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EQUILIBRIUM MOISTURE CONTENT OF PHARMACEUTICAL EXCIPIENTS

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ABSTRACT

The equilibrium moisture content (EMC) was determined for thirty pharmaceutical excipients. These data are to be included in the forthcoming publication of the Handbook of Pharmaceutical Excipients. This work was undertaken as a collaborative effort under the sponsorship of the Academy of Pharmaceutical Sciences. The results of this study are being reported herein prior to publication of the Handbook.*

The experimental procedure for determining equilibrium moisture content is included along with a method for classifying the hygroscopic property of solids.

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* A brief description of the method used in the determination of Equilibrium Moisture Content of pharmaceutical excipients as well as all experimental data will appear in expanded form in the forthcoming "Handbook of Pharmaceutical Excipients" to be published by the APhA Academy of Pharmaceutical Sciences with full copyright protection.

Introduction

The sorption of moisture by pharmaceutical solids has been examined by many workers and methods for determining equilibrium moisture content (EMC) have been reported in the literature (1-8). The present method developed by J. Callahan (12) represents a modification of one first described by Scott et al. (5)

EXPERIMENTAL

Materials

Nine plastic desiccators, Nalge/Sybron Corporation, approximately 9 inches in diameter, were obtained from a local laboratory supply house. Glass desiccators of equivalent size may be substituted for the plastic containers.

A supply of glass analytical weighing bottles with standard taper covers (25 mm. O.D. x 40 mm. ht. with 12 ml. capacity were used to contain samples for testing. Samples were weighed on an analytical balance to the nearest 0.1 mg. A series of saturated salt solutions were prepared as described in Table 1.

Procedure

EMC determinations were made by placing accurately weighed samples of each material (100-200 mg) in 2 or 3 open, tared, and numbered weighing bottles and then into a labeled desiccator containing one of the saturated salt solutions described in Table 1. A liberal amount of the saturated salt solution (with excess crystals) was placed in the well of the desiccator.

Samples were stored in each of the nine securely closed individual desiccators, each containing a different moisture atmosphere. At equilibrium (7 days storage at controlled room temperature 25°C ± 2°C) the samples were removed from the desiccators and the moisture increase

or decrease determined for each sample by obtaining the final equilibrium weight with the aid of an analytical balance. These data were recorded on moisture analysis data sheets, a sample of which is provided in Table 2.

EMC values were calculated from P (% moisture dry basis) with the aid of the equations given in Table 2. Initial moisture content (A) of each excipient was accurately determined by a suitable method, such as loss on drying to constant weight (see Table 3) and used to caclulate P. EMC values, at each relative humidity tested, were tabulated and presented in Table 2 and plotted, using coordinate graph paper, to obtain EMC vs. relative humidity curves (Figure 2).

TABLE 1

Saturated Salt Solutions for Maintaining

Constant Relative Humidity Conditions in Desiccators

Saturated Salt Solution*	Percent Relative Humidity at Temperatures (9-11) 20°C	25°C	30°C	37°C
Lithium Chloride	12	11	11	11
Potassium Acetate	24	23	23	23
Magnesium Chloride	33	33	32	31
Potassium Carbonate	44	43	42	41
Magnesium Nitrate	53	52	52	51
Sodium Nitrite	66	64	63	62
Sodium Chloride	76	75	75	75
Potassium Bromide	84	83	82	81
Potassium Nitrate	94	93	92	91

* Prepared from reagent grade salts dissolved in purified water.

Calculation*

$$P = \frac{\left[W \times \frac{A}{100}\right] \pm B \times 100}{W - \left[W \times \frac{A}{100}\right]}$$

Where P = % moisture dry basis

W = initial sample weight in grams

A = % moisture at start

B = weight change at equilibrium in grams

$$EMC = \frac{P}{P + 100} \times 100$$

$$EMC = \frac{24.2\%}{24.2\% + 100} \times 100 = 19.5\%$$

Hygroscopicity Classification

When evaluating the hygroscopic properties of solids, unprotected material is exposed for one week to varying relative humidities from 11 to 93 or 100%. The change in moisture content of the powder depends upon the initial moisture content and the relative humidity of the environmental chamber. Objectionable changes in the physical appearance of the material can occur independent of the moisture increase. For example, physical changes may appear in some materials with little increase in moisture content, whereas no physical change may occur in another product with a large increase in moisture content. These additional physical

* Derivation of the equations used for calculating EMC were provided by Drs. Kaplan and Kensler.

TABLE 2

Typical Moisture Analysis Data Sheet

Pharmaceutical Excipient:	Bentonite N.F.
Lot No.:	NG 3977
Source (Manufacturer):	Whittaker, Clark and Daniels, Inc.
Temperature:	
Initial Date:	1.22.80 , 20 °C
Final Date:	1.29.80 , 20 °C
Desiccator No.:	Nine
Salt Solution Used:	Potassium Nitrate
Relative Humidity:	94 Percent
Percent Moisture at Start:	5.74 N.F. XV, page 1210 (2 hrs. at 105°C)

	Replicate No.1	Replicate No.2	Replicate No.3
Bottle No.	17	18	
Wt. Empty Bottle (with cover)	19.6335 g	18.8080 g	
Wt. of Bottle and Sample Before Test (with cover)	19.7386 g	18.9111 g	
Wt. of Bottle and Sample After Test (with cover)	19.7562 g	18.9290 g	
Wt. of Moisture Increase or Decrease	0.0176 g	0.0179 g	
Moisture Content, Dry Basis	23.81%	24.49%	
Average Value		24.2%	

factors are also important in evaluating the hygroscopic nature of a pharmaceutical excipient.

In the case of non-hygroscopic materials, the moisture change at relative humidities below 75% may be negligible, but the increase at high relative humidities may be very large. Though these

TABLE 3

Hygroscopicity Classification (See Figure 1)

Class I - Non-Hygroscopic:

Essentially no moisture increases occur at relative humidities below 90%. Furthermore, the increase in moisture content after storage for one week above 90% R.H. is less than 20%.

Class II - Slightly Hygroscopic:

Essentially no moisture increases occur at relative humidities below 80%. The increase in moisture content after storage for one week above 80% R.H. is less than 40%.

Class III - Moderately Hygroscopic:

Moisture content does not increase above 5% after storage at relative humidities below 60%. The increase in moisture content after storage for one week above 80% R.H. is less than 50%.

Class IV - Very Hygroscopic:

Moisture increase may occur at relative humidities as low as 40 to 50%. The increase in moisture content after storage for one week above 90% R.H. may exceed 30%.

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powders can be adequately protected by suitable packaging, they could change physical form rapidly during actual use under unfavorable high humidity storage conditions. With some very hygroscopic materials the moisture content may increase at relative humidity as low as 40 to 50%. Such powders would require special low humidity areas for processing, in addition to special packaging and storage instructions.

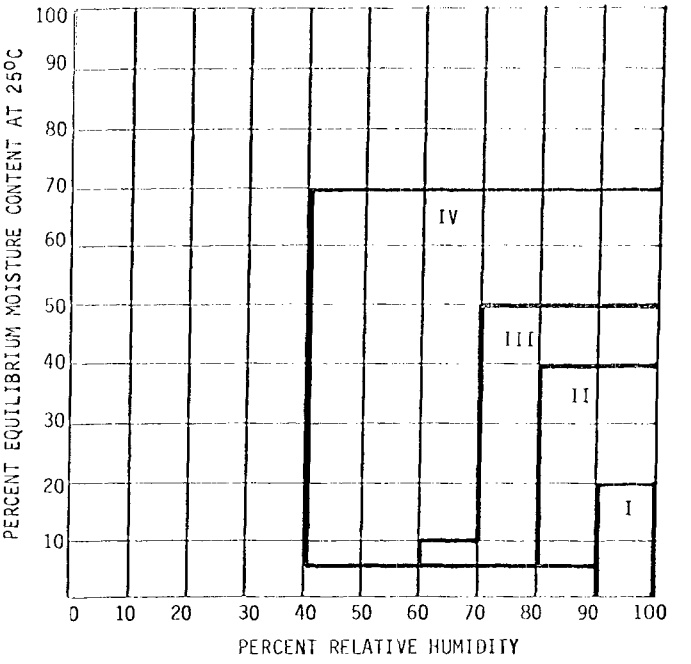

Fig. 1. - Hygroscopicity Classification

Key: Class I - Non-Hygroscopic
Class II - Slightly Hygroscopic
Class III - Moderately Hygroscopic
Class IV - Very Hygroscopic

With these factors in mind, the following classification of hygroscopic materials has been devised (12).

In general most powders are either Class I or Class II excipients. Usually these materials will require only standard packaging and will present no physical stability problems in the field.

Class III materials may or may not require special packaging depending upon the effect of moisture on the physical stability and appearance of the material. Class IV materials, with a few

exceptions, should be modified chemically to render them less hygroscopic.

This classification is not applicable if objectionable changes in the physical appearance occur at certain relative humidities. A Class II material would change to a Class III material if an objectionable physical change occurred at relative humidities below 90%. Furthermore, a Class III material would become Class IV if objectionable changes occurred at relative humidities below 75%.

In addition, observations and physical descriptions of materials afer exposure to RH experiments would be useful additional information in such studies.

RESULTS AND DISCUSSION

Powdered excipients and solids may hold water either by physical means (adsorption, absorption, or occlusion, so-called "free water") or by chemical means (water of hydration, or "bound water"). As far as EMC is concerned, sorption or desorption of moisture of water vapor from the surrounding atmosphere is primarily a physical process.

The initial moisture content of the thirty pharmaceutical excipients studied are presented in Table 4. The excipients range in moisture content from less than 0.1 percent for sucrose and anhydrous dicalcium phosphate to more than 10 percent for gelatin and polyplasdone XL. Most of these values were determined by loss on drying in a vacuum oven at 60°C.

The percent EMC at 25°C and different relative humidities for twenty-six excipients together with their hygroscopicity classification

are summarized in Table 5. Studies were conducted at 20°C for four other materials: i.e., powdered cellulose, bentonite, gelatin, and polyplasdone XL. The corresponding relative humidities at 20°C are approximately one or two percent higher than the values reported at 25°C. However, the difference in RH values is not considered significant with respect to the EMC values reported.

Almost two-thirds of the excipients tested are either Class I or II materials. These excipients are primarily tablet and capsule fillers, and conditioning agents. The rest, which are more hygroscopic, are primarily tablet binders and tablet disintegrants.

Five cellulosic film formers were also studied. They range from less hygroscopic, ethyl cellulose (I) and cellulose acetate phthalate (II) to more hygroscopic, hydroxypropyl cellulose (III), hydroxypropyl methylcellulose (III), and sodium carboxymethyl cellulose (IV).

Interestingly enough, anhydrous materials, such as dicalcium phosphate and lactose, which were presumed to hydrate rapidly in the presence of high humidity atmospheres, were found to be moisture stable, non-hygroscopic (Class I) diluents.

EMC curves for four representative excipients (anhydrous lactose, cellulose acetate phthalate, magnesium aluminum silicate and povidone) are presented in Figure 2.

CONCLUSIONS

Equilibrium moisture content (EMC) was determined for thirty common pharmaceutical excipients. A method for classifying the hygroscopic properties of powdered materials and solids was presented. Such data and the method described for determining EMC should find application in preformulation work.

TABLE 4

INITIAL MOISTURE CONTENT OF PHARMACEUTICAL

Excipient	Supplier & Lot Number
Sucrose U.S.P.	Amstar Co. (51995)
Dicalcium Phosphate, Anhyd. U.S.P.	Monsanto Co. (RNB4768)
Lactose U.S.P., Anhydrous	Humko Products (8NH22-21)
Lactose U.S.P., Monohydrate	Mallinckrodt Chem. (B1523)
Lactose U.S.P., Spray Dried	Foremost Foods (56165)
Lactose U.S.P., Beadlets	Foremost Foods (RB806)
Polyethylene Glycol 3350 N.F.	McKesson Co. (B192-8209)
Poloxamer 188	BASF Wyandotte (WPEA536B)
Silicon Dioxide, Colloidal N.F.	Cabot Corp. (IL288)
Sorbitol U.S.P.	ICI Americas, Inc. (2404J1)
Ethylcellulose N.F.	Hercules (58587)
Dical. Phosphate Dihydrate U.S.P. milled	Monsanto Co. (05587)
Sodium Starch Glycolate N.F.	Edward Mendell Co. (959)
Hydroxypropyl Methylcellulose U.S.P.	Dow Chemical Co. (QP0502-801-E)
Cellulose Acetate Phthalate N.F.	Eastman Chemical (C-2104)
Magnesium Stearate N.F.	S.B. Penick Co. (338 NBS-003)
Hydroxypropyl Cellulose	Hercules (6387)
Cellulose, Microcrystalline N.F.	FMC Corp. (1929)
Povidone U.S.P.	GAF Corp. (690429B)
Cellulose, Powdered N.F.	Brown Co. (30150)
Bentonite N.F.	Whittaker, Clark & Daniels (NG3977)
Magnesium Aluminum Silicate N.F.	R.T. Vanderbilt Co. (NV1640)
Pregelatinized Starch N.F.	National Starch (HJW103)
Starch U.S.P., Corn	National Starch (421)
Dical Phosphate Dihydrate U.S.P. unmilled	Stauffer Chemical Co. (16)
Dextrates	Edward Mendell Co. (M-10)
Dextrose U.S.P.	CPC International (CP44)
Sodium Carboxymethylcellulose U.S.P.	Hercules (76493)
Gelatin U.S.P.	Kind & Knox Gelatin Co.
Polyplasdone XL	GAF Corp. (457-28)

EXCIPIENTS USED IN THE STUDY

Initial Moisture Content	Test Method
<0.1%	USPXX Method III, p.960-16 hrs at 105°C
<0.1%	Vacuum Oven - 16 hrs. at 60°C
0.2%	USPXX Method I, p.988 (K. Fischer)
0.2%	Vacuum Oven - 16 hrs. at 60°C
0.2%	Vacuum Oven - 16 hrs. at 60°C
0.2%	Vacuum Oven - 16 hrs. at 60°C
0.3%	Vacuum Oven - 16 hrs. at 60°C
0.3%	Vacuum Oven - 16 hrs. at 60°C
0.6%	Vacuum Oven - 16 hrs. at 60°C
0.7%	USPXX Method I, p.988 (K. Fischer)
0.7%	Vacuum Oven - 16 hrs. at 60°C
1.1%	Vacuum Oven - 16 hrs. at 60°C
1.2%	Vacuum Oven - 20 hrs. at 60°C
2.1%	Vacuum Oven - 16 hrs. at 60°C
2.2%	N.F. XV, p.1219 - 2 hrs. at 60°C
3.0%	N.F. XV, p.1235 - 3 hrs. at 105°C
3.1%	Vacuum Oven - 16 hrs. at 60°C
3.6%	N.F. XV, p.1218 - 4 hrs. at 105°C
4.5%	Vacuum Oven - 16 hrs. at 60°C
5.7%	NF XV, p.1219 - 2 hrs. at 105°C
5.7%	NF XV, p.1210 - 2 hrs. at 105°C
6.0%	Vacuum Oven - 20 hrs. at 60°C
7.0%	Vacuum Oven - 20 hrs. at 60°C
7.1%	Vacuum Oven - 16 hrs. at 60°C
8.0%	Vacuum Oven - 16 hrs. at 60°C
8.2%	Vacuum Oven - 16 hrs. at 60°C
8.3%	USPXX Method III, p.960 - 16 hrs at 105°C
8.5%	USPXX Method III, p.960 - 16 hrs at 105°C
10.6%	AOAC Method, 12th Ed., p.222
11.5%	USPXX Method I, p.988 (K. Fischer)

TABLE 5

EQUILIBRIUM MOISTURE CONTENT OF

Excipient	Percent EMC at 25°C 11%RH	23%RH	33%RH	43%RH
Dicalcium Phosphate, Anhyd. U.S.P.	<0.1	---	<0.1	<0.1
Lactose U.S.P., Beadlets	0.2	---	0.2	0.2
Lactose U.S.P., Monohydrate	0.2	---	0.2	0.2
Lactose U.S.P., Spray Dried	0.5	---	0.5	1.0
Dical. Phosphate Dihydrate, USP milled	1.1	1.5	1.7	1.8
Lactose U.S.P., Anhydrous	0.2	---	0.2	0.2
Ethylcellulose N.F.	0.3	0.6	0.9	0.9
Magnesium Stearate N.F.	3.1	3.6	3.1	3.1
Dical. Phosphate Dihydrate USP unmilled	8.0	8.1	8.1	8.2
Colloidal Silicon Dioxide N.F.	0.0	---	0.6	0.6
Cellulose Microcrystalline N.F.	0.2	2.4	3.7	4.5
Cellulose Acetate Phthalate N.F.	2.2	3.2	3.7	5.1
Sucrose U.S.P.	0.0	0.2	0.3	0.6
Dextrose U.S.P.	7.7	8.6	8.4	8.6
Poloxamer 188	0.4	0.3	0.8	0.6
Powdered Cellulose N.F.*	7.4	---	9.1	7.0
Dextrates	7.7	8.1	8.6	8.8
Polyethylene Glycol 3350 N.F.	0.3	---	<0.3	0.2
Hydroxypropyl Cellulose	0.9	1.9	3.0	3.8
Hydroxypropyl Methylcellulose U.S.P.	1.9	2.6	3.5	4.3
Bentonite N.F.*	2.1	4.5	5.5	5.6
Pregelatinized Starch N.F.	5.3	---	7.8	8.7
Starch U.S.P., Corn	5.5	---	8.0	10.0
Magnesium Aluminum Silicate N.F.	3.7	---	6.0	7.4
Gelatin U.S.P.*	8.2	9.4	10.0	9.6
Sodium Starch Glycolate N.F.	3.8	---	6.2	7.7
Polyplasdone XL*	7.3	13.0	13.1	16.7
Povidone U.S.P.	5.1	8.2	12.2	14.4
Sorbitol U.S.P.	0.7	0.8	1.4	1.2
Sodium Carboxymethylcellulose U.S.P.	7.4	9.2	15.1	14.5

* EMC values determined at 20°C where relative humidities are approximately one percent greater

PHARMACEUTICAL EXCIPIENTS

and Different Relative Humidities

52%RH	64%RH	75%RH	83%RH	93%RH	100%RH	Hygroscopicity Class
<0.1	<0.1	<0.1	<0.1	0.5	7.0	I
0.2	0.2	0.2	0.2	1.0	17.0	I
0.2	0.2	0.2	0.2	0.2	17.5	I
1.0	1.0	1.0	1.0	1.5	21.5	I
1.3	1.4	1.4	1.3	1.5	----	I
0.2	0.5	1.0	1.5	3.0	27.	I
1.3	2.2	2.7	3.3	5.0	----	I
3.2	3.3	3.5	5.0	6.9	----	I
8.3	8.4	8.4	8.2	8.2	----	I
1.7	2.6	3.4	4.8	13.5	34.9	I
5.4	6.6	8.1	9.1	13.2	----	II
6.0	7.5	8.7	9.5	11.9	----	II
1.6	0.2	0.4	0.2	38.7	----	II
9.7	9.2	10.0	9.7	31.2	----	II
0.9	0.9	1.4	3.8	44.1	----	II
7.9	9.3	11.0	12.4	16.0	----	II
9.3	10.2	11.7	13.9	51.1	----	II
0.6	1.1	2.0	4.0	48.3	62.2	II
5.4	7.3	11.0	12.7	21.3	----	III
5.9	7.9	10.5	12.8	25.7	----	III
6.7	9.9	12.2	13.7	19.5	----	III
10.4	12.1	14.7	16.0	22.7	36.4	III
11.6	13.2	14.4	19.1	21.5	16.5	III
10.1	13.4	15.1	16.7	22.0	39.4	III
12.6	15.4	18.4	20.2	33.1	----	III
9.5	12.6	17.3	22.4	41.4	60.5	IV
19.0	22.2	27.7	29.6	38.0	----	IV
17.6	21.8	27.8	31.9	44.8	----	IV
1.8	2.7	28.4	36.0	50.8	----	IV
19.5	21.4	25.8	30.8	46.2	----	IV

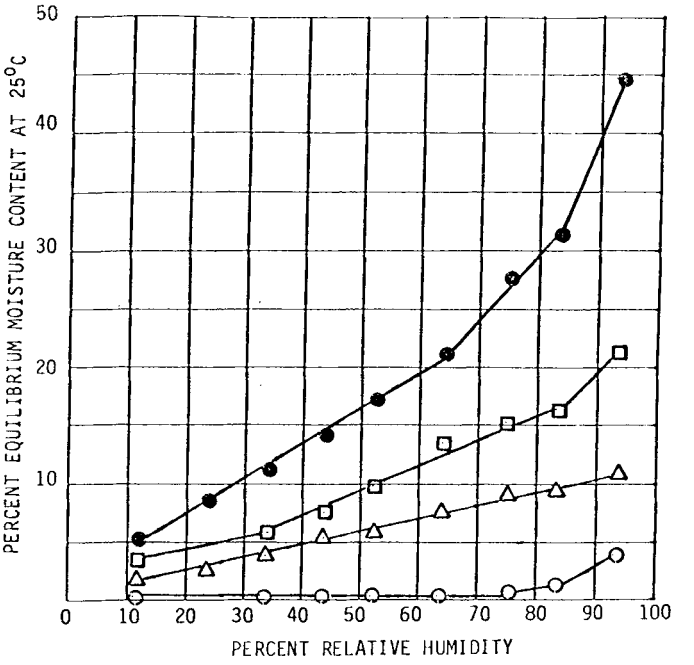

Fig. 2. - EMC Curves for Representative Excipients According to Hygroscopic Classification

Key:
- ○ Class I - Non-Hygroscopic (Anhydrous Lactose USP)
- △ Class II - Slightly Hygroscopic (Cellulose Acetate Phthalate N.F.)
- □ Class III - Moderately Hygroscopic (Magnesium Aluminum Silicate N.F.)
- ● Class IV - Very Hygroscopic (Povidone U.S.P.)

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