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Aging of nitrofurantoin tablets containing Carbopol 934 as a binder

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Summary

This paper reports the effects of temperature, humidity and storage time on the hardness and dissolution rate of four nitrofurantoin tablet formulations containing Carbopol 934 as binder. In dissolution tests none of the four formulations complied with USP XXI Ed. assay for nitrofurantoin tablets when freshly made, but all did after six months' storage. In view of these alterations in dissolution rate, it seems possible that the age of the tablets used may have been a cause of earlier failures to find in vivo–in vitro correlations for nitrofurantoin. It is recommended that in future in vivo and in vitro studies be carried out with tablets of various ages if Carbopol 934 is employed as sustained release matrix or binder.

Introduction

The influence of the nature and quantity of binder on the dissolution rate of a number of drugs is now fairly well documented (Davies and Gloor 1973; Georgakopoulos and Malamataris, 1976; Benkerrour et al., 1982; Wells and Walker, 1983) but dissolution rates have nevertheless failed to correlate well with bioavailability. Vila-Jato et al. (1986a), for example, has found the presence of gelatin to have a significant effect on the dissolution rate but not on the bioavailability of spironolactone and Rubinstein and Musikabhumma (1978) have reported that the use of starch paste and stearic acid reduces the bioavailability of furosemide tablets.

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Carbopol 934 is a vinylcarboxylic polymer whose properties make it suitable for a number of pharmaceutical applications and whose toxicological harmlessness has been proved by exhaustive testing. Parotti (1970) has reported its advantages as a binder in tablets, and Baun and Walker (1971) have proposed its use in sustained release tablets. Buri and Doelker (1980) have reviewed the use of Carbopol 934 in acid form to control the release of basic drugs such as dicycloverine hydrochloride (Christenson and Dale, 1962), ammonium chloride (Cotta and Arancibia, 1969) and quinidine sulphate (Devissaguet et al., 1975).

Vila-Jato et al. (1986b) in a 2^2 factorial design (2 levels of Carbopol 934 and 2 compression forces) have studied the effect of these factors on the hardness, friability, disintegration time, dissolution rate and bioavailability of four nitrofurantoin tablet formulations.

This article reports a study undertaken to

evaluate the effects of temperature, relative humidity and storage time on the hardness and dissolution rate of nitrofurantoin tablets containing Carbopol 934 as binder.

Materials and Methods

Formulations

Four tablet formulations, each containing 50 mg of micronized nitrofurantoin (Liade Laboratories, Spain), were made up with the compositions and under the compression forces listed in Table 1. All the formulations were prepared by the conventional wet granulation method and the granulates were compressed using a single-punch tablet machine (Korch-Erweka G.m.b.H., F.R.G.) with a 9 mm punch.

Storage conditions

The four formulations were stored for six months at 20°C and 40°C and a relative humidity of 30% and 60%.

Hardness

Hardness of samples of 4 tablets was measured using an Erweka TB-24 durometer.

Dissolution rate

The Dissolutest (Prolabo, France) apparatus employed complies with the USP XXI Ed. Dissolution Method I for nitrofurantoin tablets. Dissolution was carried out in 500 ml of phosphate buffer of pH = 7.2 and dissolved nitrofurantoin was determined spectrophotometrically at 380 nm using the same phosphate buffer as blank.

Experimental design, analysis of variance and response surfaces

A $2 \times 2 \times 3$ factorial design (Cochran and Cox, 1957) with two levels of temperature (T), two levels of relative humidity (H) and three storage times (t) was employed. Analysis of variance were carried out for models of the form:

$$Y_{ijk} = \mu + t_i + T_j + H_k + (t \times H)_{ik} + (T \times H)_{jk} + (t \times T \times H)_{ijk} + e_{ijk}$$

where Y_{ijk} represents the observed value of the dependent variable (i) for storage time, temperature (j) and relative humidity (k); μ is the overall mean and e_{ijk} is the background error, which is assumed to be normally distributed with mean zero and variance, σ^2.

The use of equally spaced levels of the three factors under study allows the use of orthogonal polynomials (Snedecor and Cochran, 1967) to distinguish linear, quadratic, cubic, etc. contributions to the effects of the factors and to fit response surfaces of the form:

$$Y = b_0 + b_1 \cdot t + b_2 \cdot t^2 + b_3 \cdot t^3 + b_4 \cdot t^4 + b_5 \cdot T + b_6 \cdot H + b_7(t \times T) + b_8(t \times H) + b_9(T \times H) + b_{10}(t \times T \times H)$$

In our case only linear and quadratic contributions were tested.

Results

Table 2 lists the mean weight, hardness, friability and disintegration time of the four formula-

TABLE 1

COMPOSITION AND COMPRESSION FORCES APPLIED TO THE FOUR FORMULATIONS STUDIED

Formulation	Nitrofurantoin (mg)	Wheat starch (mg)	Lactose (mg)	Compritol * (mg)	Carbopol 934 (mg)	Compression force (Nw)
A	50	140	60	1.25	0.625	2500
B	50	140	60	1.25	0.625	4800
C	50	140	60	1.25	1.250	2500
D	50	140	60	1.25	1.250	4800

* Compritol is a glyceryl behenate (Gattefossé, France).

TABLE 2

TECHNOLOGICAL CHARACTERISTICS OF THE 4 FORMULATIONS STUDIED

Formulation	Mean weight [1] (mg)	Hardness [2] (kg)	Friability [3]	Mean disintegration time [4] (s)
A	269.5	3.5	2.37	25
B	270.2	8.2	0.89	24
C	250.0	3.7	0.84	23
D	264.1	8.0	0.77	15

[1] According to U.S.P. XXI Assay.
[2] Mean of 10 tablets.
[3] % loss of weight after 18 min at 20 rpm in a Erweka Friabilometer.
[4] According to U.S.P. XXI Assay.

tions when freshly made, and Tables 3 and 4 their hardness and nitrofurantoin release characteristic (% of nitrofurantoin dissolved after one hour) after storage for various lengths of time under various conditions.

Hardness

Analysis of variance (Table 5) shows that the hardness of Formulations A and B was significantly affected by all the factors studied and these factors modulated each other's effects. No evidence was found at the $\alpha = 0.01$ level for a direct effect of storage time on the hardness of Formulation C, nor for that of Formulation D being directly affected by humidity, though in both cases the factor in question modified the effect of other factors. The response equations obtained for the hardness h (kg) of the four formulations are as follows:

Formulation A:

$$h = 3.43 - 0.179 \cdot t + 0.052 \cdot t^2 - 0.015 \cdot T + 0.011 \cdot H - 0.012 \cdot (t \times T) - 0.00264 \cdot (t \times H)$$

$$(r^2 = 0.819)$$

Formulation B:

$$h = 8.24 - 0.708 \cdot t + 0.208 \cdot t^2 - 0.029 \cdot T + 0.0182 \cdot H - 0.0309 \cdot (t \times T)$$

$$(r^2 = 0.937)$$

Formulation C:

$$h = 4.756 - 0.0477 \cdot T + 0.0068 \cdot H - 0.082 \cdot (t \times T) + 0.00013 \cdot (t \times T \times H)$$

$$(r^2 = 0.625)$$

Formulation D:

$$h = 10.19 + 0.0187 \cdot t + 0.0718 \cdot t^2 - 0.067 \cdot T - 0.0337 \cdot (t \times T) - 0.00017 \cdot (T \times H) + 0.00025 \cdot (t \times T \times H)$$

$$(r^2 = 0.664)$$

Release of nitrofurantoin

Table 6 shows storage time to have significantly affected the release of nitrofurantoin by all four Formulations ($\alpha = 0.01$). Temperature affected release by Formulations A and D, and humidity release by Formulation D. The effect of storage time on release by Formulation C was modulated by humidity. The equations of the response surfaces obtained for the percentage of nitrofurantoin dissolved after one hour (D_{60}) are as follows:

Formulation A:

$$D_{60} = -9.84 + 8.475 \cdot t + 0.075 \cdot T + 0.1047 \cdot (t \times H)$$

$$(r^2 = 0.843)$$

Formulation B:

$$D_{60} = 11.522 + 39.293 \cdot t - 4.40 \cdot t^2$$

$$(r^2 = 0.9975)$$

TABLE 3

HARDNESS (kg) OF TABLETS OF THE FOUR FORMULATIONS STUDIED AFTER STORAGE FOR VARIOUS TIMES UNDER VARIOUS CONDITIONS OF TEMPERATURE AND HUMIDITY

Storage time (months)	Formulation A				Formulation B				Formulation C				Formulation D			
	20°C 30%R.H.	20°C 60%R.H.	40°C 30%R.H	40°C 60%R.H.	20°C 30%R.H.	20°C 60%R.H.	40°C 30%R.H.	40°C 60%R.H.	20°C 30%R.H.	20°C 60%R.H.	40°C 30%R.H.	40°C 60%R.H.	20°C 30%R.H.	20°C 60%R.H.	40°C 30%R.H.	40°C 60%R.H.
0	3.4	3.4	3.4	3.4	8.2	8.2	8.2	8.2	4.0	4.0	4.0	4.0	8.3	8.3	8.3	8.3
	3.0	3.0	3.0	3.0	8.7	8.7	8.7	8.7	4.0	4.0	4.0	4.0	7.7	7.7	7.7	7.7
	3.2	3.2	3.2	3.2	8.0	8.0	8.0	8.0	3.7	3.7	3.7	3.7	7.5	7.5	7.5	7.5
	4.2	4.2	4.2	4.2	7.7	7.7	7.7	7.7	3.0	3.0	3.0	3.0	8.2	8.2	8.2	8.2
3	3.0	4.5	1.5	2.3	7.9	6.1	3.0	4.2	3.8	4.8	2.2	1.5	10.2	10.1	4.0	4.1
	2.4	4.2	1.6	2.7	6.5	8.1	2.9	4.0	3.9	5.0	2.2	2.2	9.2	10.1	3.5	3.8
	2.5	4.7	1.5	1.8	6.4	6.6	3.0	3.0	3.0	5.7	1.8	2.6	9.9	9.2	3.5	3.7
	2.5	4.1	1.5	3.0	6.8	7.2	3.2	3.5	2.5	4.1	1.8	2.9	8.2	9.5	3.3	3.7
6	3.7	4.0	2.0	2.2	6.8	9.2	3.2	4.2	3.4	3.2	2.2	3.5	8.9	8.2	4.0	5.0
	3.4	3.9	1.8	2.5	6.0	7.2	3.6	4.4	4.2	5.4	2.0	3.0	8.2	6.8	4.2	7.6
	3.8	3.9	1.8	2.2	7.0	9.2	3.5	4.2	4.3	4.0	2.2	3.6	10.0	6.2	3.3	6.8
	2.3	3.3	1.8	2.4	7.8	8.5	3.9	5.0	4.3	4.0	2.0	3.5	7.9	7.5	3.5	7.8

TABLE 4

PERCENTAGES OF NITROFURANTOIN DISSOLVED AFTER 1 h ACCORDING TO THE USP XXI METHOD I

Storage time (months)	Formulation A				Formulation B				Formulation C				Formulation D			
	20°C 30%R.H.	20°C 60%R.H.	40°C 30%R.H.	40°C 60%R.H.	20°C 30%R.H.	20°C 60%R.H.	40°C 30%R.H.	40°C 60%R.H.	20°C 30%R.H.	20°C 60%R.H.	40°C 30%R.H.	40°C 60%R.H.	20°C 30%R.H.	20°C 60%R.H.	40°C 30%R.H.	40°C 60%R.H.
0	15.50	15.50	15.50	15.50	12.26	12.26	12.26	12.26	7.82	7.82	7.82	7.82	18.19	18.19	18.19	18.19
	12.80	12.80	12.80	12.80	16.58	16.58	16.58	16.58	7.95	7.95	7.95	7.95	29.92	29.92	29.92	29.92
	21.02	21.02	21.02	21.02	10.92	10.92	10.92	10.92	29.65	29.65	29.65	29.65	15.63	15.63	15.63	15.63
	25.47	25.47	25.47	25.47	6.33	6.33	6.33	6.33	23.18	23.18	23.18	23.18	20.62	20.62	20.62	20.62
3	14.48	16.52	88.56	66.86	92.88	69.00	94.03	95.30	52.73	37.36	31.77	75.48	58.96	35.96	84.12	84.75
	14.87	26.94	86.66	75.09	90.22	91.99	95.04	86.40	46.89	55.40	18.04	73.70	66.84	38.37	88.82	71.54
	16.39	14.99	96.17	61.50	82.85	89.45	93.39	95.55	62.64	67.85	12.07	65.82	77.13	37.23	91.74	74.84
	30.62	15.63	78.78	80.18	91.36	90.60	90.34	88.44	48.67	41.55	10.55	31.26	64.55	47.01	74.33	47.65
6	77.76	82.72	96.19	91.74	90.34	87.93	89.96	81.07	52.35	39.26	68.87	59.21	77.76	46.76	80.30	67.98
	72.81	89.71	94.28	90.09	89.71	94.66	93.52	92.12	57.69	63.28	70.90	60.99	69.25	31.89	80.56	50.70
	84.75	82.46	96.71	94.03	87.29	86.15	92.38	91.74	49.94	28.72	75.60	53.37	50.32	36.21	83.61	33.04
	84.50	82.21	98.60	95.81	93.52	79.03	82.85	89.83	69.25	27.70	71.79	65.06	64.42	30.62	86.02	28.08

TABLE 5

ANALYSIS OF VARIANCE OF THE HARDNESS OF THE FORMULATIONS STUDIED

Source of variance	D.F.	Formulation A		Formulation B		Formulation C		Formulation D	
		S.S.	F	S.S.	F	S.S.	F	S.S.	F
Treatments	11	32.94	17.61 ***	159.59	53.88 ***	33.73	10.96 ***	207.14	43.79 ***
Storage time (t)	2	5.85	17.21 ***	80.85	122.48 ***	2.53	4.50 **	18.64	21.67 ***
Linear	1	3.51	20.65 ***	43.48	131.76 ***	0.55	1.98 *	14.18	32.98 ***
Quadratic	1	2.34	13.76 ***	37.37	113.24 ***	1.98	7.07 **	4.46	10.37 ***
Temperature (T)	1	12.60	74.12 ***	71.30	216.06 ***	14.52	51.86 ***	96.61	224.67 ***
Humidity (H)	1	3.85	22.65 ***	3.57	10.82 ***	3.63	12.96 ***	1.36	3.16 *
t×T	2	6.37	18.73 ***	35.67	50.04 ***	7.98	14.25 ***	68.00	79.07 ***
t×H	2	3.06	9.00 ***	3.37	5.11 **	1.94	3.46 **	1.12	1.30 *
T×H	1	0.41	2.41 *	0.01	0.03 *	0.00	0.00 *	6.69	15.56 ***
t×T×H	2	0.80	2.35 *	0.82	1.24 *	3.13	5.59 **	14.72	17.12 ***
Error	36	6.27		11.73		9.93		15.64	
Total	47	39.21		207.32		43.66		222.78	

*** Significant at the level $\alpha = 0.01$.

** Significant at the level $\alpha = 0.01$–0.05.

* Not significant.

S.S. = sum of squares.

TABLE 6

ANALYSIS OF VARIANCE OF THE PERCENTAGE OF NITROFURANTOIN DISSOLVED AFTER 1 h BY TABLETS OF THE FOUR FORMULATIONS STUDIED

Source of variance	D.F.	Formulation A		Formulation B		Formulation C		Formulation D	
		S.S.	F	S.S.	F	S.S.	F	S.S.	F
Treatments	11	54864.05	153.14 ***	64767.52	211.95 ***	20010.67	13.42 ***	27250.43	27.71 ***
Storage time (t)	2	39090.66	600.10 ***	64602.58	1162.75 ***	13572.00	50.08 ***	17824.43	99.70 ***
Linear	1	38865.41	1193.29 ***	47875.01	1723.36 ***	12783.21	94.33 ***	10573.49	118.28 ***
Quadratic	1	225.41	6.92 **	16727.57	602.14 ***	788.79	5.82 **	7250.94	81.12 ***
Temperature (T)	1	7078.35	217.33 ***	42.15	1.52 *	38.88	0.29 *	1810.57	20.25 ***
Humidity (H)	1	87.07	2.67 *	34.04	1.22 *	44.58	0.33 *	3962.15	44.32 ***
t×T	2	8095.24	124.27 ***	60.01	1.08 *	1701.44	6.28 **	1151.03	6.44 **
t×H	2	201.03	3.09 *	18.27	0.33 *	2540.31	9.37 ***	2280.10	12.75 ***
T×H	1	186.64	5.73 **	6.97	0.25 *	869.90	6.42 **	4.23	0.05 *
t×T×H	2	125.06	1.92 *	3.50	0.06 *	1243.56	4.59 **	217.92	1.22 *
Error	36	1173.43		1000.24		4878.32		3218.12	
Total	47	56036.48		65767.76		31327.66		30468.55	

*** Significant at the level $\alpha = 0.01$.

** Significant at the level $\alpha = 0.01$–0.05.

* Not significant.

S.S. = sum of squares.

Formulation C:

$$D_{60} = 20.016 + 5.309 \cdot t + 0.0753 \cdot (t \times T) - 0.0201 \cdot (t \times H)$$

$$(r^2 = 0.6625)$$

Formulation D:

$$D_{60} = 14.455 + 28.56 \cdot t + 2.90 \cdot t^2 - 0.29 \cdot T - 0.495 \cdot H - 0.1073 \cdot (t \times T) + 0.1854 \cdot (t \times H)$$

$$(r^2 = 0.960)$$

Discussion

In biopharmaceutical stability studies it is important to verify that the active principle itself remains unaltered throughout the study. In the work reported here the nitrofurantoin content of the formulations tested was periodically checked using the USP XXI method, which has proved sufficiently accurate (Caldwallader and Jun, 1976). Under no set of storage conditions was any degradation of nitrofurantoin observed during the six-month duration of the experiment.

Changes in the hardness of the formulations were most marked when a storage temperature of 40°C was employed, especially when the higher compression force had been used to prepare the tablets. This is reflected in the equations of the response surfaces by all having a negative coefficient for the temperature term, and temperature is the factor most significantly affecting the results. The predictive power of the response is very poor, however, only that of Formulation B approaching the value of $r^2 = 0.95$ considered by Guitard et al. (1978) as minimal for good prediction by quadratic equations; and although Guitard et al. (1978) mention that the regression equation for the logarithm of the dependent variable sometimes has significantly greater predictive power than that of the variable itself, in the present case this transformation produces even lower values of r^2.

The predictive power of the response surface equations for nitrofurantoin dissolved after one hour is much greater in the case of Formulations B and D (the former especially). For Formulation A the predictive power is again rather low, particularly as regards nitrofurantoin release from freshly prepared tablets, while the response surface equation for Formulation D has practically no utility for predictive purposes. Again the regression of the logarithm of the dependent variable exhibits no improvement upon these results.

In a previous article (Vila-Jato et al., 1986b) it was reported that the USP XXI Method I was not suitable for dissolution tests of nitrofurantoin tablets when the binder used was Carbopol 934 because the percentage of the drug dissolved after one hour was less than the required minimum even though the urinary excretion kinetics of these tablets showed their bioequivalence with capsules containing the same dose of micronized nitrofurantoin. A similar lack of correlation between results obtained in vitro and in vivo has also been reported by Meyer et al. (1974) and, more recently, by Gouda et al. (1984), who observed capsules containing macrocrystals of nitrofurantoin to exhibit a marked decline in dissolution rate that was not paralleled by bioavailability data. In the light of the results reported here, it is clear that although our earlier criticism of USP XXI Method I for nitrofurantoin tablets was too sweeping, it is not appropriate for nitrofurantoin tablets with Carbopol 934 binder to be evaluated by dissolution tests of freshly prepared tablets. The possible validity of tests using aged tablets now requires to be established by in vitro–in vivo comparisons carried out with tablets of various different ages. The need for such studies is especially urgent in view of Carbopol 934's having occasionally been used as a matrix in the belief that it ensured gradual release of nitrofurantoin from high-dosage tablets (Capan, 1983). This belief must now be questioned.

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