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Effect of humidity and packaging on the long-term aging of commercial sustained-release theophylline tablets

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Summary

This paper discusses the influence of relative humidity and packaging on the dissolution rate of three commercial brands of theophylline controlled-release tablets, paying particular attention to the experimental design and data treatment. The reduction in the amount of theophylline released during an 8 h period after 3 years' storage varied depending on the product and storage conditions; the greatest reduction observed amounted to 41% of the original content. To interpret the data, a statistical model was used, based on the subdivision of the sum of the squares of the term 'treatments' from the variance analysis by orthogonal polynomials chosen in terms of the design of the storage conditions. In all instances, the factors responsible for the reduction could be indentified.

Introduction

Unlike assays of solid dosage forms for chemical stability, which may be interpreted by ad hoc kinetic models (Harrison, 1969; Carstensen, 1988; Carstensen et al., 1990) there are at present no adequate theoretical models for the prediction and evaluation of the development of the physical properties of these dosage forms, including the release rate of the active principle.

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Physical stability assays are usually planned according to a factorial design: the factors most often studied are humidity, time, temperature, light and, occasionally, the type of packaging, as well as the constituents of the formulation. The observed responses tend to be numerous (weight, hardness, disintegration time, etc.) and are not invariably independent of one another; moreover, the problems posed by the interpretation of the release curves of the active principle must also be taken into account.

The difficulties arising from the joint evaluation of all the data by some statistical technique, generally ANOVA (analysis of variance), mean that many results are given in a basically descrip-

tive form (Chowhan, 1980; Saarnivaara and Kahela, 1985; Sarisuta and Parrott 1988; Dawoodbhai and Rhodes, 1989; Herman et al., 1989) and very rarely are ANOVA or other statistical techniques applied in an overall evaluation (Rubino et al., 1985; Vila-Jato et al., 1986, 1987). However, three features in the construction of an ANOVA model have been overlooked:

One is the time factor. Although storage time may be introduced as a crossed factor with the others, in practice, time is understood to be that elapsed since the outset of the study and as such cannot really be considered to be a cross factor.

Two, the experiment is generally planned according to a factorial design; nonetheless, a series of observations are made at zero time, independent of the storage conditions, which distort the design scheme.

Three, many comparisons between the observed results may be made but their statistical independence must be maintained; if it is not, then the real significance level will be greater than the nominal.

This paper gives the results of a study of the release rate attained by three commercial preparations of theophylline after storage. Particular attention is paid to the statistical model used to evaluate the data.

Materials and Methods

Dissolution assay

Method I described by the USP XXI Rev. (1985) was used, at 100 ± 1 rpm, 37.0 ± 0.1°C, with distilled water as the dissolution mean (Turú Grau, Model D-6).

Analytical method

The released theophylline was determined by UV spectrophotometry at 271 nm, using anhydrous theophylline (Sigma Chemical Co.) as standard. The precision of the analytical method proved to be equal to 0.56% when evaluated according to the method proposed by Hunter and Lamboy (1981).

Experimental design

Three commercial preparations in two sizes were studied and are coded as follows; A-100 (Theo-Dur 100 mg, batch V-2); A-300 (Theo-Dur 300 mg, batch V-10); B-175 (Theolair 175 mg, batch V-6); B-250 (Theolair 250 mg, batch V-10); C-175 (Eufilina Retard 175, batch V-4, equivalent to 140.9 mg anhydrous theophylline); and C-350 (Eufilina Retard 350, batch V-15, equivalent to 281.7 mg anhydrous theophylline). In accordance with Spanish legislation, all batches identified with the letter 'V' were made up in 1984. Formulations A and B contained anhydrous theophylline; C contained theophylline monohydrate and ethylenediamine chlorohydrate (1.86 : 1).

The tablets were stored at room temperature in the dark at 56% relative humidity ($Mg(NO_3)_2 \cdot 6H_2O$ saturated solution) and at 90% relative humidity ($ZnSO_4 \cdot 7H_2O$ saturated solution). To study the role of the packaging (polyethylene blisters backed with foil in all cases), some of the tablets were stored packaged and others without this protection. The results of the first series of dissolution assays were used as control and were obtained in 1985; 3 years later the dissolution rates of the stored tablets were measured under the conditions shown.

The release rate was quantified according to the whole amount released over a period of 8 h and was determined both at the outset of the experiment and at the end of 3 years.

Statistical analysis

A variance analysis model with only one factor, T, was used, as follows:

$$X_{ij} = \mu + T_j + e_{ij} \qquad (1)$$

where X_{ij} (amount of theophylline released by the end of 8 h) is the i-th observation made on the j-th treatment T_j, μ denotes the general mean and e_{ij} is the experimental error assumed to be normally distributed with zero average and σ^2 variance. To evaluate the effect of time, humidity and the presence of packaging, the sum of the squares of 'treatments' of the ANOVA was subdivided using the orthogonal polynomials set out in Table 1; the orthogonality of these assures

TABLE 1

Orthogonal polynomials used in the subdivision of the sum of squares of the term 'treatments' of the ANOVA

Hypothesis	Polynomial				
Control vs others	−4	1	1	1	1
Humidity	0	−1	−1	1	1
Packaging	0	1	−1	1	−1
Humidity vs packaging	0	−1	1	1	−1

the statistical independence of the various hypotheses formulated.

There were five treatments in all; one consisted of the observations made at zero time (control) and the other four were the different possibilities arising from the factorial design for the storage conditions (two degrees of humidity and the presence or absence of packaging).

The mean square of the term treatments of ANOVA thus had four degrees of freedom (df) which were divided amongst the orthogonal contrasts specified in Table 1, each having one df. The calculations are described in detail in statistical textbooks (such as Winer, 1962).

Results and Discussion

Table 2 lists out the mean values and standard deviations for the six readings taken for each combination of time, relative humidity and packaging. Table 3 gives the ANOVA results for each formulation, interpreted geometrically in Fig. 1. Since the interaction between the factors could have been due to an effect of scale (Winer, 1962, p. 449) the data were analysed in duplicate, with and without logarithmic transformation. The conclusions reached were identical and so henceforth we shall refer only to the non-transformed data.

In all cases the hypothesis of equality amongst the five treatments was rejected as was the first contrast hypothesis and it could therefore be deduced that the storage of all the formulations under the conditions indicated produced a statistically significant reduction of the amount released in 8 h.

TABLE 2

Mean and standard deviation (n = 6) of the amount of theophylline released after 8 h for coded formulations before and after 3 years

	Zero time	3 years			
		56% R.H.		90% R.H.	
		+	−	+	−
A-100	75.6	63.8	77.0	59.8	55.4
	(9.16)	(8.16)	(5.04)	(8.29)	(2.78)
A-300	252.6	223.7	254.5	112.7	102.9
	(12.7)	(20.7)	(12.8)	(8.52)	(10.9)
B-175	96.4	91.7	87.1	93.3	84.1
	(5.84)	(5.10)	(3.67)	(2.19)	(4.58)
B-250	131.8	129.0	119.0	126.5	121.0
	(7.19)	(7.96)	(7.42)	(2.79)	(2.57)
C-175	71.7	63.1	61.6	44.7	65.6
	(0.556)	(0.404)	(3.68)	(0.719)	(1.13)
C-350	127.5	112.6	102.9	64.0	106.6
	(2.88)	(1.08)	(1.78)	(0.486)	(0.94)

R.H., relative humidity; +, packaging present; −, packaging absent. Values in parentheses indicate S.D.

The formulation A-100 and particularly A-300 were basically sensitive to humidity and although the presence of packaging was not significant, there was an interaction between packaging vs humidity as can be seen from Fig. 1a. This behaviour seems reasonable if we take the duration of the assay, 3 years, into account, as opposed to the time needed for a tablet to reach equilibrium humidity, even assuming that this is longer than the 3 days specified by Amidon and Middleton (1988).

TABLE 3

Summary of one-way ANOVA findings for each coded formulation; tabulated values less than 0.05 equivalent to the rejection of null hypothesis

Formulation	Aging	Relative humidity	Packaging	Interaction humidity × control
A-100	0.001	< 0.001	0.149	0.006
A-300	< 0.001	< 0.001	0.073	0.001
B-175	0.001	0.697	< 0.001	0.218
B-250	0.082	0.923	0.005	0.371
C-175	< 0.001	< 0.001	< 0.001	< 0.001
C-350	< 0.001	< 0.001	< 0.001	< 0.001

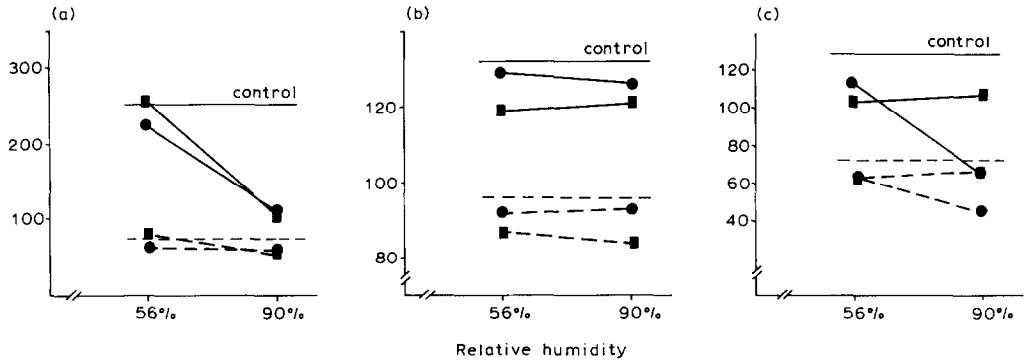

Fig. 1. Amount of theophylline released in 8 h vs relative humidity for products coded as A-300 (———) and A-100 (— — —) (panel a); B-250 (———) and B-175 (— — —) (panel b); C-350 (———) and C-175 (— — —) (panel c). Control, time zero; remainder, after 3 years of storage. (●) With packaging; (■) without packaging.

Formulations B-175 and B-250 benefited from the protection of the blister against humidity; as above, interaction between humidity and packaging was statistically significant although the extent of its effect was not particularly relevant (Fig. 1b) Among the factors involved in the reduction of the amount released, the transformation of anhydrous theophylline to less soluble theophylline hydrate should be noted (Herman et al., 1989).

Formulations C-175 and C-350 showed similar behaviour; both the main effects and the humidity vs packaging interaction were significant. This may be explained by the fact that they contained ethylenediamine chlorohydrate, a substance which is very soluble in water, which is why it will behave as a deliquescent solid if the humidity is high enough. Thus, the presence of drops of water in the blister is explained for the tablets stored at 90% relative humidity for 3 years as well as the strong interaction between humidity and packaging (Fig. 1c).

It is not possible to confirm these or any other hypotheses so long as the composition and manufacturing methods of the formulations are only partly known (Shangraw, 1988). However, the statistical model described enables the findings of this type of study to be adequately interpreted while the number of factors under study may be increased with ease.

References

Amidon, G.E. and Middleton, K.R., Accelerated physical stability testing and long-term predictions of change in the crushing strength of tablets stored in blister packages. *Int. J. Pharm.*, 45 (1988) 79–89.

Carstensen, J.T., Effect of moisture on the stability of solid dosage forms. *Drug Dev. Ind. Pharm.*, 14 (1988) 1927–1969.

Carstensen, J.T., Gerhardt, A., Morris, T. and Nikfar, F., Effect of moisture on solid dosage forms. Can the Arrhenius equation be used as a predictor? *Drug Dev. Ind. Pharm.*, 16 (1990) 2267–2281.

Chowhan, Z.T., Role of binders in moisture-induced hardness increase in compressed tablets and its effect on in vitro disintegration and dissolution. *J. Pharm. Sci.*, 69 (1980) 1–4.

Dawoodbhai, S. and Rhodes, C.T., The effect of moisture on powder flow and on compaction and physical stability of tablets. *Drug Dev. Ind. Pharm.*, 15 (1989) 1577–1600.

Harrison, L.G., The theory of solid phase kinetics. In Bamford, C.H., Tipper, C.F.H. and Compton, R.G. (Eds), *The Theory of Kinetics*, Elsevier, New York, 1969, pp. 377–462.

Herman, J., Visavarungroj, N. and Remon, J.P., Instability of drug release from anhydrous theophylline-microcrystalline cellulose formulations. *Int. J. Pharm.*, 55 (1989) 143–146.

Hunter, W.G. and Lamboy, W.F., A bayesian analysis of the linear calibration problem. *Technometrics*, 23 (1981) 323–328.

Rubino, J.T., Halterlein, L.M. and Blanchard, J., The effects of aging on the dissolution of phenytoin sodium capsule formulations. *Int. J. Pharm.*, 26 (1985) 165–174.

Saarnivaara, K. and Kahela, P., Effect of storage on the properties of acetylsalicylic acid tablets coated with aqueous hydroxypropyl methylcellulose dispersion. *Drug Dev. Ind. Pharm.*, 11 (1985) 481–492.

Sarisuta, N. and Parrott, E.L., Effects of temperature, humidity, and aging on the disintegration and dissolution of acetaminophen tablets. *Drug Dev. Ind. Pharm.*, 14 (1988) 1877–1881.

Shangraw, R.F., Design and formulation of sustained-release theophylline dosage forms. *Drug Dev. Ind. Pharm.*, 14 (1988) 319–335.

U.S. Pharmacopeia, National Formulary, XXI Rev., Ed. United States Pharmacopeial Convention, Inc., 1985, pp. 1243–1244.

Vila-Jato, J.L., Alonso, M.J., Blanco, J., The aging of solid dispersion of glybornuride in polyethylenglycol 6000. *Drug Dev. Ind. Pharm.*, 12 (1986) 1545–1552.

Vila-Jato, J.L., Concheiro, A. and Seijo, B., Effect of aging on the bioavailability of nitrofurantoin tablets containing Carbopol 934. *Drug Dev. Ind. Pharm.*, 13 (1987) 1315–1327.

Winer, B.J., *Statistical Principles in Experimental Design*, McGraw-Hill, New York, 1962.