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Effect of Mixing on the Dissolution Kinetics of Nitrofurantoin Capsules.

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ABSTRACT

A study was done of the effect of blending time on similar mixtures containing nitrofurantoin both in crystalline and macrocrystalline forms. The powder mixture operations were performed using a Twin-Shell Blender (V-type). Firstly, the ingredients were blended long enough to obtain an absolute homogeneity, and this point was established as zero time. Then mixing was continued, an intensifier bar was placed inside the blender, and samples were collected at different times of blending. Gelatin capsules were filled with these samples and subsequently dissolution rate tests were carried out according to Methods I and II described in U.S.P. XXI.

From the results obtained through the above mentioned test, it is possible to notice a decrease in the dissolution rate values for crystalline nitrofurantoin during blending time, while these parameters do not show important differences when the assay is performed employing the macrocrystalline form of the drug.

INTRODUCTION

The absorption rate of a drug administered orally is controlled by several factors, being dissolution rate one of the most important (1, 2). Particle size acquires particular relevance when drugs have poor dissolution properties.

Bioavailability of nitrofurantoin (NF) is influenced by particle size. This fact has been studied by several investigator (3, 4, 5) by "in vitro" and "in vivo" test. From these studies, it has been concluded that macrocrystalline NF presents slower absorption than the crystalline form when given by the gastrointestinal route. The same differences have been observed when adverse effects such as nausea and vomits are studied. However it has not been possible to establish if such reactions are originated at CNS level or if they are a consequence of

a direct irritation caused to the gastrointestinal mucousa, because the same secondary effects are obtained when nitrofurantoin is administered by means of an I.V. injection (3, 4, 5).

On the other hand, the nature and amount of lubricant employed in the formulation may also affect the dissolution rate of a drug included in a dosage form. It has been noted that an increase in the percentage of magnesium stearate in the dosage form brings about a simultaneous decrease on the dissolution rate of the drug, due to the hydrophobic characteristics of this lubricant (6, 7, 8, 9).

Lerk and Bolhuis (10) have demostrated that both the intensity and time of blending during the manufacturing process are important factors which may affect the dissolution rate of active ingredients. As a consequence of the blending, magnesium stearate is adhered to the drug particles, creating and hydrophobic film.

From these facts, it is possible to expect that dissolution and possibly bioavailability could be altered by the influence of the amount of lubricant employed and by the intensity and the time of blending, since these factors affect directly the dissolution rate of the dosage forms.

The present work studies the influence of blending time on the dissolution kinetics of nitrofurantoin capsules using two different particle size of the drug.

EXPERIMENTAL

Two types of nitrofurantoin capsulas were prepared using two different particle sizes of the active ingredient (NF), but maintaining the same basic formula, "capsules A", containing crystalline nitrofurantoin (10-50u diameter)* and "capsules B", containing macrocrystalline nitrofurantoin (70-180 u diameter)** . In both cases Scherer hard gelatin capsules N° 1 were used.

Particle sizes were measured using a Leitz microscope calibrated according to the projected diameter method (11).

Blending was carried out in a twin-shell dry blender (Patterson-Kelley Co., East Stroudsburg, Pennsylvania), where 800 g of Nitrofurantoin, 2,000 g of Lac-

* Kindly supplied by Laboratorio Forgen. Santiago, Chile.

** Kindly supplied by Farmoquímica del Pacífico S.A.

tose U.S.P. and 56 g of magnesium stearate were passed through a 80 mesh sieve. Then, the ingredient were blended during 30 minutes to obtain complete homogeneity ("zero" time). Finally, an activant bar was adapted to the blender and samples were collected at 0 - 5 - 15 - 30 and 45 minutes of blending.

Capsules with a net weight of 375 ± 7 mg (equivalent to 83 mg of nitrofurantoin) were filled with the samples collected at the mentioned times. Dissolution kinetic tests were performed employing methods I and II of the U.S.P. XXI. The dissolution medium consisted of 900 mL of pH 7·2 phosphate buffer maintained at 37°C in a constant temperature bath, and the basket and paddle were rotated at 100 rpm.

Samples were assayed using a Perkin Elmer Spectrophotometer, model 550 according to the U.S.P. XXI procedure (12).

Dissolution rate constant (K), time for 50% of dissolution ($t_{50\%}$) and lag-time (L_T) were calculated for each formulation.

The Analysis of Variance (ANOVA) (13) and the Dunnett Test (14) were employed for assessing the dif

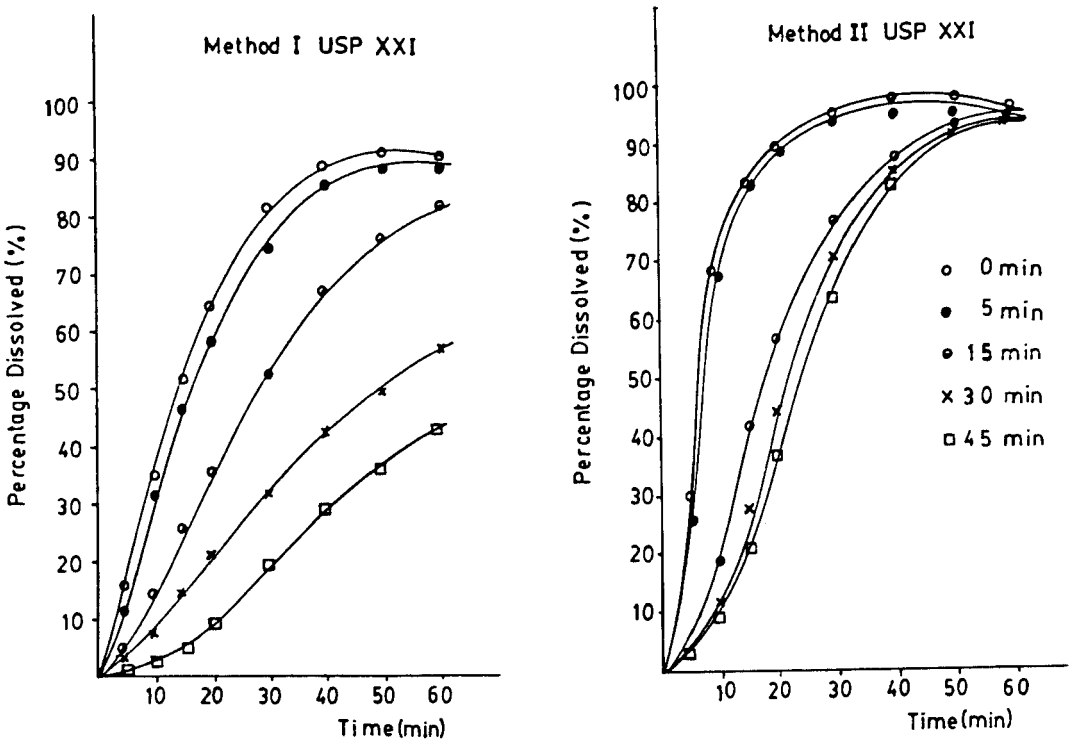

FIGURE 1 Dissolution profiles of "Capsules A" obtained at different mixing times, employing USP XXI methods

ferences between the values of dissolution rate obtained in the experiments.

RESULTS AND DISCUSSION

Figure 1 shows the dissolution profiles of "capsules A" obtained at different times of blending. It can be observed that the dissolution rates of preparation A decrease as the blending time of the powders increases.

TABLE I

Dissolution parameters of crystalline nitrofurantoin capsules prepared after different mixing time obtained using the U.S.P. XXI Method I.

Mixing Time (min)	$K(min^{-1}) \pm SD$	$t_{50}(min) \pm SD$	$L_T(min) \pm SD$
0	0.055 ± 0.007	12.73 ± 1.68	2.38 ± 1.37
5	0.048 ± 0.007	14.74 ± 2.18	1.75 ± 1.19
15	0.030 ± 0.006	23.76 ± 5.17	4.49 ± 2.67
30	0.016 ± 0.007	48.61 ± 15.17	4.64 ± 3.16
45	0.011 ± 0.002	66.00 ± 10.08	8.44 ± 1.17

Dissolution parameters of "capsules A" obtained using methods I and II U.S.P. XXI are shown in Table I and II respectively. It can be seen that $t_{50\%}$ as well as lag-time increase proportionally with the time of blending.

The ANOVA and Dunnett tests applied to both experimental situations showed that there are statiscally significant differences in the $t_{50\%}$ of dissolution between 30 minutes of blending and longer and zero time.

TABLE II

Dissolution parameters of crystalline nitrofurantoin capsules prepared after different mixing time, obtained using the U.S.P. XXI Method II.

Mixing Time (min)	$K(min^{-1}) \pm SD$	$t_{50}(min) \pm SD$	$L_T(min) \pm SD$
0	0.142 ± 0.057	5.72 ± 2.66	2.16 ± 1.04
5	0.156 ± 0.058	5.01 ± 1.82	2.52 ± 0.74
15	0.071 ± 0.025	10.70 ± 3.14	6.57 ± 2.25
30	0.063 ± 0.010	11.21 ± 1.85	8.71 ± 3.17
45	0.057 ± 0.015	12.87 ± 3.24	9.23 ± 1.94

From these results, it can be assumed that when the time of blending is higher, a greater covering of the particle of drug with magnesium stearate is obtained. The same phenomenon has been observed by Lerk and Bolhius (10).

When the dissolution profiles in Figure 1 are compared, it can be established that the dissolution rate is higher with method II, obtaining 90% of drug dissolved before the first hour. Moreover, it is observed

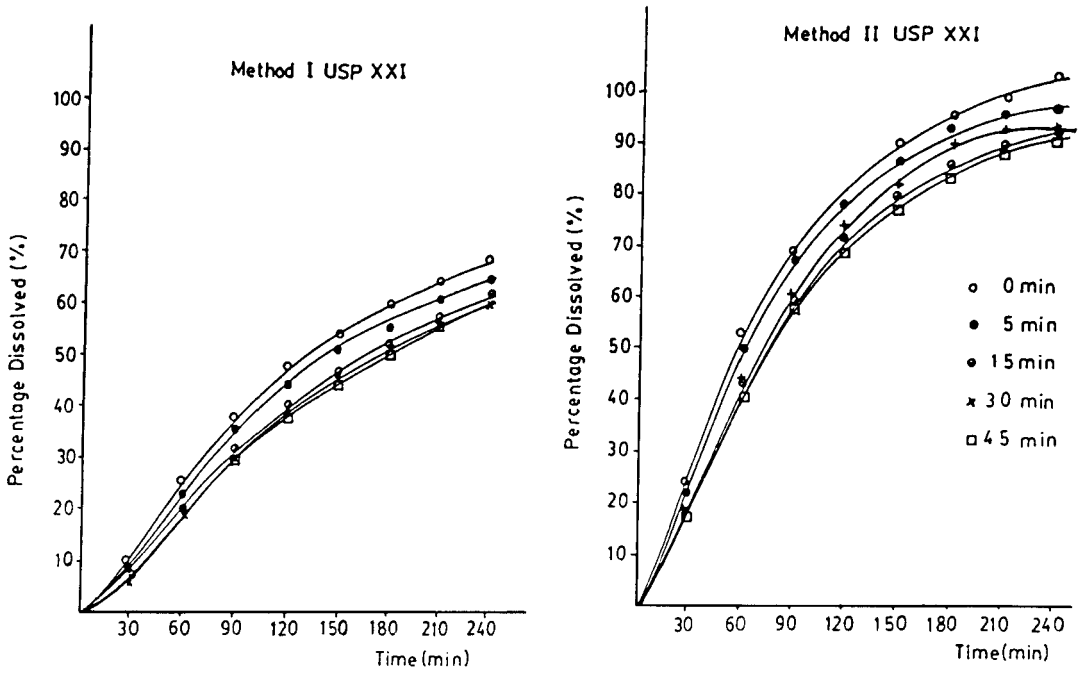

FIGURE 2 Dissolution profiles of "Capsules B" obtained at different mixing times, employing USP XXI methods

that time of blending has lower influence in the dissolution rate when method II is used, and the values obtained with it are in a narrower and superior rank than those obtained by method I. Therefore, it can be suggested that method I would be more adequate for evaluating the influence of blending time on the dissolution rate of nitrofurantoin capsules.

Figure 2 shows the dissolution profiles of "capsules B". Dissolution rate using method I is slower

TABLE III

Dissolution half life of macrocrystalline nitrofurantoin capsules prepared after different mixing time obtained by the U.S.P. XXI Methods.

Mixing Time (min).	Method I	Method II
	t_{50}(min) ± S D	t_{50}(min) ± S D
0	145.47 ± 42.65	41.46 ± 23.66
5	160.31 ± 26.63	44.36 ± 9.22
15	173.13 ± 11.54	69.83 ± 39.21
30	175.08 ± 18.81	51.63 ± 16.38
45	176.25 ± 29.55	62.44 ± 26.76

with respect to that of capsules manufactured with crystalline nitrofurantoin, reaching a dissolved amount ranging from 60 and 68% after 4 hours.

Table III contains dissolution half-life of "capsules B" obtained by U.S.P. XXI methods. The ANOVA test applied to the data obtained by both methods showed that there are not significant differences in dissolution between capsules obtained at different mixing times of the powders.

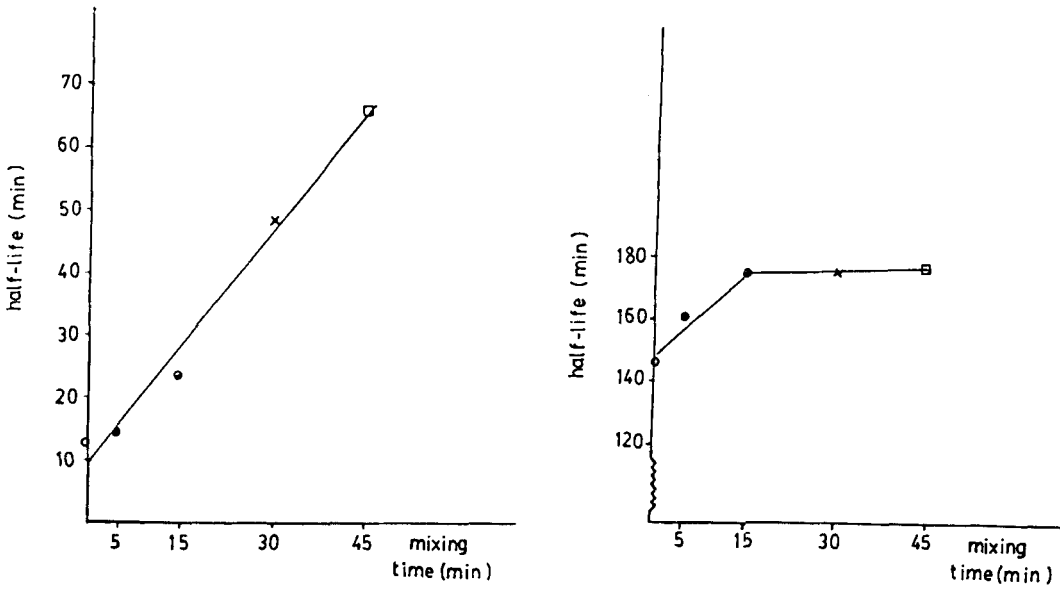

FIGURE 3 Correlation between half-life of dissolution and time of blending for Capsules A and B employing method I of USP XXI

A good correlation was found between $t_{50\%}$ of the microcrystalline nitrofurantoin and time of blending at all times studied (r = 0.992 when method I was used). However, this correlation for the macrocrystalline nitrofurantoin is found only for the three initial mixing times (r = 0,973 when method I was used) (Figure 3).

From these results we can conclude that time of blending does not affect significantly the dissolution rate of macrocrystalline nitrofurantoin. It seems clear that the higher specific surface presented by the smaller

microcrystalline particles can create a more extended hydrophobic area, which delays dissolution.

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