DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 5(3), 227-244 (1979)

MOISTURE TRANSFER TESTS IN BLISTER PACKAGE TESTING

M. Veillard*, R. Bentejac**, D. Duchêne* and J.T. Carstensen*

ABSTRACT

Lactose and dicalcium phosphate tablets have been made by six different manufacturing methods. These two types of tablet were packaged in blister packs and subjected to accelerated moisture tests. Methods are described whereby the diffusion coefficient of the blister film can be calculated from the moisture absorption curves. It is shown that the excipient effect (plasticizer) in the film increases the diffusion coefficient by at least an order of magnitude over and above the pure polymer. It is shown that, except for extruded granules, tablets made by the various methods exhibited approximately the same moisture absorption characteristics. The effects of this absorption on the hardness of the tablets are variable and demonstrate the necessity of adapting the formula and the manufacturing procedure to the particular blister.

* Laboratoire de Pharmacie Galénique, Faculté de Pharmacie, Université de Paris-Sud, 92290 Châtenay Malabry, France

** Laboratoires Spécia, 94700 Maisons Alfort, France

INTRODUCTION

The testing of packaging materials (for each individual product) is an important aspect of pharmaceutical development and quality control. In evaluation of films and package assemblies, tests are frequently carried out to assure that the polymer is an adequate barrier and that the package is sealed in a proper manner (1,2). A package may, however, be an adequate container for a product without providing total protection, and in this case the kinetics of moisture uptake of the actual product in the actual package is of importance. It is part of the purpose of this study to establish a realistic method or experimental protocol for such a study.

In product design, it is frequently assumed that the moisture uptake is a function of the compositional form of the ingredients, and that the moisture uptake rate and extent is solely a function of the formula. Since the physical state of the solid matter could be expected to play a role in at least the kinetic aspects, the formulae tested were prepared in six industrially common ways, and the kinetics of water uptake studied.

EXPERIMENTAL

Tablets were made with the formulae shown in Table 1. One of these is a water insoluble base (dicalcium phosphate dihydrate, $CaHPO_4 \cdot 2H_2O$) and one is a water soluble base (lactose hydrate). They will be referred to in the following as phosphate and lactose base tablets. The method of manufacture was to blend and to produce granules by each of the following methods: (1) direct compression; (2) roll-slugging[1]; (3) wet granulation in a planetary mixer[2]; (4) wet

TABLE 1

Formulae used. Percentages per weight of dried formulation

	lactose formula	phosphate formula
lactose monohydrate	89%	-
dibasic calcium phosphate dihydrate	-	89%
carboxymethyl starch*	6%	6%
colloidal silica**	4%	4%
magnesium stearate U.S.P.	1%	1%

* Primojel L.V.
** Levilite

granulation in a sigma-chopper mixer[3]; (5) wet granulation by extruder[4]; (6) wet granulation by spray granulation[5].

Pretreatment of granulations

A 60 kg mixture was made of each of the two formulae shown in Table 1, but with only one half of the magnesium stearate stated. This powder was processed through a precompactor[1] at minimum pressure. The particle size distribution after precompaction is shown in Table 2 (under the heading direct compression). This was done to provide a common basis for all the processes listed above. It is realized that the expression "direct compression" as used here does not totally correspond to the usual definition of the term. 10 kg of the precompacted material was lubricated with the remaining 0.5% of magnesium stearate and compressed in a die of diameter 12 mm, at a weight of 600 mg and using a rotary press[6]. The compression pressures were such that the hardness of the tablets were 6 to 8 kg as measured by the Spécia hardness tester[7] described in Figure 1. These tablets are referred to below as

TABLE 2

Sieve analysis of granulations used

	method	size (cm)							
		< 0.0125	0.0125/ 0.0200	0.0200/ 0.0315	0.0315/ 0.040	0.0400/ 0.063	0.0630/ 0.080	0.0800/ 0.100	>0.100
lactose formula	direct compression	75.5	15	5	3	0.5	0	0	0
	roll compaction	34	15	18.5	23	8	0	0	0
	spray granulation	17	26	20.5	14	18	4	1	0
	extruder	36.5	16.5	7	4.5	12	12	9.5	0
	sigma-chopper	28	23.5	12	7	14	10	5.5	0
	planetary mixer	23	11.5	6.5	5.5	17.5	20	14.5	0
phosphate formula	direct compression	71	12	9	7.5	0.5	0	0	0
	roll compaction	11	2	7	9	26.5	23.5	19	0
	spray granulation	34	22	17	11.5	11.5	1.5	0	0
	extruder	43	20	10	6.5	11	6	2	0
	sigma-chopper	38	11.5	5.5	4.5	14	14	11	0
	planetary mixer	36	12.5	9	7	17	12.5	4.5	0

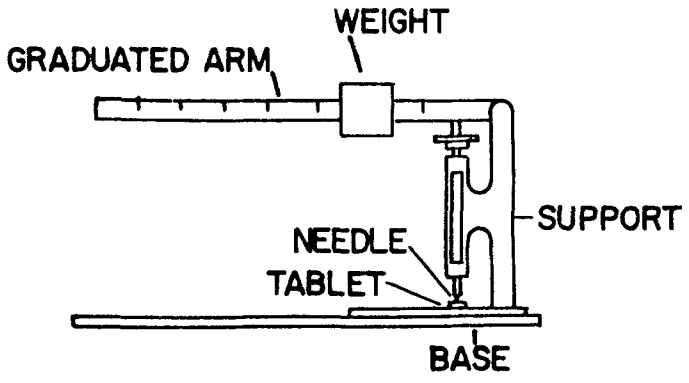

Figure 1 Spécia hardness tester

"direct compression". Another 10 kg of granulation was lubricated with the remaining 0.5% of magnesium stearate and compacted at a pressure of 12 tons in the compactor. These compacts were milled, and compressed as above and are referred to below as tablets made from "compacted granulation".

Manufacturing method for tablets made by wet non-fluidized methods

10 kg of precompacted power were granulated with water. The amounts of water used are shown in Table 3. The granulation was dried in a tray drying oven[8] at 45° C to a moisture content of 2.1% for the lactose granulation and 3.5% for the phosphate granulation as determined by loss on drying at 95° C under infrared light[9]. The drying time was usually eight hours. The moisture end points are the moisture contents of the raw materials prior to water addition. The granules were milled in a hammer mill[10] and the mesh analysis is shown in Table 2. The dried milled granulation was lubricated with the remaining lubricant and compressed as described above.

TABLE 3

Amounts of water used in the wet procedures. Amounts listed are per 10 kg of dry weight of granulation

procedure	liters of water per 10 kg of granulation	
	lactose granulation	phosphate granulation
spray granulation[5]	7.3	8.7
chopper-sigma[3]	5.15	6.8
planetary[2]	4.8	6.4
extruder[4]	2.5	5.0

Manufacturing method for spray granulated granulation

10 kg of precompacted powder were loaded in three stages into the spray granulator[5]. The powder was fluidized at 30° C and the water was added at a constant flow rate over a period (4) of 20 minutes. Drying was effected by increasing the air temperature to 80° C for a period of about 30 minutes. To adjust the moisture content to exactly 2.1% (for the lactose granulation) and 3.5% for the phosphate granulation, the spray dried granules were placed on trays and dried at 40° C in an oven[8] until the proper moisture level had been achieved. The granules were not milled. They were lubricated with the remaining 0.5% of magnesium stearate and were then compressed as described above. The particle size distribution is shown in Table 2.

Packaging in blister packs

The tablets produced by the six methods above were packed in polyvinylchloride on 30 micron aluminum/polyethylene blisters

and heat-sealed on a blister pack machine[11]. The blisters and a control of unprotected tablets were subjected to 35° C and 90% relative humidity, which is a common humidity test employed in the pharmaceutical industry. Samples were removed at prespecified times and tested for hardness on the Spécia hardness tester[7] (Figure 1) and for moisture content by weight uptake. The characteristics of the polyvinylchloride film and the aluminum base film are shown in Figure 2.

RESULTS AND DISCUSSION

For packaged materials it is always a problem (a) to decide whether a certain polymeric material is indeed satisfactory for packing a particular product, (b) if so, whether the modifications (plasticizers) necessary to transform the polymer into a packing material (blister) have an adverse effect, and (c) whether the mechanical operation in forming the package has adverse effects. Moisture permeation (and other diffusional) constants for many materials are listed in the literature, but it is not a priori evident how these can be compared with package test data. Point (c) can be pinpointed as described by Carstensen (3). The following discussion concentrates on points (b) - and (a) - and methods of comparison.

To examine the moisture absorption curve in blisters, it is recalled that the diffusion through a film (4) occurs according to:

$$dm/dt = \frac{DA}{\ell} [S_o - S_i] = \frac{DA\Pi}{\ell} [P_o - P_i] \qquad \text{Eq.1}$$

m is here the amount of water (g) diffusion through a film of

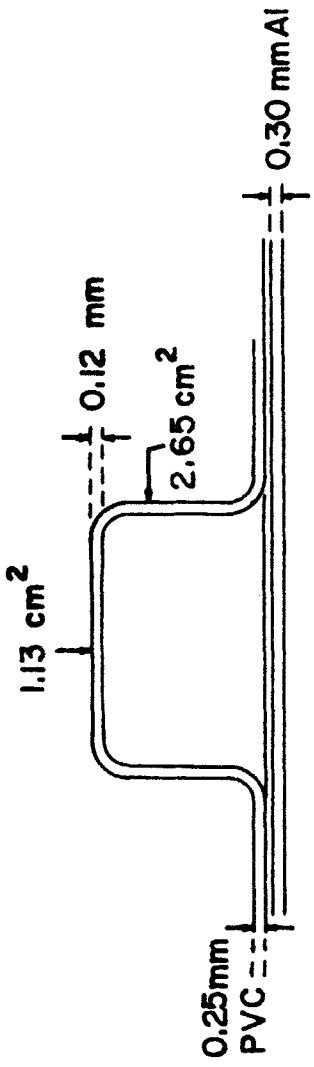

Figure 2 Dimensions of blister used

thickness ℓ cm and surface area A cm^2 in time t (sec). S is the solubility of water (g/cm^3) in the plastic, P is water vapor pressure and the subscripts "o" and "i" indicate one side (outside) and the other side (inside) of the film. Π is the Henry's law constant (in g cm^{-3} atm^{-1}).

If there are M g of solid present inside the blister and if there is steady state, then the amount of moisture passing through the film in a time unit is equal to the increase in moisture content of the solid, i.e.

$$x = m/M \qquad \text{Eq.2}$$

is the moisture content of the solid (in g/g or mg/g). It is furthermore assumed that there is a linear relation between P and x, i.e.

$$P_i = qx \qquad P_o = qx_\infty \qquad \text{Eq.3}$$

q is a proportionality constant in units of (g/g)/atm and x_∞ is the final moisture content corresponding to final equilibrium (i.e. when the inside and outside pressures have equalized). For a good film, this will not occur in a short length of time, but x_∞ of course can be estimated by exposure of unprotected tablets to the defined atmosphere used for the blisters.

Introducing equation 2 and equation 3 into equation 1 and integrating gives:

$$\ln[x_\infty - x] - Qt + \ln(x_\infty) \qquad \text{Eq.4}$$

Use has been made of the initial condition that the unbound moisture

content, at the onset, is zero. The (negative) value of the slope is:

$$Q = \frac{DA\Pi}{q\,\ell M} \qquad \text{Eq.5}$$

The (selfconsistent) units are here: Q in sec^{-1}, D in $cm^2\ sec^{-1}$, A in cm^2, ℓ in cm, M in g, q in g/g, and Π in $g\ cm^{-3}\ atm^{-1}$.

For unprotected tablets, the diffusion equation is:

$$dm/dt = \alpha A(P_o - P) \qquad \text{Eq.6}$$

where α is a mass transfer coefficient. A series of arguments parallel to the ones used above leads to equation 4, where now:

$$Q' = \alpha Aq/M \qquad \text{Eq.7}$$

The moisture absorption curves of unprotected tablets made by the various methods are shown in Figure 3. It is seen that within a formula the absorption isotherms do not differ (significantly) one from the other. However the moisture absorbed (x mg/g) in the lactose formula, as expected, differs from that of the calcium phosphate formula (Friedman test, $P < 0.05$ (5)).

The data in Figure 3 are presented in the form of equation 6 in Figure 4. x is the value obtained after eight days of exposure. This did not differ significantly from the value after 12 days (65 and 56 mg/g). The least squares fits of the lines in Figure 4 are:

lactose:

$$\ln[x_\infty - x] = -0.0204\ t + \ln(62) \quad (r^2 = 0.995) \qquad \text{Eq.8A}$$

phosphate:

$$\ln[x_\infty - x] = -0.0214\ t + \ln(52) \quad (r^2 = 0.984) \qquad \text{Eq.8B}$$

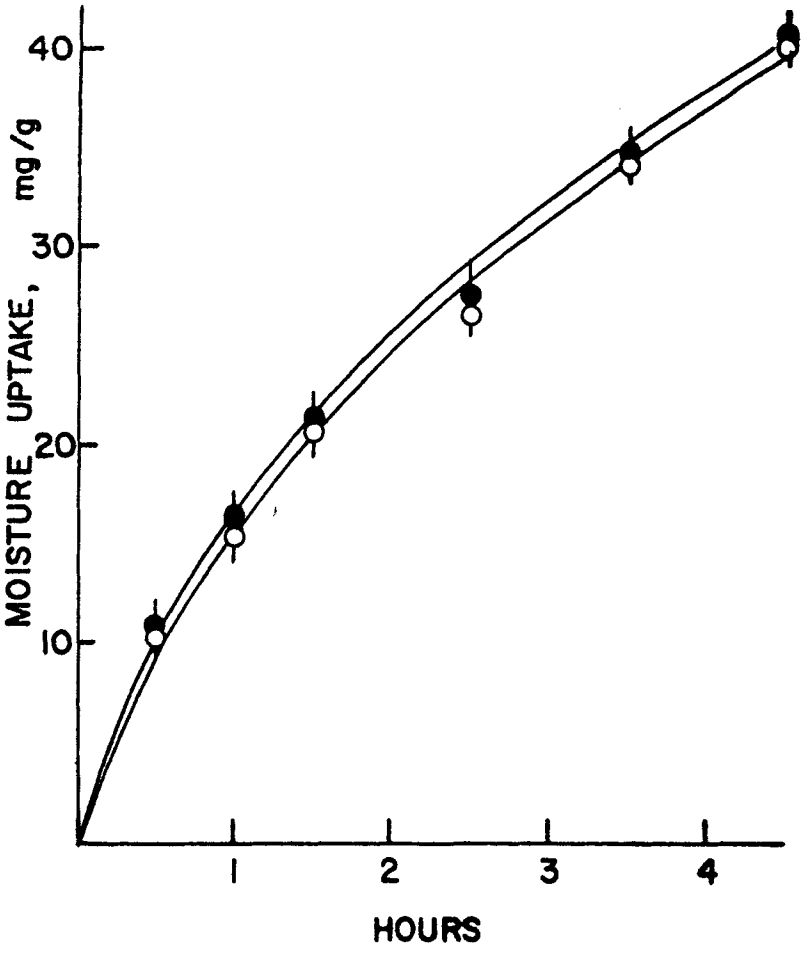

Figure 3 Moisture uptake curves for unprotected tablets exposed to 90% relative humidity at 35° C.
Key: lactose tablets: O phosphate tablets:

where x is in mg/g and where t is in hours. It is noted that the intersections ln(62) and ln(52) are close to those dictated by the asymptotes (65 and 56).

When packaged in blisters the tablets pick up moisture more slowly. This is exemplified by the lactose formula shown in

Figure 5. The extruded granules are slightly (but significantly) lower on the graph than tablets produced by the other methods. In the case of the phosphate formula, all the data points are closer, and fail to exhibit significant differences. The data, when pooled for each formula separately and treated according to equation 4, give plots such as those shown in Figure 6. The linearity is good as demonstrated by least squares fit shown below:

lactose:

$$\ln[x_\infty - x] = -0.0206\ t + 4.129 \quad (r^2 = 0.996) \qquad \text{Eq.9A}$$

phosphate:

$$\ln[x_\infty - x] = -0.0217\ t + 3.950 \quad (r^2 = 0.986) \qquad \text{Eq.9B}$$

The value used for x_∞ here is the same as found (experimentally) for the unprotected tablets. t is here in days.

To evaluate D in equation 5, values applying to the system for the various parameters are inserted. From equation 9 Q is seen to be 0.021 $days^{-1}$ = 2.43 . 10^{-6} sec^{-1}. q (in g/g) is obtained from the fact that for the unprotected tablets x = 0.05 g/g at P_{H_2O} = 0.05 atm (35° C, 90% RH). Hence q = 1.0 (g/g)/atm. From Figure 2 it is seen that A = 3.78 cm^2 and ℓ = 0.02 cm. Π is obtained from tabulated literature (6) for polyvinylchloride (and water) to be 2.1 . 10^{-3} $g/cm^3/atm$. M is 24 tablets each weighing 0.6 g, i.e. 14.4 g. Inserting these values into equation 5 gives:

$$10^{-6}\ 2.43 = \frac{D\ 3.78\ 2.1\ .\ 10^{-3}}{0.02\ \ 1.0\ \ 14.4} \quad \text{or } D = 8.8\ .\ 10^{-5}\ cm^2/sec \qquad \text{Eq.10}$$

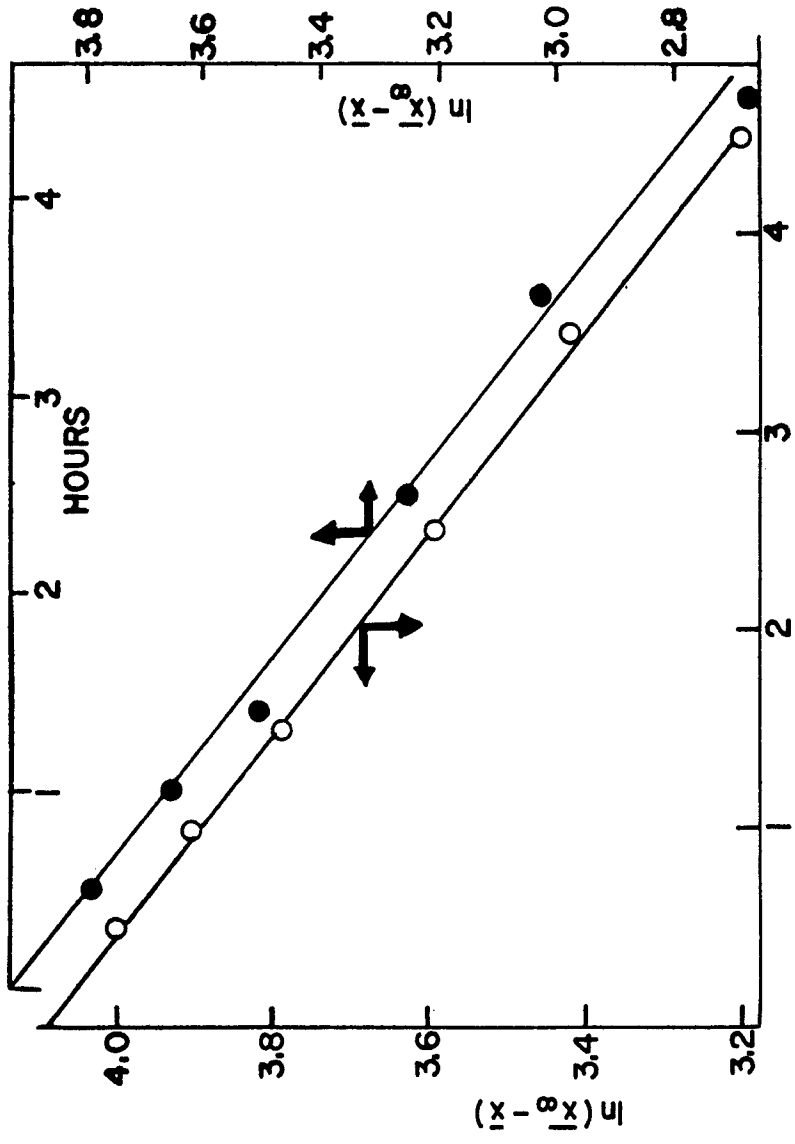

Figure 4 The data from Figure 3 presented in the form of equation 6 (equation 8).

Phosphate ● top and right-hand scale;
lactose O bottom and left-hand scale

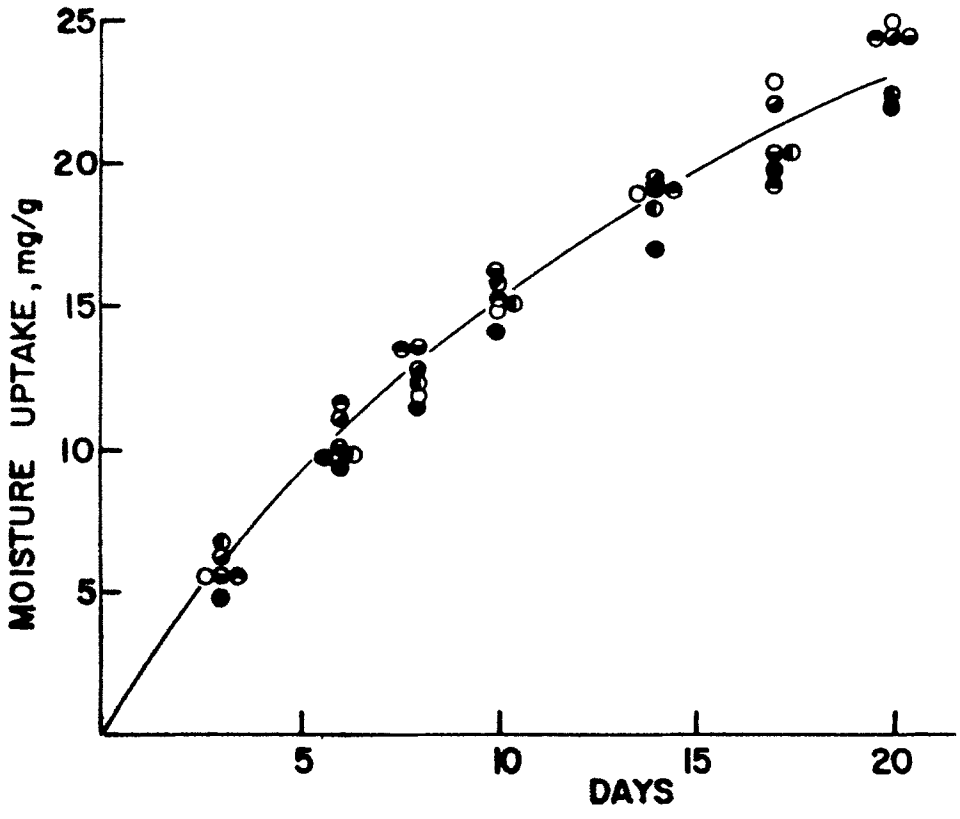

Figure 5 Moisture uptake data of the lactose formula in blisters exposed to 35° C and 90% relative humidity. Key:

direct compression: ◐ compactor: ○

spray granulator: ⊖ chopper-sigma blender: ◑

planetary mixer: ⊖ extruder: ●

This value is two orders of magnitude larger than that reported for polyvinylchloride, and hence it is obvious that plasticizers and other excipients in the packing film affect the water transport properties significantly.

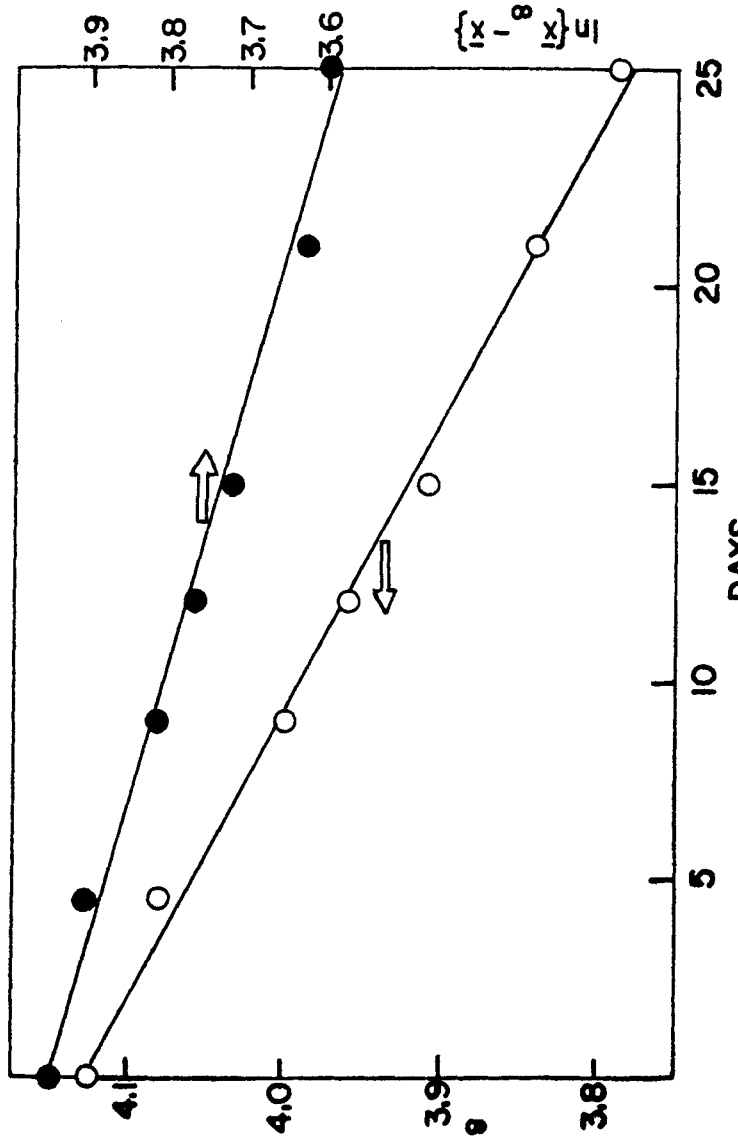

Figure 6 Moisture uptake data of the lactose formula in blisters (left ordinate) and of the phosphate formula ● in blisters (right ordinate) plotted according to equation 6. The points are averages of all the six processes

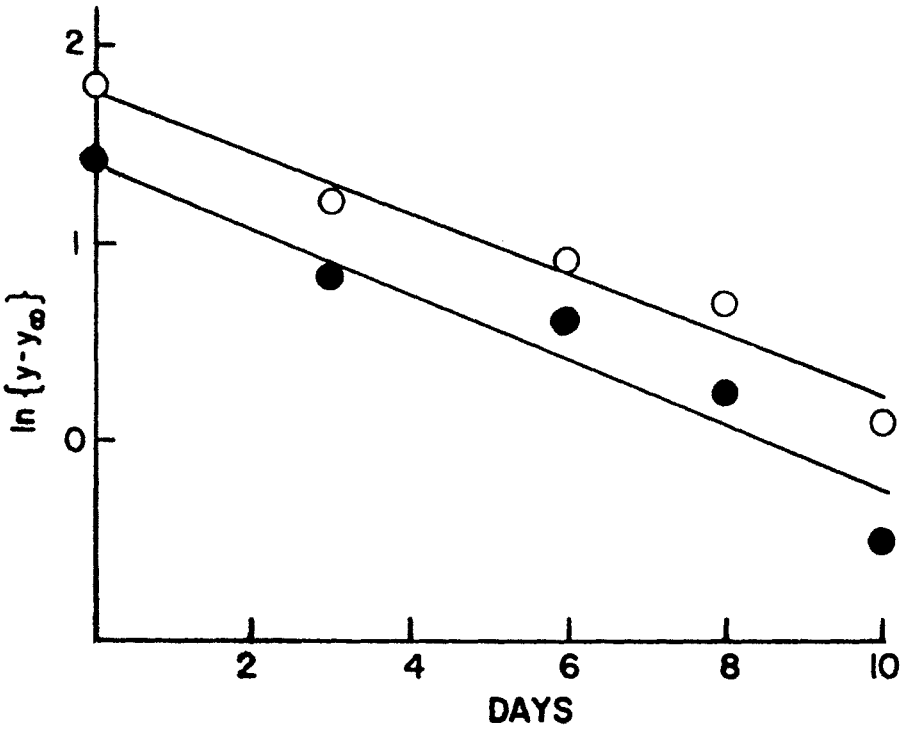

Figure 7 Hardness data (kg) plotted according to equation 11. lactose formula: ● phosphate formula. ○ The graph is composite for all the formulae. The least squares fits are: lactose: $\ln[y - y_\infty] = -0.172\ t + 1.457$ ($r^2 = 0.93$) and phosphate: $\ln[y - y_\infty] = -0.155\ t + 1.787$ ($r^2 = 0.97$). The infinity values are $y_\infty = 2.6$ kg for lactose and $y_\infty = 1.2$ kg for phosphate

The hardness of a tablet is a function of its moisture content. Beyond a certain moisture content, a tablet will become softer, the higher its moisture content. Since the tablets absorb moisture, their hardness will be a function of time. It is

shown here, phenomenologically, that the hardness (y kg) adheres to an equation similar to equation 4, i.e.

$$\ln(y - y_\infty) = -Q'' t + \ln(y_o - y_\infty) \qquad \text{Eq.11}$$

y_∞ is estimated by iteration and the hardness versus time curves shown in Figure 7. It is seen (and is statistically significant at P = 0.99) that dry processing is superior in the case of the lactose formula, but that the wet process is better for the phosphate formula. The internal structure of the tablets studied (porosity, specific surface, behavior under compression) is being studied and could to some extent explain these differences.

ACKNOWLEDGEMENTS

The authors wish to express their thanks to Professor F. Puisieux for the helpful cooperation he provided throughout the preparation of this work.

FOOTNOTES

1 Compactor, Alexanderwerk, WP 50, Aktiengesellshaft, 563 Remscheid 1, Germany

2 Planetary mixer: Bonnet, Villefranche S/Saône, France

3 Lödige Maschinen Bau GmbH, 479 Paderborn, Germany

4 Extruder (SCUR), Société Chimique des Usines du Rhône-Spécia, 180 rue Jean Jaurès, 94700 Maisons Alfort, France

5 Glatt Lufttechnische Apparate, Maltingen, Binzen/ Baden, Germany

6 Rotary press: Kilian type pharma, Kilian and Co. GmbH, 5 Cologne 60 (Niehl), Germany

7 Spécia Hardness Tester, Spécia, 180 rue Jean Jaurès, 94700 Maisons Alfort, France

8 Drying oven: 66 rue François de Paule, 94490 Ormesson

9 Mettler moisture balance: Mettler Instruments AG, 8606 Greifensee, Zurich, Switzerland

10 Hammer mill: Stokes Machine Company, Philadelphia 20, Pennsylvania, USA

11 Blister pack machine: ILIG, EPF, 16 rue Eugène Baudoin, 92170 Vanves, France

REFERENCES

(1) L.T. Grady and J.T. Reamer, J.Pharm.Sci., 65, 630 (1976)

(2) "The United States Pharmacopeia", 19th Rev., Mack Publishing Co., Easton, Pa. (1975), p.647

(3) J.T. Carstensen, "Theory of Pharmaceutical Systems", Volume I, Academic Press, New York (1972), p.237

(4) Ibid, p.219

(5) Ibid, pp.12/13

(6) "Polymer Handbook", Second Edition, Ed. J. Brandrup, E.H. Immergut, Wiley Interscience, New York (1975), p.III 237