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EFFECT OF AGING ON THE BIOAVAILABILITY OF NITROFURANTOIN TABLETS CONTAINING CARBOPOL 934

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ABSTRACT

This article reports a study of two nitrofurantoin tablet formulations differing in the percentage of Carbopol 934 used as binder. The tablets of both formulations each contained 50 mg of nitrofurantoin. Those of formulation A contained 0.625 mg of Carbopol 934, and those of formulation B 1.25 mg. When freshly prepared, tablets of both formulations were bioequivalent to capsules containing 50 mg of nitrofurantoin, but a year's storage at 40ºC and 60% relative humidity caused a significant decrease in the bioavailability of nitrofurantoin from formulation B, whereas formulation A was still bioequivalent to capsules. USP XXI Ed. Method II successfully reflected the observed variations in bioavailability, but not Method I.

INTRODUCTION

Under normal conditions, tablets should retain their original shape, colour, hardness and friability, and the bioavailability of their active principle should remain unalte-

red. In order to investigate compliance with these requirements, it is necessary to study the influence of environmental factors (temperature, relative humidity, light intensity, etc) on parameters measuring the characteristics which should remain invariant. Aging studies of this kind have been carried out with tablets containing hydrochlorothiazide (1), phenylbutazone (2), cyproheptadine (3), naproxene (4, 5), chlorpropamide and tolbutamide (6), prednisone (7), prednisolone (8), pyridoxin (9) and digoxin (10), and in most cases changes in hardness, disintegration time and dissolution rate have been detected. There has nevertheless been relatively little research on the influence of storage conditions on the bioavailability of the drug contained in the tablets studied (11; 12; 13; 14).

Most studies of the bioavailability of nitrofurantoin in tablets have drawn attention to the importance of particle size (15; 16; 17). Vila-Jato et al. (18) have recently evaluated the effects of temperature, relative humidity and storage time on the hardness and dissolution rate of nitrofurantoin tablets containing Carbopol 934 as binder. This article follows up our earlier communication by reporting the influence of storage conditions on the bioavailability of nitrofurantoin in tablets containing Carbopol 934.

MATERIALS AND METHODS

Formulations-. Two 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 9 mm punch in a single-punch tablet machine (Korch Erweka, FRG). Capsules containing 50 mg of micronized nitrofurantoin were also freshly prepared in the bioavailability studies (Formulation C).

TABLE 1

Composition of the two formulations studied, and the compression force applied.

	Formulation A	Formulation B
Nitrofurantoin (mg)	50	50
Wheat starch (mg)	140	140
Lactose (mg)	60	60
Compritol* (mg)	1.25	1.25
Carbopol 934 (mg)	0.625	1.25
Compression Force (Nw)	4800	4800

* Compritol (Gattefossé, France) is a glyceryl behenate

Storage conditions-. The two tablet formulations were stored for a year at 40ºC and a relative humidity of either 30% and 60%.

Dissolution rate-. The apparatus used was the Dissolutest (Prolabo, France) complying with USP XXI Ed. specifications. Tablets were subjected to dissolution rate assays employing both USP XXI Ed. methods, Method I in accordance with the conditions laid down by USP XXI Ed. for nitrofurantoin tablets, and Method II at a speed of 50 r.p.m. Four tablets of each formulation were tested by each method, and the dissolution curves obtained were characterized by the percentages of nitrofurantoin dissolved after 60 and 120 minutes (D_{60} and D_{120}).

Analytical Methods-. The concentration of nitrofurantoin in samples obtained during dissolution studies were determined using the method described in USP XXI Ed. The method of Albert et al. (19) was used to determine nitrofurantoin in urine. Urine samples were collected and stored in opaque flaks at -30ºC until analysed.

Clinical Protocol-. Fifteen healthy male and female volunteers aged between 20 and 30 years and lacking any history of kidney

complaints were used in a 3 x 3 Latin square design with five replicates.

Pharmacokinetic Analysis-. Excretion of nitrofurantoin was characterized by means of the statistical moments proposed for plasma level curves by Yamaoka et al. (20) and adapted for urinary excretion curves by Vila-Jato et al. (21). In the present study these parameters were the total quantity of nitrofurantoin excreted in the 12 hours following administration (E_{12}), the mean residence time (MRT) and the variance of the residence time (VRT).

Statistical Analysis-. The E_{12}, MRT and VRT data were processed by two-way multivariant analysis of variance (MANOVA) (22). The null hypothesis was subjected to the greatest eigenvalue test (23). Data regarding weight, hardness, disintegration time, D_{60} and D_{120} were processed by one-way analysis of variance.

RESULTS AND DISCUSSION

Figure 1 shows mean urinary excretion curves for nitrofurantoin administered in Formulations A, B and C after 1 year's storage at 40ºC and 60% relative humidity. Table 2 lists the statistical moments characterizing the excretion of nitrofurantoin by each individual for each formulation, and Table 3 displays the results of the multivariant analysis of variance. C_s, the greatest eigenvalue of $H.E^{-1}$ is 2.673, so that $C_s/C_s+1=$ = 0.728, which exceeds the critical value 0.425 given by Hecks charts for α = 0.01 and the present distribution parameters s = 2; m = 0 and n = 12. The null hypothesis may therefore be rejected. Table 4 shows that Roy's test for multiple contrasts (24) reveals significant differences between Formulation B and the other Formulations as regards E_{12}, whereas Formulation A may be considered bioequivalent to the capsule (Formulation C).

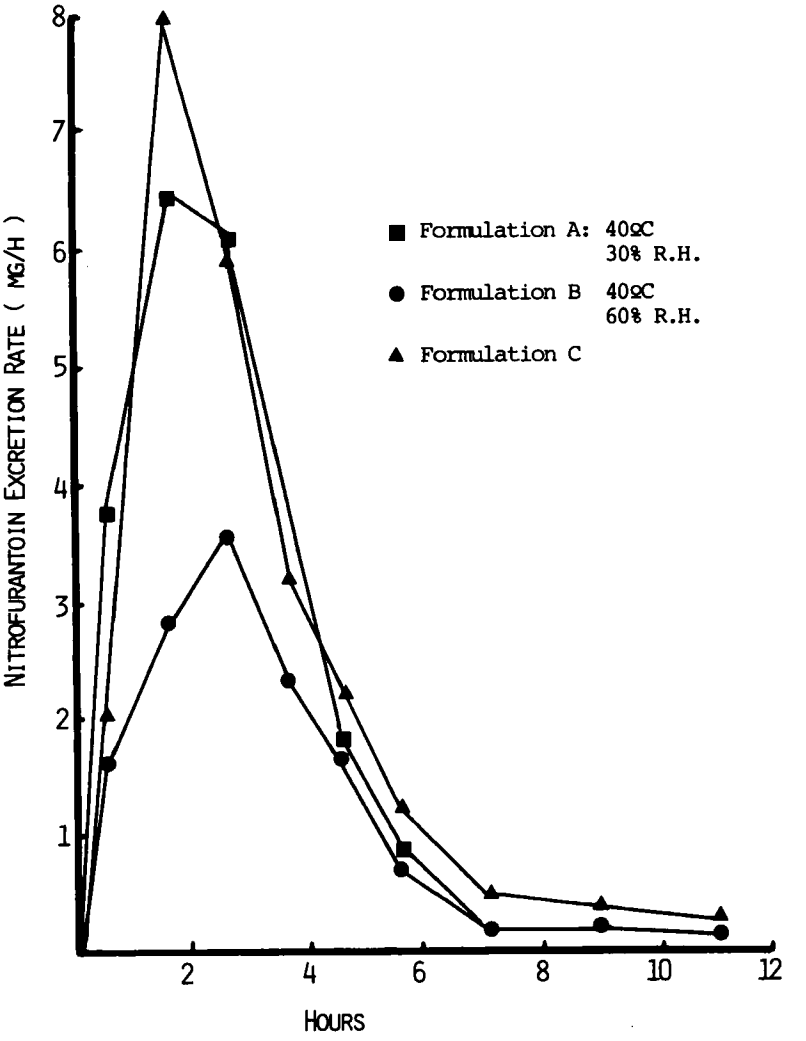

FIGURE 1

Mean urinary excretion curves for Nitrofurantoin administered in Formulations A, B (one-year's storage) and C (capsules freshly prepared)

TABLE 2

Statistical moments of urinary excretion curves of nitrofurantoin for each subject and formulation

Volunteers	Formulation	E^{12} (mg)	MRT (h)	VRT (h^2)	Formulation	E^{12} (mg)	MRT (h)	VRT (h^2)	Formulation	E^{12} (mg)	MRT (h)	VRT (h^2)
1		16.293	2.192	2.123		20.586	1.902	1.334		23.424	2.104	1.930
2		13.304	2.093	1.268		29.905	2.216	1.411		25.860	1.572	0.953
3	B	10.798	3.128	2.210	A	15.663	2.730	2.431	C	19.725	2.670	4.583
4		12.681	4.052	3.039		29.716	3.503	1.573		16.731	3.234	2.575
5		14.804	2.365	1.295		23.640	1.862	0.905		28.441	4.251	7.694
6		16.504	1.381	3.831		29.974	2.263	0.676		11.257	4.350	0.618
7	A	21.820	1.551	2.553	C	21.257	2.113	2.958	B	7.547	1.075	0.625
8		19.834	1.388	2.234		30.648	3.757	3.429		9.435	2.286	2.924
9		26.694	2.653	1.168		17.775	3.458	4.166		10.680	4.476	2.269
10		21.409	2.194	0.575		20.180	1.593	0.657		14.715	2.085	0.580
11		20.630	3.202	2.740		15.048	2.444	2.370		21.226	2.887	2.311
12	C	29.514	3.543	1.612	B	16.879	3.893	2.786	A	25.779	3.796	3.304
13		30.809	2.613	2.948		5.846	2.044	0.994		21.938	3.389	2.047
14		22.626	3.053	3.547		17.745	2.406	1.791		24.772	1.816	1.259
15		23.052	2.864	4.507		17.235	3.370	3.473		20.383	2.774	2.004

TABLE 3

Results of the multivariant analysis of variance (MANOVA)

Source of Variation	Matrix	Sums of squares and products		
Formulations	H	1095.8577		
		- 17.1248	1.725	
		70.6776	2.156	11.851
Subjects	S	212.1248		
		11.5079	16.815	
		- 1.9613	11.165	23.877
Error	E	540.7339		
		22.4448	14.357	
		- 6.6973	9.351	46.978
Total	T	1848.7764		
		16.8279	32.897	
		62.0190	22.672	82.706

TABLE 4

Roy´s test for multiple contrasts

Parameter	A vs B	A vs C	B vs C	Minimum value; α =0.01
E_{12}	9.707	11.092	1.385	7.30
MRT	0.494	0.078	0.416	1.19
VRT	0.038	1.107	1.069	2.15

Formulations A and B had the same composition and compression characteristics as the formulations labelled E and F in our earlier study (25) of the bioavailability of nitrofurantoin in seven freshly prepared formulations. In that study the two formulations in question were bioequivalent to each other, and both were bioequivalent to capsules containing 50 mg of nitrofurantoin. The results of present study clearly show that a year´s storage at 40ºC and 60% relative humidity brought about a significant reduction in the bioavailability of nitrofurantoin

in Formulation B tablets (those with the higher proportion of Carbopol 934). It may be pointed out that degradation of the active principle was periodically checked for using the USP XXI Ed. method, which is known to be sufficiently accurate for suchs purposes (26), and that no degradation of nitrofurantoin was observed under either set of storage conditions during the one-year duration of experiment.

Vila-Jato et al. (18) have recently found that the technological characteristics of nitrofurantoin tablets containing Carbopol 934 were significantly altered by six months' storage at 20º or 40ºC and 30 60% relative humidity. As a result, they suggested that the reported (27; 28) lack of " in vitro-in vivo " correlations for nitrofurantoin tablets might not hold for aged tablets. In order to compare the bioavailability results presented above with " in vitro " data obtained under the same conditions, the technological characteristics of Formulations A and B were studied before and after the one year storage period. Tables 5 and 6 list the mean values obtained for D_{60}, D_{120}, weight, hardness (measured with an Erweka TB-24 Durometer), friability (measured by subjecting the tablets to 18 minutes in an Erweka Friabilometer) and disintegration time (measured as for USP XXI Ed.) The values of F calculated by analysis of variance are also shown, and Table 7 lists the corresponding least significant differences (29) and the presence or absence of significant differences between the initial values and the values after a year's storage under the two conditions employed.

The results displayed in Table 7 show that the hardness of tablets of both formulations decreased markedly during the one year storage period. The difference between the relative humidities at which the stored tablets were maintained had a significant effect on those of Formulation A but not on those of Formulation B. These findings agree with those of the earlier study (18), in which it was found that in the formulations with less

TABLE 5

Mean values of weight, hardness, friability, disintegration time D_{60} and D_{120} for Formulation A

Parameter	Initial	40ºC 30% R.H.	40ºC 60% R.H.	D.F.	F
Mean weight (mg)	270.32	260.43	262.28	2/27	37.97
Hardness (Kg)	7.90	3.49	4.92	2/12	265.64
Friability (%)	0.89	0.36	0.59		
Disintegration time (sec.)	24.50	108.70	169.83	2/15	100.08
D_{60} (Method I)	20.99	92.72	91.36	2/9	478.00
D_{120} (Method I)	25.94	93.62	93.10	2/9	298.20
D_{60} (Method II)	73.28	89.42	79.54	2/9	3.79
D_{120} (Method II)	73.55	89.04	77.57	2/9	4.77

TABLE 6

Mean values of weight, hardness, friability, disintegration time D_{60} and D_{120} for Formulation B

Parameter	Initial	40ºC 30% R.H.	40ºC 60% R.H.	D.F	F
Mean weight (mg)	264.14	256.81	259.17	2/27	5.53
Hardness (Kg)	8.06	5.42	6.35	2/12	55.87
Friability (%)					
Disintegration time (sec.)	15.50	252.16	301.83	2/15	117.23
D_{60} (Method I)	11.52	70.52	26.59	2/9	464.09
D_{120} (Method I)	16.03	76.59	36.91	2/9	288.48
D_{60} (Method II)	74.44	48.67	12.90	2/9	50.82
D_{120} (Method II)	76.64	57.43	18.17	2/9	46.75

TABLE 7

Least significant differences for the weight, hardness, disintegration time and dissolution rates of Formulations A and B

Parameter	Formulation	Least significant difference	Initial vs 40ºC;30% R.H.	Initial vs 40ºC;60% R.H.	40ºC;30% R.H. vs 40ºC;60% R.H.
Mean weight(mg)	A	6.30	+	+	-
	B	11.37	-	-	-
Hardness (Kg)	A	0.79	+	+	+
	B	1.00	+	+	-
Disintegration time (sec.)	A	43.29	+	+	+
	B	83.37	+	+	-
D_{60} (Method I)	A	9.96	+	+	-
	B	7.55	+	+	-
D_{120} (Method I)	A	11.96	+	+	-
	B	9.61	+	+	+
D_{60} (Method II)	A	22.18	-	-	-
	B	23.09	+	+	+
D_{120} (Method II)	A	19.52	-	-	-
	B	18.14	+	+	+

+ : Significant difference

Carbopol 934 relative humidity had a direct influence on the effects of six months´storage on hardness, whereas the hardness of the tablets with more Carbopol 934 was only affected indirectly by humidity, by modulation of the effect of temperature.

The disintegration time of both formulations increased during the year´s storage. Again, the extent of this effect was influenced by relative humidity in the case of Formulation A but not in that of Formulation B.

The percentages of nitrofurantoin dissolved after 60 and 120 minutes by USP XXI Ed. Method I increased for both formulations. In this case it was in Formulation B that the extent of the effect depended on relative humidity, whereas no such dependence was observed for Formulation A. This agrees with the findings of the earlier study (18), in which the D_{60} response surface for the formulations with less Carbopol 934 was found to depend essentially on the storage time, whereas the formulations with the higher Carbopol 934 level were also affected by the relative humidity maintained during storage.

The percentages of nitrofurantoin dissolved from Formulation A tablets after 60 and 120 minutes by USP XXI Ed. Method II were not significantly affected by a year´s storage, but the differences were highly significant in the case of Formulation B. These findings parallel bioavailability results.

The observed reduction in the bioavailability of nitrofurantoin in Formulation B tablets may be due to humidity causing the binder to swell and gelify, in which state it would prevent the penetration of water into the tablet (30). This hypothesis is supported by the fact that a year´s storage at 40ºC and 30% relative humidity had no significant effect on the bioavailability of nitrofurantoin in Formulation A tablets (those with less Carbopol 934).

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