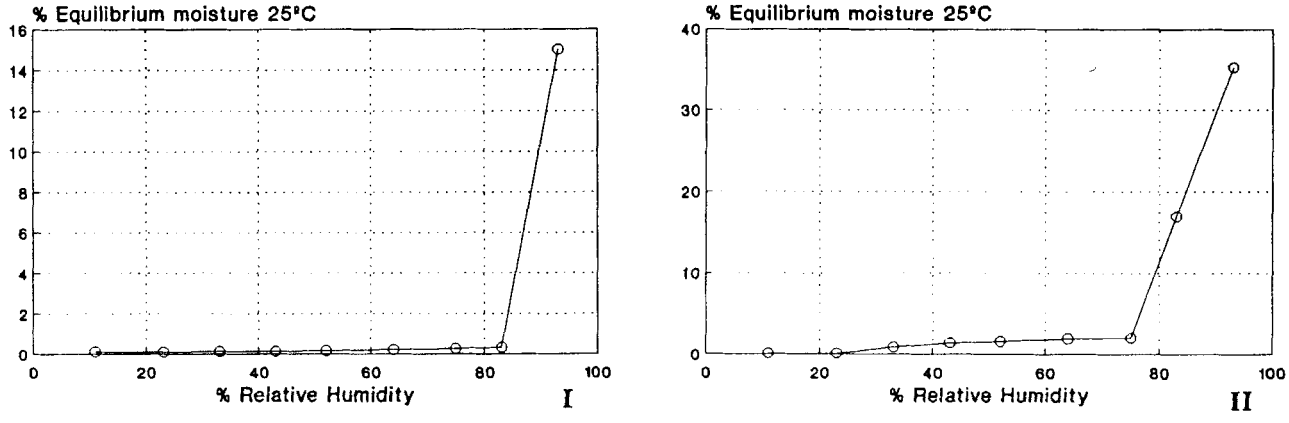

Figure 8. Sorption isotherms of sodium bicarbonate (I) and sodium bicarbonate treated (II).

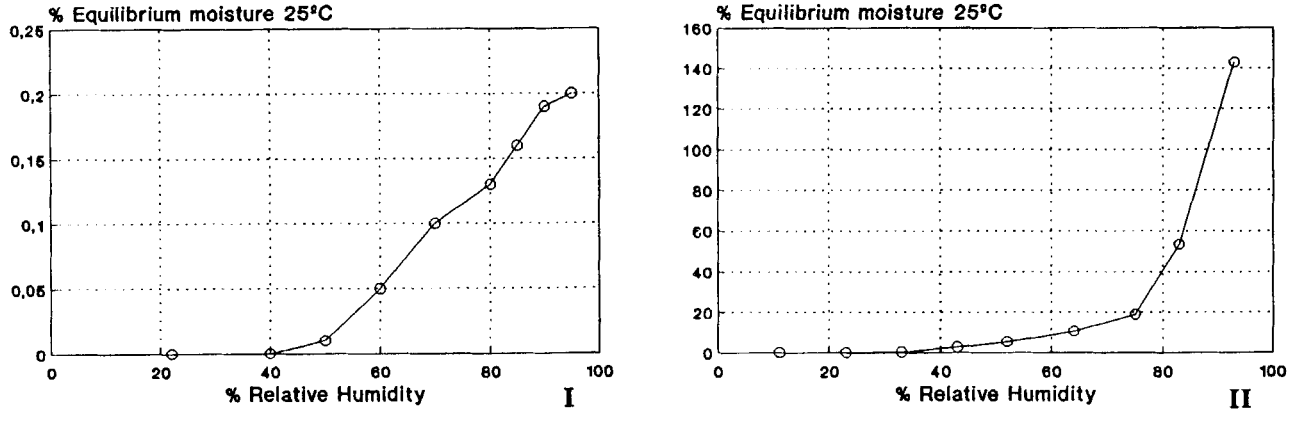

Figure 9. Sorption isotherms of glycine and sodium carbonate (I) and sodium carbonate anhydrous (II).

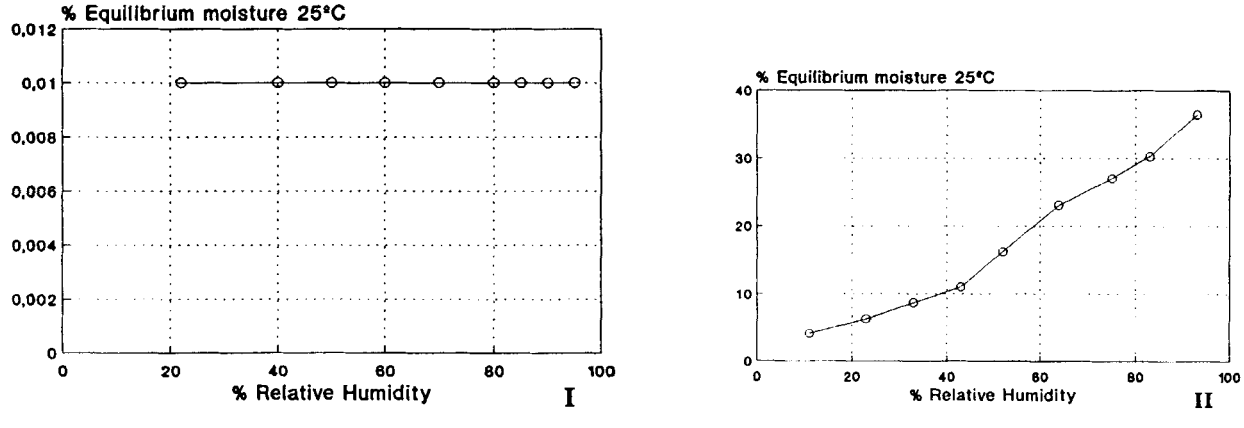

Figure 10. Sorption isotherms of glycine (I) and Kollidon 25 (II).

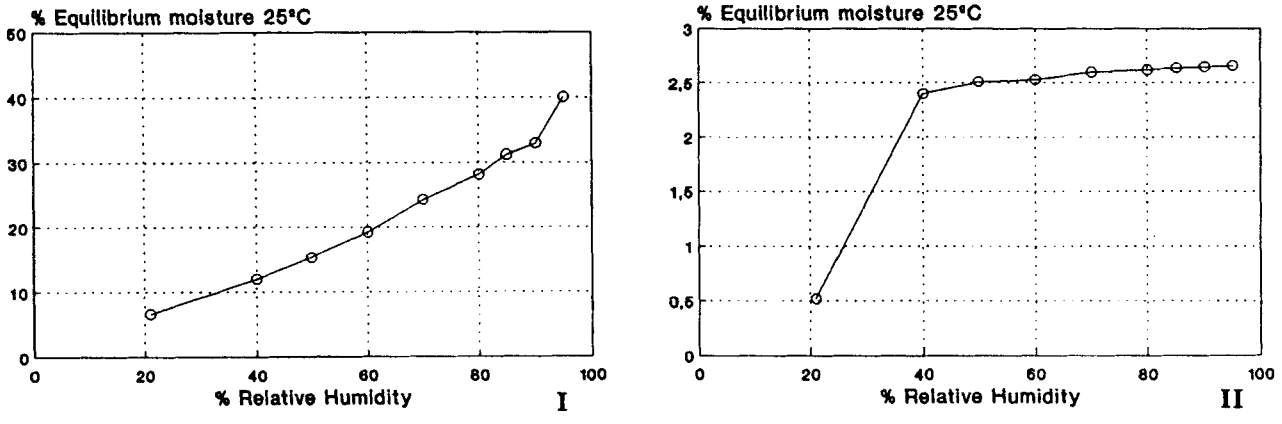

Figure 11. Sorption isotherms of PVP 40 (I) and saccharine sodium (II).

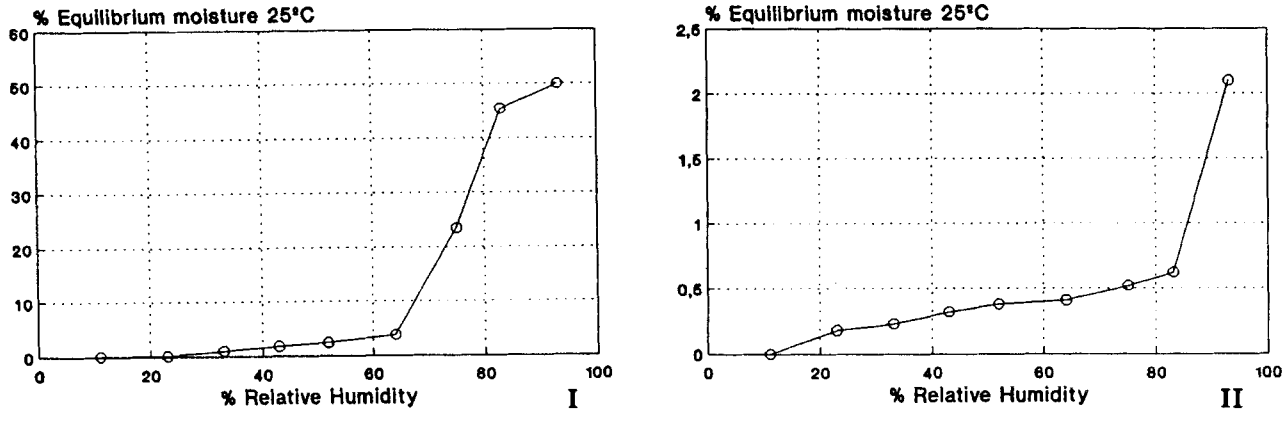

Figure 12. Sorption isotherms of Sorbitol Instant (I) and Mannitol FG (II).

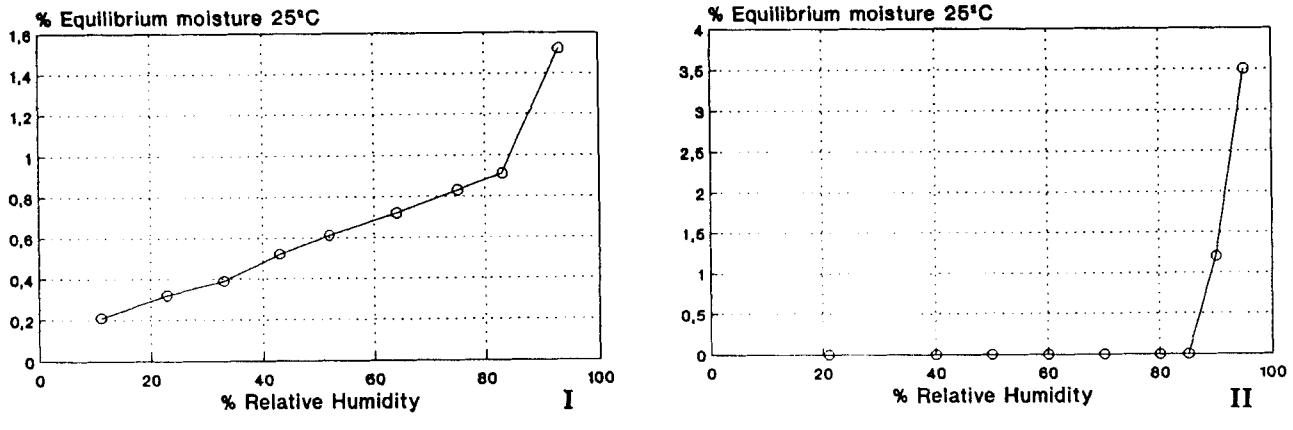

Figure 13. Sorption isotherms of Lactose Fast Flo (I) and Pharmatose DCL 21 (II).

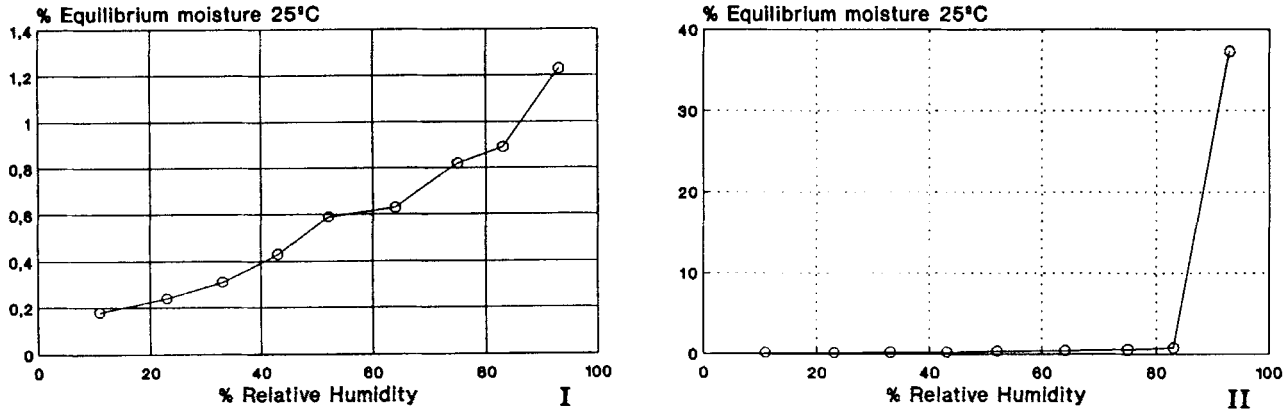

Figure 14. Sorption isotherms of Tablettose (I) and Sucrose 227-A·2R (II).

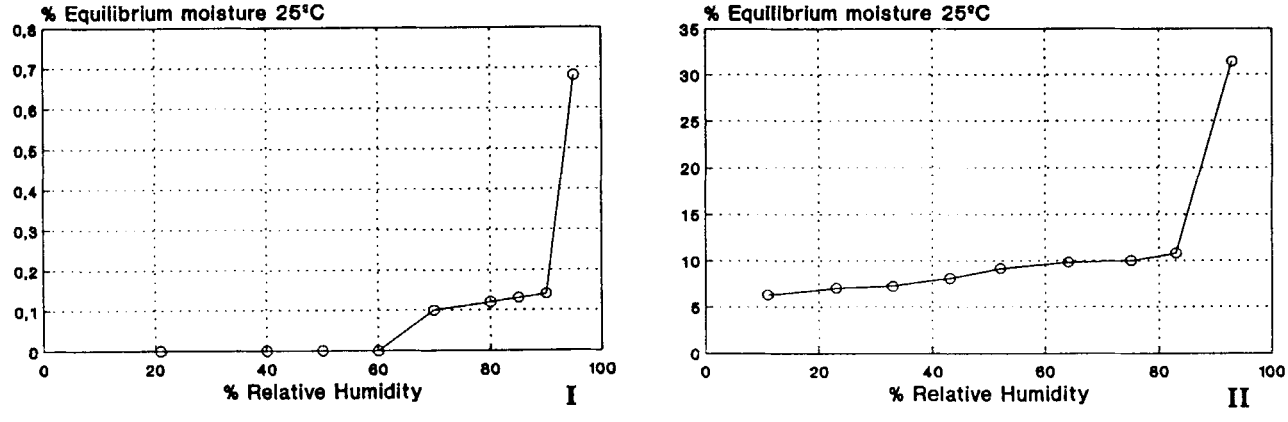

Figure 15. Sorption isotherms of Dextrose 070-A·14 (I) and Emdex (II).

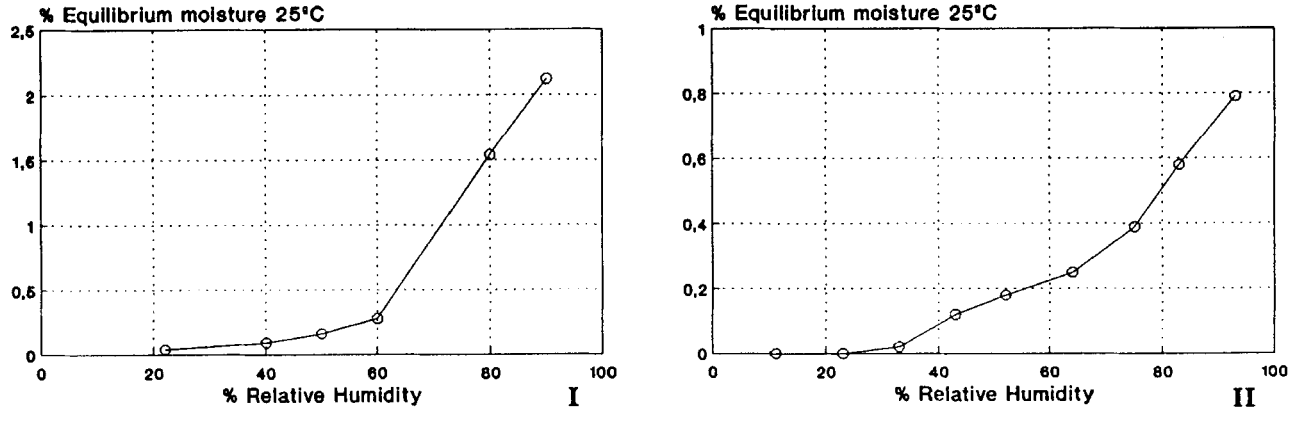

Figure 16. Sorption isotherms of sodium benzoate (I) and PEG 6000 (II).

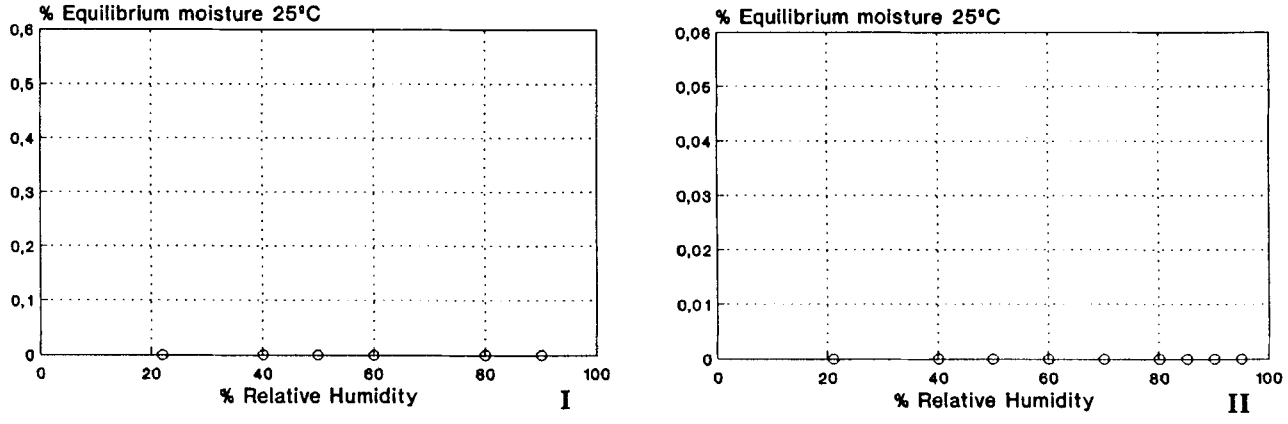

Figure 17. Sorption isotherms of fumaric acid (I) and adipic acid (II).

Regarding electrostatics, most of the products studied have a slight positive charge, which will never represent a problem when tablets are manufactured.

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