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PREFORMULATION
- THE ROLE OF MOISTURE IN SOLID DOSAGE FORMS -

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ABSTRACT

Moisture plays an important role in the individual stages of preformulation studies for solid dosage forms. Examples are given to demonstrate this.

The first stage involves chemical tests with the pure active substance using a reliable storage scheme. Then compatibility testing between active and inactive substances is performed. Under the general heading of sorption tests, the determination of sorption isotherms using special apparatus and their correlation with the physical and chemical changes which occur in the samples are discussed. With the results of these tests it is often possible to influence the sorption properties of the finished dosage form, for example by selection of the excipients and the salt form of the active substance, or by deferring the point of ansorption.

Finally, as an example of special tests used in preformulation, the development of compound preparations is described and the galenical pre-stages are discussed.

INTRODUCTION

"Preformulation testing can be defined as an investigation of the physical and chemical properties of a drug substance - alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass-produced (1)."

As far as solid dosage forms are concerned, moisture plays a very significant role in this testing (2).

The most important aspects of the role of moisture for the preformulation of solid dosage forms and methods of evaluating these aspects will be discussed using practical examples.

CHEMICAL STABILITY OF THE PURE ACTIVE SUBSTANCE

Chemical stability tests show the resistance of the pure active ingredient to extrinsic factors and also supply the data required to develop a stable dosage form.

The most important extrinsic factors which can have an effect on the stability of a drug substance are light, oxidation, pH and temperature, as well as moisture. Table 1 combines these factors to give a storage scheme (3). In this storage scheme
- moisture is a 1 % aqueous solution or suspension,
- oxidation is brought about by 0.3 % hydrogen peroxide solution,

TABLE 1

Initial Experiments with the active Substance: Storage Scheme

External influences	Pure sub-stance	1% in	Storage Duration	Tempe-rature	Open	Closed	In the dark	Xenon-lamp
moisture	+		constant weight	RT	at 80% rel. humid.		+	
		H_2O	≥ 1 Month	RT		+	+	
light		H_2O	24 h			+		+
	+		24 h		+			+
	+		24 h			+		+
oxidation	+		≥ 1 Month	RT	+		+	
	+		≥ 1 Month	61°C	+		+	
		0.3% H_2O_2	24 h	RT		+	+	
		0.3% H_2O_2	24 h			+		+
hydronium or hydroxyl ions		0.1 N HCL	≥ 1 Month	RT		+	+	
		buffer pH 3	≥ 1 Month	RT		+	+	
		buffer pH 7	≥ 1 Month	RT		+	+	
		buffer pH 9	≥ 1 Month	RT		+	+	
		0.1 N NaOH	≥ 1 Month	RT		+	+	
		0.1 N HCL	24 h			+		+
		buffer pH 3	24 h			+		+
		buffer pH 7	24 h			+		+
		buffer pH 9	24 h			+		+
		0.1 N NaOH	24 h			+		+
gastric juice		+	3 h	37°C		+	+	
temperature	+		≥ 1 Month	61°C		+	+	

- the pH is brought about by 0.1 N HCL increasing over various buffers up to 0.1 N NaOH and
- the storage temperature is 61°C.

Storage is completed after 1-2 months.

The storage scheme also provides for storage of the dry active substance.

The stored samples are examined using organoleptic tests and normally also by thin-layer chromatography. If distinct decomposition is determined in an acid environment, additional storage is carried out in artificial gastric juice at 37°C for a minimum of 3 hours.

TABLE 2

AZ-DF 265 ZW (Solid Substance)
stored as in Table 1

Effect of	Results (Changes)
daylight (24 h Xenotest)	slight discoloration of the substance from white to yellowish-white
room temperature (daylight excluded)	no changes
temperature: 61°C (daylight excluded)	slight discoloration of the substance from white to yellowish-white
80 % rel. humidity	substance is not hygroscopic

The storage scheme, and the possible conclusions that can be drawn from it, are shown by two examples.

AZ-DF 265 ZW (= (±4)-[(2-Piperidino-benzhydryl)amino carbonylmethyl]benzoic acid)

AZ-DF 265 ZW was tested clinically as an oral antidiabetic. Using this storage scheme the dry substance showed slight discoloration when exposed to light and to increased temperatures (Table 2). Thin-layer chromatography showed no evidence of chemical decomposition. In a solution or suspension (Table 3) the active substance was only stable when light was excluded. When exposed to light slight discoloration also occurred, and in an alkaline environment slight chemical decomposition set in.

Thus, for the development of a tablet the conclusion could be drawn that the active substance must be pro-

TABLE 3

AZ-DF 265 ZW (Solution/Suspension)
stored as in Table 1

Effect of	Results (Changes)	
	Effect of daylight (24 h Xenotest)	Daylight excluded (37 days r.t.)
acid pH-range	slight white-yellow discoloration of the suspension	
neutral pH-range	slight white-yellow discoloration of the suspension	
alkaline pH-range	slight decomposition on the TL plate = approx. 1-2 %, slight white-yellow discoloration of the suspension	
oxidation substance (H_2O_2)	slight white-yellow discoloration of the suspension	
artificial gastric juice		

tected from light either by a suitable coating or by suitable packaging.

Bisacodyl, USP XXI

When stored in dry conditions the active substance showed slight discoloration and minor decomposition only at increased temperatures (Table 4). In solution or suspension (Table 5) on the other hand, considerable decomposition occurred, depending on the pH. It was only in a neutral pH environment that the active substance was relatively stable, at lower or higher pH values decomposition increased rapidly. Distinct sensitivity to oxidation was also observed. The test with artificial gastric juice confirmed the sensitivity

TABLE 4

Bisacodyl (Solid Substance)
stored as in Table 1

Effect of	Results (Changes)
daylight (24 h Xenotest)	no changes
room temperature (daylight excluded)	no changes
temperature: 61°C (daylight excluded)	slight discoloration decomposition < 1 %
80 % rel. humidity	the substance is not hygroscopic

TABLE 5

Bisacodyl (Solution/Suspension)
stored as in Table 1

Effect of	Results (appearance after TLC)	
	Effect of daylight (24 h Xenotest)	Daylight excluded (45 days r.t.)
in 0.1 N HCL in buffer pH 3	pale yellow approx. 50 % decomposed no discoloration approx. 5 % decomposed	no discoloration approx. 80 % decomposed no discoloration approx. 1 % decomposed
in H_2O	no discoloration approx. 1 % decomposed	no discoloration approx. 1 % decomposed
in buffer pH 9 in 0.1 N NaOH	no discoloration approx. 10 % decomposed yellowish approx. 100 % decomposed	no discoloration approx. 10 % decomposed yellowish approx. 100 % decomposed
in 0.3 % H_2O_2	slight discoloration approx. 20 % decomposed	slight discoloration approx. 40 % decomposed
in artifical gastric juice		after 1h: approx. 3% decomposed after 3h: approx.10% decomposed after 5h: approx.15% decomposed after 7h: approx.20% decomposed

to an acid environment. These results led to the development of an oral dosage form which permits drug release only in a neutral pH environment.

COMPATIBILITY BETWEEN ACTIVE AND INACTIVE SUBSTANCES

Exactly as the sensitivity of the pure active substance to extrinsic factors can be investigated, as described in the previous section, the compatibility tests are designed to determine and eliminate any interaction that may arise between active and inactive substances in the development of certain formulations.

To make these tests as efficient as possible the models are designed individually for the various stages of the galenical development.

When designing the models it is, of course, essential to take the results of the chemical stability testing of the pure active substance into account. For example, it would be irrational to store an active substance in a moist environment if the chemical stability tests have established sensitivity to moisture!

Test Material

Since solid dosage forms generally contain several inactive substances, it is always necessary to decide whether the inactive substances should be tested separately or in groups, and if so, what ratios should be chosen between the individual components.

The question of how to mix the components also has to be considered. It is quite logical that different results can be expected according to whether the

components have been lightly stirred, triturated or even compressed (4).

If only a few components are under consideration a factorial design can be very helpful (5, 6).

Storage Conditions

Along with the results of the chemical stability of the active substance the following factors should normally be considered:

- temperature
- moisture
- light

When choosing the temperature it is important to note that certain substances, some antibiotics for example, undergo considerable changes at stress temperatures, which do not occur during realistic long-term tests. An increased storage temperature can also release crystal water, which is not available for chemical decomposition reactions under normal conditions (7).

Evalution of Experiments

Organoleptic examination should be performed first. Colour charts have been found useful for the objective evaluation of discoloration.

It depends on the specific data required, whether a qualitative determination, for example by thin-layer chromatography is adequate or if quantitative determination is necessary, as for example in the case of acetyl salicylic acid, where the decomposition products, i.e. salicylic acid and acetic acid, evaporate.

TABLE 6

Review of organoleptic Changes in ARL 115-Mixtures after 10 weeks' Storage

Substance trituration 1:1 with	Room-temp. (22°C) dry trituration	Room-temp. (22°C) moist trituration	41°C dry trituration	Trituration at 41°C with H_2O	61°C dry trituration	Trituration at 61°C with H_2O
cornstarch soluble snow flake 5591 M		yellow-grey discoloration mould formation		yellow-beige discoloration mould formation	slight beige discoloration	dark brown discoloration
Aerosil^R 200				slight yellow discoloration		slight yellow discoloration
Kollidon^{R}25				yellow discoloration		dark yellow to slight brown discoloration
magnesium-stearate						grey-beige discoloration
Kollidon^{R}CL						yellow-beige discoloration
carboxy-methylcel-lulose 7H3SF		slight yellow-grey discoloration		slight yellow-grey dis-coloration		grey-brown discoloration
Methocel^R Typ E5 Premium		very slight yellow dis-coloration		beige to light brown discoloration	beige discoloration	brown to dark brown discoloration

The use of differential scanning calorimetric analysis has also been described for this purpose (8, 9). This method offers the advantage of being able to dispense with storage.

Finally, the compatibility tests are elucidated using the example of the active substance ARL 115 BS, 2-[(2-methoxy-4-methylsulfinyl)phenyl]-3H-imidazo[4,5-b] pyridine, which was exposed to a series of tablet excipients. Table 6 shows the results of the organoleptic examination of a selection of the excipients.

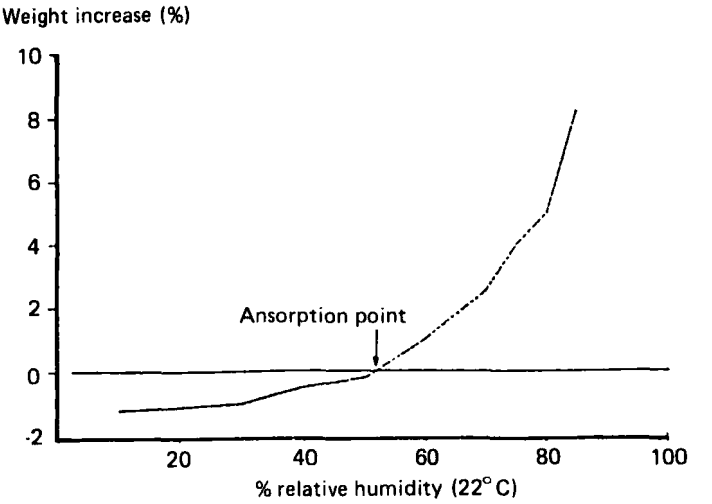

FIGURE 1

Sorption Isotherm of a Tablet Formulation

The individual excipients were triturated with the active substance at a ratio of 1:1 and then stored for 10 weeks under exclusion of light - the active substance is light sensitive - in a dry and moist environment at 22°C, 41°C and 61°C. With the exception of 2 samples, stored at 61°C discoloration only occurred in connection with a moist environment.

The thin-layer chromatogram showed no significant decomposition in any of the samples.

SORPTION STUDIES

In the previous two sections moisture has been dealt with only as a qualitative factor. The sorption studies are designed to show quantitative relationships between the samples and moisture.

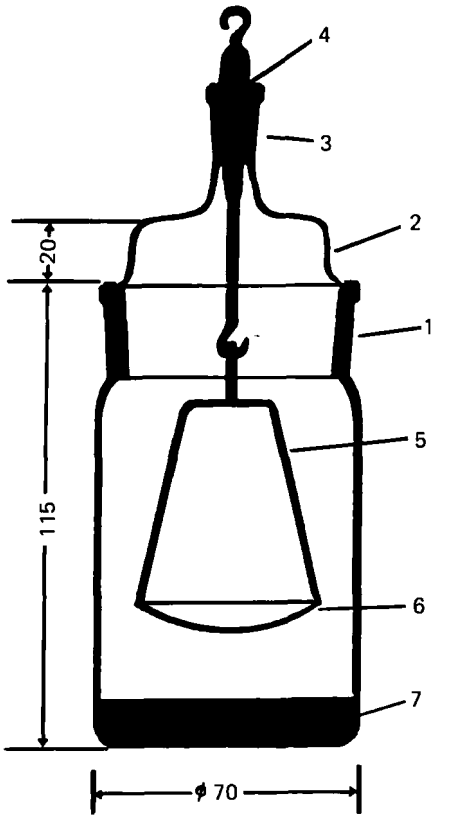

FIGURE 2
Hyqrostat with simple and reliable Sample Balance made of glass

1. and 3. normal ground-glass neck
4. Ground-glass stopper
5. Glass bar
6. Watchglass for sample
7. Solution for adjustment of relative humidity

Sorption Isotherm

Determination of the sorption isotherm is one of the most common investigations of this kind (Figure 1). The isotherm shows the equilibrium between the sample and the air surrounding it at various humidities at a given temperature.

The hygrostat shown in Figure 2 provides a gravimetric determination of the sorption isotherm

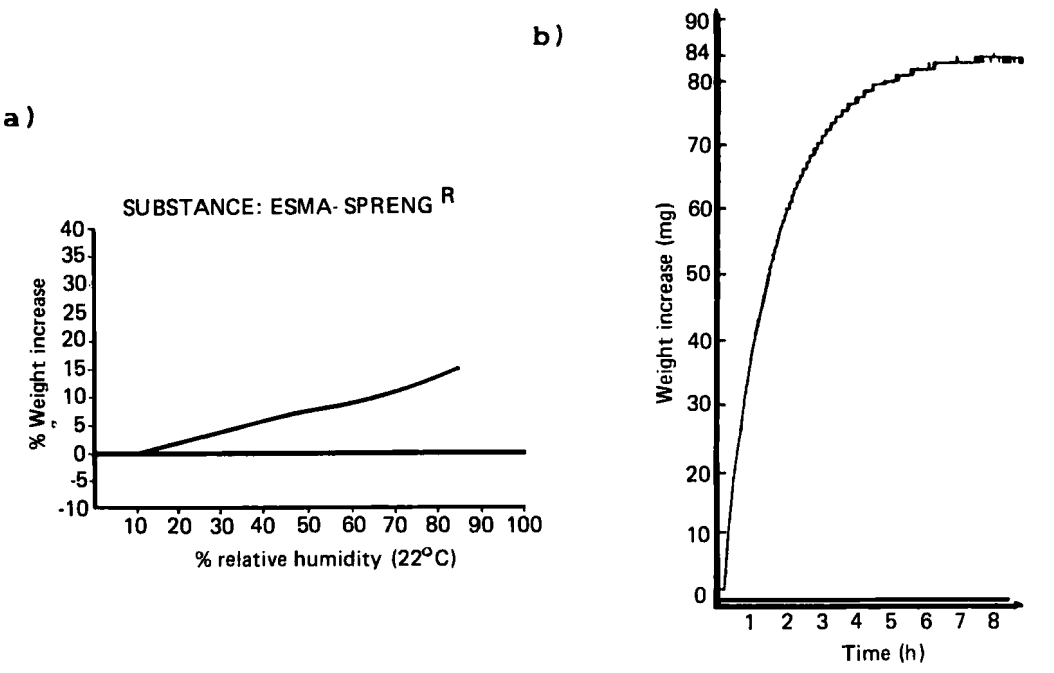

FIGURE 3

a) Sorption Isotherm of Esma-Spreng R
b) Sorption Speed of Esma-Spreng R at 54% relative humidity (22°C)

which is relatively free of disturbances (10). The sample is placed on a watchglass above the solution used to adjust the relative humidity. To weigh the sample, the ground-glass stopper is lifted slightly and suspended in a below-weighing balance.

By leaving this narrow opening, a disturbance of the hygrostatic environment can be avoided to a great degree. If the balance can be connected to a computer, the determination of the sorption isotherm becomes almost completely automated.

Speed of Sorption

This describes the speed of adsorption or desorption of a sample at a given relative humidity and temperature. The use of this determination is, however, rather limited, one of the reasons being that generally no definite decisions have been made at this stage of the preformulation regarding the surface of the finished dosage form.

Figure 3 shows the sorption isotherm of Esma-Spreng^{R}, a formaldehyde casein, and its sorption speed at 22°C and 54 % relative humidity: After only 2 hours this extremely effective tablet disintegrant had adsorbed about two thirds of the saturation moisture from the air.

Thus open processing of this substance at the normal relative humidity of between 50 and 60 % would not be advisable.

The results of the sorption speed determinations depend very much on the individual test conditions, such as the thickness of the sample layer, and can therefore only be compared with results obtained under similar conditions. The determination in the case of Esma-Spreng^{R} was performed in a combined apparatus, consisting of a hygrostat, a balance giving a continuous reading of the weight and an on-line printer (Figure 4).

Methods of changing Sorption Properties

The most common method of dealing with unfavourable sorption properties is a steam-proof package, perhaps combined with a dessicant additive. The disadvantages of such packaging are well known.

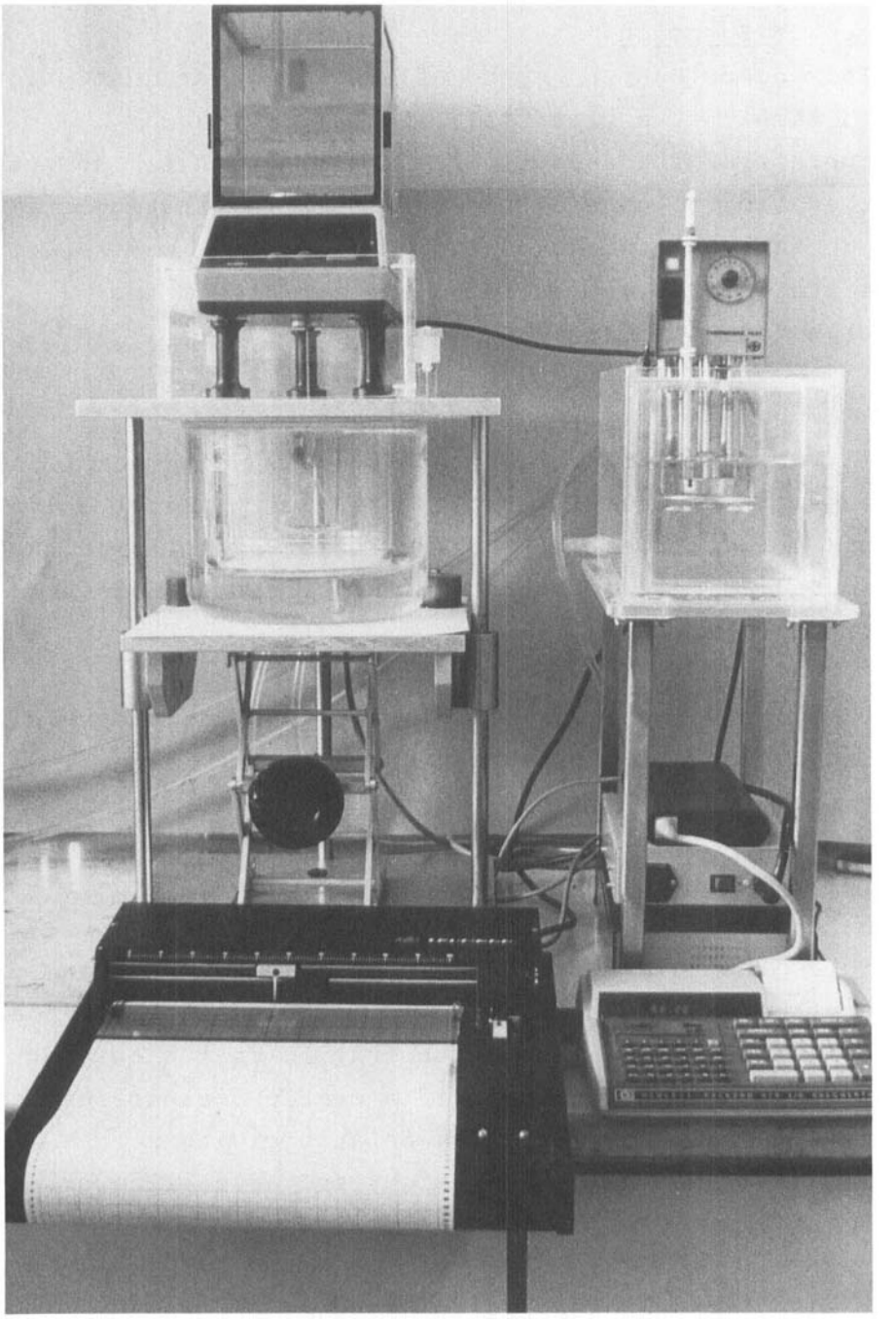

FIGURE 4

Apparatus for measuring the Sorption Speed: Combination of Hygrostat, a Balance giving a continuous Reading of the Weight and an on-line Printer

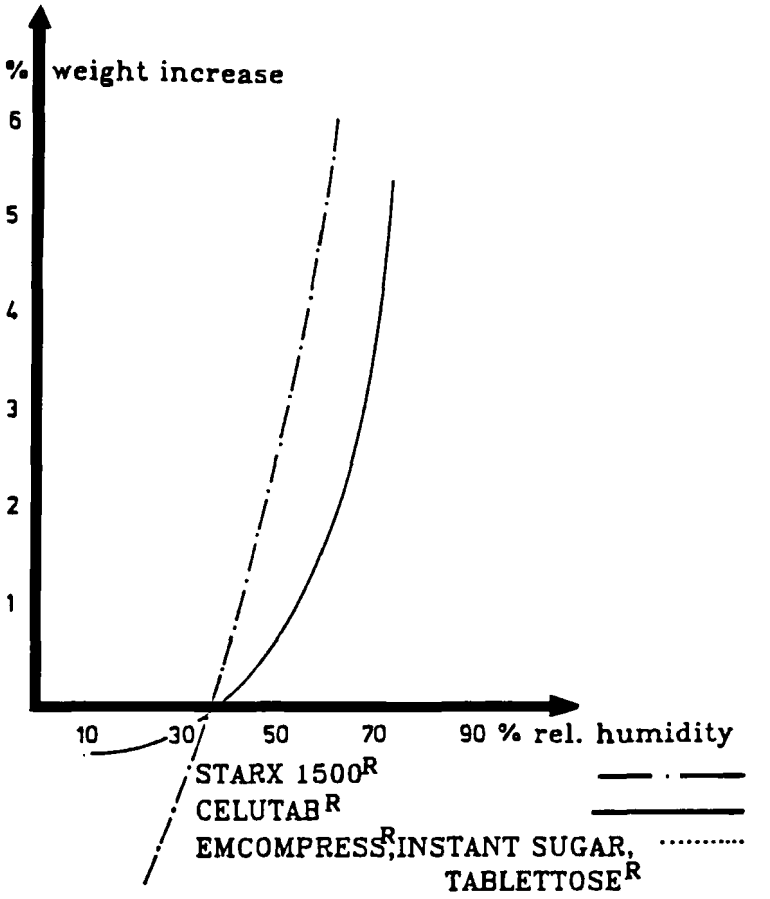

FIGURE 5

Sorption Isotherms of inactive Ingredients for direct Compression

Well-planned preformulation studies can often avoid such unfavourable sorption properties from the very start (11). This will be illustrated by some examples.

Example with Excipients suitable for direct Tableting

It is often possible to ensure that a formulation shows the sorption properties desired by careful selection of the excipients. Figure 5 lists the

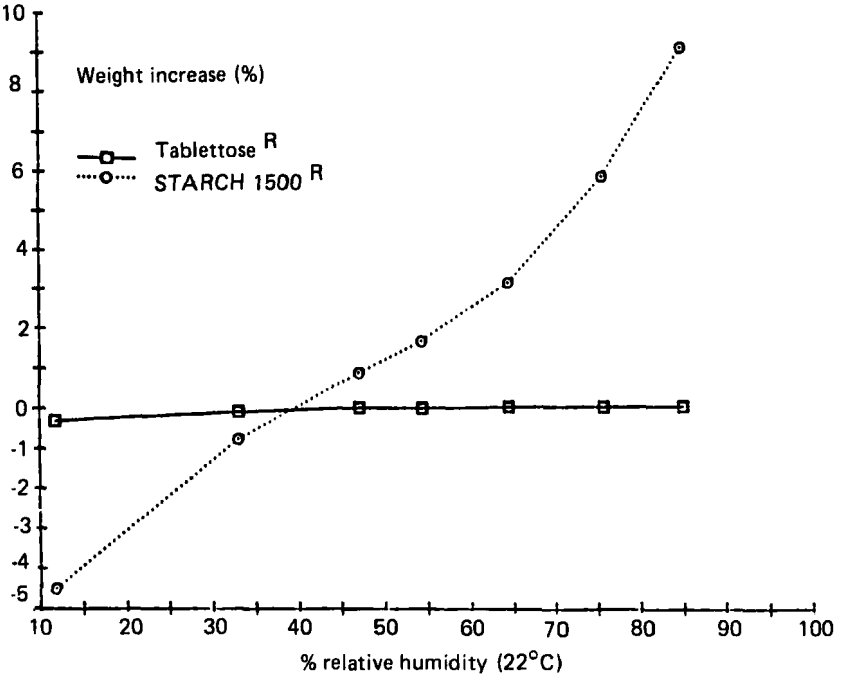

FIGURE 6
Sorption Isotherms of Tablets made of Tablettose^{R} in comparison with Tablets made of STARCH 1500^{R}

sorption isotherms of five excipients which are suitable for direct tableting. Three of these, Encompress^{R} (dibasic calcium phosphate dihydrate), instant sugar and Tablettose^{R} (α-lactose-monohydrate), show no significant sorption between 11 and 84 % relative humidity. In contrast, the other two substances, STARCH 1500^{R} (a physically modified starch) and Celutab^{R} (maltodextrin) show very distinct sorption.

These very pronounced differences between the sorption properties are also passed on to the finished tablets (Figure 6) and to capsules (Figure 7).

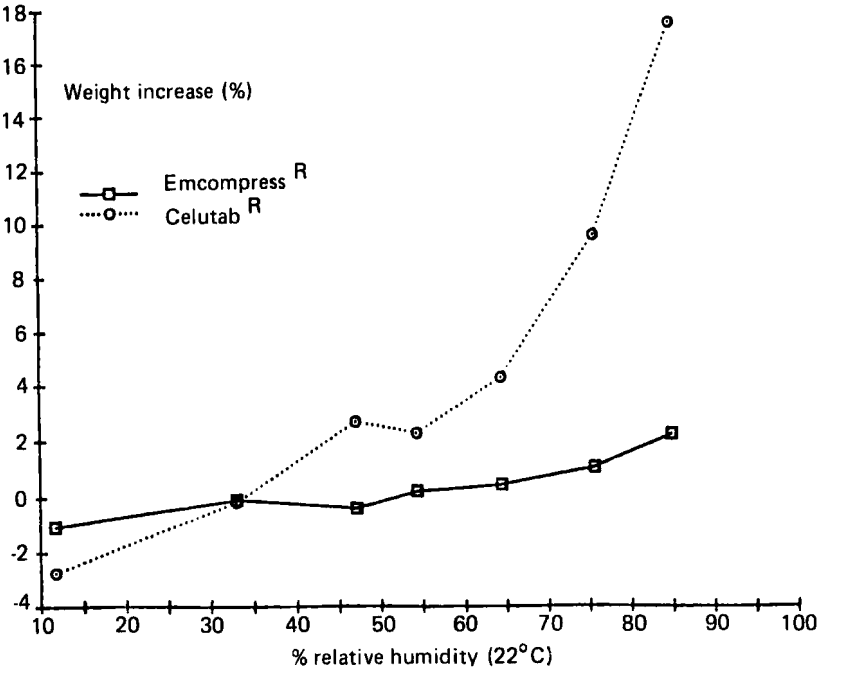

FIGURE 7

Sorption Isotherm of Capsules$_R$ with Celutab^R in Comparison with Capsules with Emcompress^R

Example: Salt Form

If the preformulation studies go so far as to assist in the selection of the most suitable salt form of the active substance, as described by C. Graffner et al. (12) in Figure 8, the possibility of achieving the desired sorption properties are even greater.

In the example it can be seen that methane sulfonate shows a higher degree of hygroscopicity than the oxalate of the same active substance.

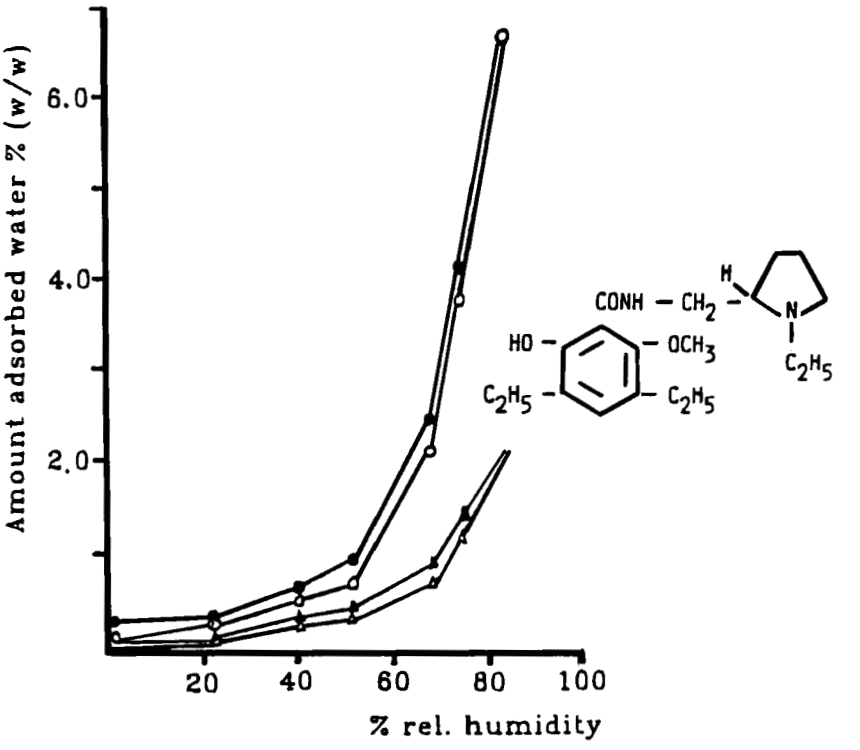

FIGURE 8

Water Sorption Isotherms for the Methanesulfonate (0) and Oxalate ( ) Salts. Open Symbols denote Sorption, closed Symbols denote Desorption (12).

Example: Deferring the Point of Ansorption

The point of ansorption is the point of intersection of the sorption curve with the x-axis, i.e. the point on the curve at which, from the very start, the moisture of the sample and the surrounding air were in equilibrium. In certain cases this point can be taken as a measurement of the hygroscopicity of the sample. The point of ansorption can often be deferred without difficulty, as illustrated in Figure 9 (13): The hardness of this tablet formulation decreased rapidly

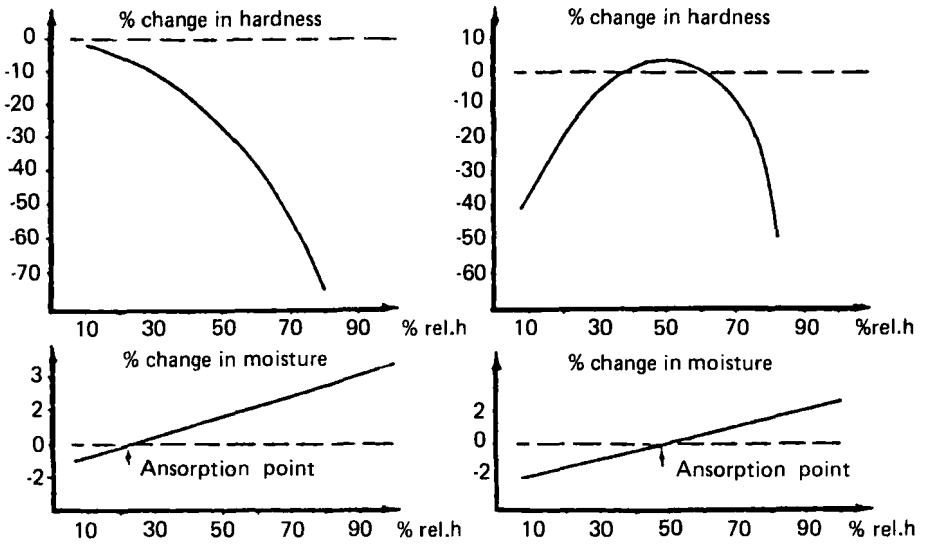

FIGURE 9
Tablets pressed to 4.8% or 7.8% Moisture

above a relative humidity of about 15 %. Parallel to this an ansorption point was determined at approximately the same relative humidity.

By altering the moisture content of the tablet granulate from 4.8 % to 7.8 % and thus effecting a shifting of the ansorption point, a step which did not entail any technical difficulties, it was possible to distinctly stabilize the tablet hardness for relative humidity values of 30 % to 60 %.

Changes caused by Sorption

These changes can be determined by correlating the sorption isotherm with the concomitant physical and/or chemical changes (see also Figure 9).

TABLE 7

Organoleptic Changes in BHT 933 CL_2 after Storing at different relative Humidities for 2 Weeks

% relative humidity	one week	two weeks
11.8		
33.0		
47.1	4/A3	4/A3
54.3	4/A3	4/A3
64.4	partly dissolved 4/A3-4/A6	partly dissolved 4/A6
75.6	dissolved 4/A3-4/A6	dissolved 4/A6
84.8	dissolved 4/A3-4/A6	dissolved 4/A6

There are three main types of changes:

- organoleptic changes
- chemical changes
- changes in the flow properties

Example of organoleptic Changes

BHT 933 CL_2, 2-amino-ethyl-5,6,7,8-tetrahydro-4H-oxazolo[4,5-d]azepine-dihydrochloride, was clinically tested as an antihypertensive agent.

During determination of the sorption isotherm discoloration occurred, which was evaluated according to a colour chart, as shown in Table 7.

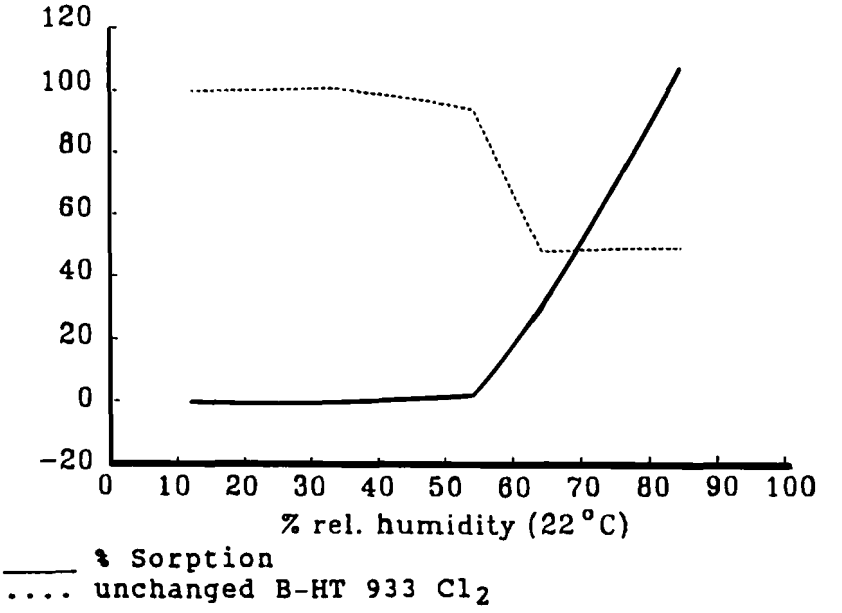

FIGURE 10

Connection between Sorption and Stability of B-HT 933 Cl_2

Example of chemical Changes

The same active substance, BHT 933 CL_2, shows a moisture-dependent decomposition after 4 weeks' storage at 22°C (Figure 10). At the start of adsorption, at about 55 % relative humidity, decomposition sets in, which stabilizes at about 50 % at a relative humidity of just over 60 %.

Figure 11 shows how realistic these investigations are. Tablets manufactured with BHT 933 CL_2 show the same decomposition trend as the pure active substance after only a few days storage at 33 %, 54.3 % and 75.6 % relative humidity and 22°C.

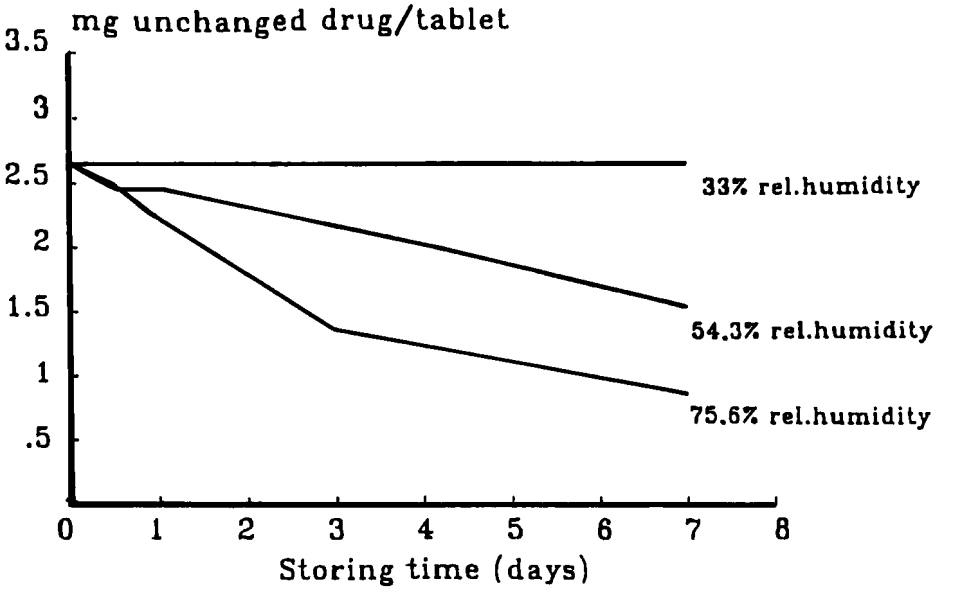

FIGURE 11

B-HT 933 Cl_2 Tablets 2.5 mg stored at different relative Humidities ($22^{\circ}C$)

Example of Changes in the Flow Properties

Figure 12 shows the flow properties of a granulate depending on the relative humidity during storage. Shortly after an abrupt increase in the sorption curve above a relative humidity of 60 %, the flow ability falls sharply and stops completely at 70 % relative humidity.

SPECIAL INVESTIGATIONS

In this section special tests in the development of compound preparations will be described and the increasingly common pre-stages in the galenical development for the preformulation will be discussed.

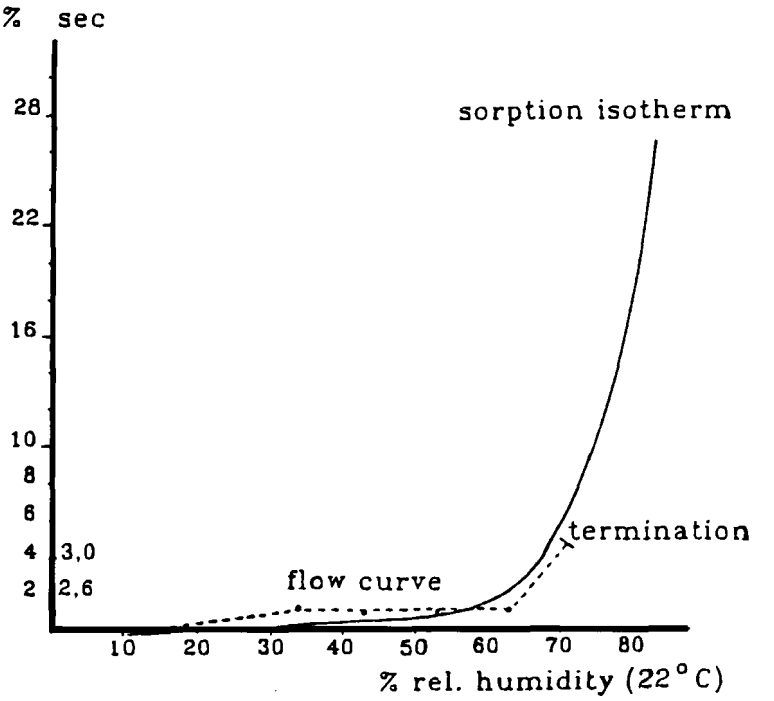

FIGURE 12

Sorption Isotherms and Flow Characteristics of a Granulate

Compound Preparations

It is not only excipients that prove to be incompatible with individual active substances. Incompatibility can also be encountered between two active substances in a compound preparation. And generally it is moisture that plays such a decisive role, as in the case of the acetyl salicylic acid/ Dipyridamole, USP XXI compound. It was only when the active substances were separated - Dipyridamole, in the form of a sugar-coated core was filled into a capsule with acetyl salicylic acid - that the stability became satisfactory.

TABLE 8

Stability of enteric coated
Bisacodyl Substance
(Compact Solution)

Production using	% decomposition after 3 days at 51°C
0.5 parts/weight acetic acid anhydride	2 %
5 parts/weight acetic acid anhydride	--

Galenical Pre-stages

Example: Enteric coated Bisacodyl Substance

The tendency of Bisacodyl to decompose in the presence of moisture outside the neutral point has already been discussed (compare Table 5). Whilst attempting to incorporate the active substance into an enteric coat, i.e. a weak acid, the anticipated problems arose with stability. Only after addition of a sufficient amount of acetic acid anhydride, as a "water-catcher" to the solution of the coating material and the active ingredient (Table 8) was it possible to achieve a stable incorporation.

Example: Corrosion Tests

The active substance Pirenzepin, L-S 519 CL_2, is present in the tablets in the form of a highly acid dihydrochloride. A corrosion test of the tablet granulate (Figure 13) at 33 % and 54 % relative humidity in a die showed distinct corrosion after 4 days, which increased at a higher relative humidity and more intense contact between granulate and metal.

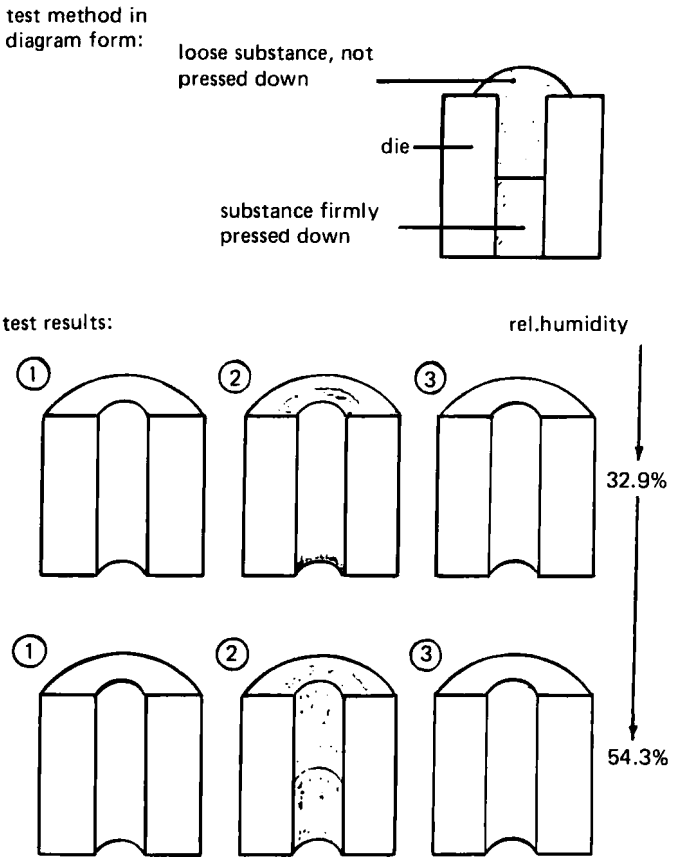

FIGURE 13

Corrosion Test with LS 519 Cl_2 Granulate at 32.9% and 54.3% relative Humidity (22°C). Dies 1 and 3 were stored in parallel without Granulate, Die 2 after 4 Days loaded with Granulate.

A consequence of this test is that the tools of the tableting machine used in the manufacture are cleaned during intermissions of production to remove all traces of tablets and granulate.

CONCLUSIONS

The role of preformulation studies is becoming more and more important because these help to avoid errors

in the development of pharmaceuticals. The need for expansion of these studies - either in the selection of salt and crystal forms of the active substance (14, 15) or the galenical pre-stages - is becoming increasingly recognised.

Moisture plays a very significant, and generally a very negative role in preformulation. Many of the changes that are shown to take place result directly from the effect of moisture. This is a very contradictory situation for the galenical scientist dealing with solid dosage forms, because he would prefer to profit from the positive aspects of moisture. This contradiction requires a good deal of compromise between preformulation and galenical development and close cooperation beween these two fields.

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