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RESEARCH PAPER

The Effects of Some Physico-chemical Factors and Pharmaceutical Excipients on the Bioavailability of Nitrofurantoin Oily and Aqueous Suspensions in Rats

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ABSTRACT

The effects of some physico-chemical factors and various excipients, i.e., sucrose, aluminum stearate, hydrogenated castor oil, Cab-o-sil, and lecithin, either alone or in combination, from suspensions in fractionated coconut oil and distilled water have been investigated. In vitro drug release studies were performed according to the flask–stirrer method. In addition to adsorption and solubility studies, determination of partition coefficients and rheological measurements have been carried out. The experimental design was based on an 8×8 latin square using rats as the test animals. The results of the study showed that the rate and extent of absorption of nitrofurantoin are decreased significantly by the use of an oily rather than an aqueous vehicle. In vitro drug release data showed some correlation with in vivo parameters, and also with the apparent viscosity of the vehicles. However, no correlation was detectable between in vivo parameters and the apparent viscosity of the vehicles.

Key Words: *Bioavailability; Dosage forms; Formulation; Fractionated coconut oil (FCO); Gastric emptying rate (GER); Nitrofurantoin; Oily vehicle*

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INTRODUCTION

Several reports indicate that the bioavailability of nitrofurantoin is affected by co-administration of food (1–3). In addition, the effects of formulation factors (4–8), dosage forms (9–11), viscosity (12–14), and the route of administration (15) on the bioavailability of nitrofurantoin have been widely studied and reviewed. The in vitro release rate of nitrofurantoin from different formulations and dosage forms has also received attention (16–20). However, the majority of the above-mentioned investigations were done on solid dosage forms, e.g., tablets or capsules, and bioavailability studies on nitrofurantoin administered in liquid dosage form as a suspension have received little attention (2,12–14). These latter investigations were done on aqueous suspensions. Information on the bioavailability of nitrofurantoin administered as a suspension in a non-aqueous vehicle (e.g., oil) and the effects of oil and various excipients on the bioavailability of nitrofurantoin is virtually non-existent, even though this type of dosage form may, in some circumstances, offer advantages over the use of more conventional ones (21). In view of this deficiency, and because oily vehicles for pharmaceutical formulations have been patented (21,22), the present work was undertaken in order to investigate the effects of oil and various excipients, either alone or in combination, on the bioavailability of nitrofurantoin from a suspension of this compound in fractionated coconut oil. The in vivo study was carried out using rats as the test animals. It was complemented by in vitro drug release and adsorption studies, and by partition and rheological measurements.

MATERIALS

Nitrofurantoin was obtained from Sigma Chemical Co., (Leicester, England). The reagents used in the determination of nitrofurantoin in urine, i.e., nitromethan (BDH Chemicals Ltd., Leicester, England), hyamine in absolute methanol (Packard Instrument Co., Inc., USA), and *N*,*N*-dimethylformamide (Sigma Chemical Co., Leicester, England), were used as obtained from the suppliers. Fractionated coconut oil (FCO) BPC (Alembic Products Ltd., Chester, Cheshire, England), aluminum mono- and distearates (Witco Chemical, USA), xanthan gum (Keltrol, food grade) (Kelco Co., USA), colloidal silica (Cab-o-sil), lecithin 90% (refined grade) (BDH Chemicals Ltd., Leicester, England), and hydrogenated castor oil (Akzo Chemie Ltd., UK) were also used as obtained from the suppliers. Powdered sucrose previously sieved (63–75 μm) was obtained from The British Sugar Corporation Ltd. (Leicester, England).

METHODS

Preparation of Vehicles

The vehicles used in the preparation of suspensions containing 0.1% w/v of nitrofurantoin were prepared using the same method as described previously (23). The eight formulations (vehicles) are listed together with their coding letters in Table 1. Xanthan gum was used in the aqueous vehicles (C and D) to prevent flocculation of nitrofurantoin. A low concentration (0.25%) was used in order to avoid a high viscosity relative to that of the oily suspension (A).

Preparation of Suspensions

Suspensions containing 0.1% w/v of nitrofurantoin previously sieved (53–63 μm) in vehicles A–H were prepared by stirring in an Ultra-Turrax mixer at 1000 rpm for 1 min. They were placed in flasks, which were covered by aluminum foil to provide protection from light, and then stored overnight at room temperature. On the following morning they were warmed to 37°C and shaken vigorously before use.

Rheological Measurements

Rheological measurements of the vehicles were carried out using the procedure described previously (23). A Haake Rotovisco viscometer was used, fitted with concentric cylinder sensors, measuring head 500, and a temperature-controlled water jacket at 37°C.

Determination of Apparent Partition Coefficient and Solubility

Fifty milliliters of solution containing 100 mg of nitrofurantoin in 100 mL of 0.1 M HCL was

Table 1

Experimental Design for In Vivo Studies[a]

	Time Period							
Rat No.	1	2	3	4	5	6	7	8
1	A	B	C	D	E	F	G	H
2	B	D	H	F	C	A	E	G
3	C	H	E	B	G	D	A	F
4	D	F	B	H	A	G	C	E
5	E	C	G	A	H	B	F	D
6	F	A	D	G	B	E	H	C
7	G	E	A	C	F	H	D	B
8	H	G	F	E	D	C	B	A

[a]The letters indicate the particular formulation administered to a given rat at a given time. The formulations (suspensions) used contained nitrofurantoin 0.1% w/v in: A, FCO; B, 20% w/v sucrose in FCO; C, 0.25% w/v xanthan gum in distilled water; D, 0.25% w/v xanthan gum+20% w/v sucrose in distilled water; E, 1% w/v Cab-o-sil in FCO; F, 0.5% w/v aluminum stearate (50:50 mixture of mono- and distearate)+0.7% w/v lecithin+0.35% w/v hydrogenated castor oil+20% w/v sucrose in FCO; G, 20% w/v sucrose+0.3% w/v Cab-o-sil in FCO; H, 20% w/v sucrose+1% w/v Cab-o-sil in FCO.

equilibrated with 50 mL of fractionated coconut oil (FCO) for 24 hr in a 250 mL glass-stoppered conical flask kept at 37°C in a shaking water bath and agitated at 100 oscillations per minute. The drug concentrations in the HCL were assayed spectrophotometrically at 369 nm. Preliminary studies showed that equilibrium was attained within 5 hr. The experiment was carried out in the dark. The apparent partition coefficient of nitrofurantoin was calculated by means of the following equation:

$$\text{apparent partition coefficient} = \frac{C_1 - C_2}{C_2}$$

where C_1 is the original concentration of the drug in the HCL and C_2 is the equilibrium concentration in the HCL.

The solubility studies of nitrofurantoin in both 0.1 M HCL and FCO were carried out as follows. An excess amount of nitrofurantoin was added to 100 mL of the particular solvent and kept at 37°C for a week with occasional shaking. Samples were taken periodically from the supernatant solution to predict the equilibrium solubility, filtered through a 0.45 μm Millipore filter, and then diluted to an appropriate extent with the particular solvent. The concentration of the drug (solubility) was assayed spectrophotometrically and calculated from the previously made calibration curves in the HCL and FCO at 369 nm and 363 nm, respectively. Equilibrium solubility was attained in 3 days in all cases. The experiment was carried out in the dark.

Adsorption Studies

Half gram quantities of Cab-o-sil were placed in a 100-mL glass-stoppered conical flask containing 50 mL of nitrofurantoin solution of specified concentration in FCO (0.2–4.0 mg/100 mL). The flask was shaken in a 37°C shaking water bath at 100 oscillations per minute for 24 hr. Preliminary experiments had shown that equilibrium was attained in less than 5 hr. The drug concentrations in the supernatant solutions were determined spectrophotometrically at 363 nm after centrifugation at 8000 rpm for 10 min. The experiment was carried out in the dark.

In Vitro Drug Release Studies

The flask–stirrer method used in this drug release study was based on the apparatus described by Poole (24) with minor modifications.

While the stirrer was in motion, 10 mL of an overnight-aged suspension was injected into the dissolution medium (1480 mL of 0.1 M HCL solution) through the side neck from a 10-mL graduated syringe. The latter was washed out with

10 mL of 0.1 M HCL and the washings were also added to the flask. Using 10 mL of a 0.1% w/v nitrofurantoin suspension in 1490 mL of dissolution medium provided sink conditions for the drug, because its solubility in 0.1 M HCL at 37°C is 15.59 mg/100 mL (see Results and Discussion).

Exposure of the nitrofurantoin solutions, i.e., the standard solutions and the solution in the dissolution flask, to light was minimized as far as possible by wrapping the containers with aluminum foil or with black plastic film. Five milliliter samples were taken from the flask at specified time intervals and immediately replaced by the same volumes of 0.1 M HCL. The samples were filtered through a Millipore filter assembly (0.45 μm pore size). The absorbance of each solution at 369 nm was determined using 0.1 M HCL as the reference solution.

In Vivo Bioavailability Studies

A dose of 10 mg/kg body weight (equivalent to a dose volume of 1 mL/100 g body weight) was administered to adult male Wistar rats (body weight range 380–569 g) via a catheter inserted into the stomach. The choice of this dose was based on the work of Conklin and Hollifield (25). The catheter and syringe were flushed out with one-third of the dose volume of oil or water, according to the formulation used, before removal from the animal. The rats were starved for 20 hr with free access to water before dosing, and were kept in metabolic cages. At the end of this period the collected urine was used as zero time sample. During the first 10 hr after dosing, the animals had free access to water followed by a liquid diet containing 5% w/v glucose and 0.05% w/v sodium chloride for up to about 36 hr. This was the maximum period over which nitrofurantoin was detectable in the urine obtained from any of the rats.

The design of this experiment was based on an 8×8 latin square as shown in Table 1. A minimum "wash-out" period of 7 days was allowed between successive experiments. Due to the difficulties of obtaining urine samples, it was decided to collect them over the following periods: 0–4, 4–8, 8–24, 24–27, 27–30, 30–32, 32–34, 34–36 hr after dosing. Samples were collected during the later periods only if the previous sample had been shown to contain nitrofurantoin. All samples were assayed immediately after collection by the method of Conklin and Hollifield (25), and all studies were initiated at the same time of day in order to eliminate the possible effect of circadian variation.

RESULTS AND DISCUSSION

In Vitro Studies

Apparent Viscosity of Vehicles (η_{app}), Solubility, and Partition Coefficient

The solubility of nitrofurantoin in both 0.1 M HCL and FCO is 15.59 and 4.47 mg/100 mL, respectively. The partition coefficient of the drug between the oil and HCL is 0.48. The results presented are mean values of three determinations.

Plots of shear rate vs. shear stress, to give the rheogram for each vehicle, are shown in Fig. 1. These figures are extended to a maximum shear rate of 436 sec^{-1} for the sake of clarity.

Rheograms of the measurements obtained in this study indicate the differences in the flow properties of the vehicles. These range from newtonian flow for FCO, through varying degrees of pseudoplastic behavior for the rest of the vehicles except vehicle F, which shows pseudoplastic behavior with slight thixotropy. The apparent viscosities at an arbitrarily chosen low shear rate of 100 sec^{-1} are shown later in Table 3.

Adsorption Studies

The negligible adsorption of nitrofurantoin by Cab-o-sil indicates that the effects of this suspending agent in the in vitro and in vivo studies were unlikely to involve any adsorption phenomena.

Drug Release Studies

Table 2 shows the mean percentages of drug dissolved at different times in the dissolution medium for each formulation.

Plots of these percentages against sampling times, to give the dissolution rate curve for each formulation, are shown in Fig. 2. The time required for 50% of the drug to appear in solution, i.e., $t_{50\%}$, calculated from individual dissolution rate curves for each formulation, was used as an index of the

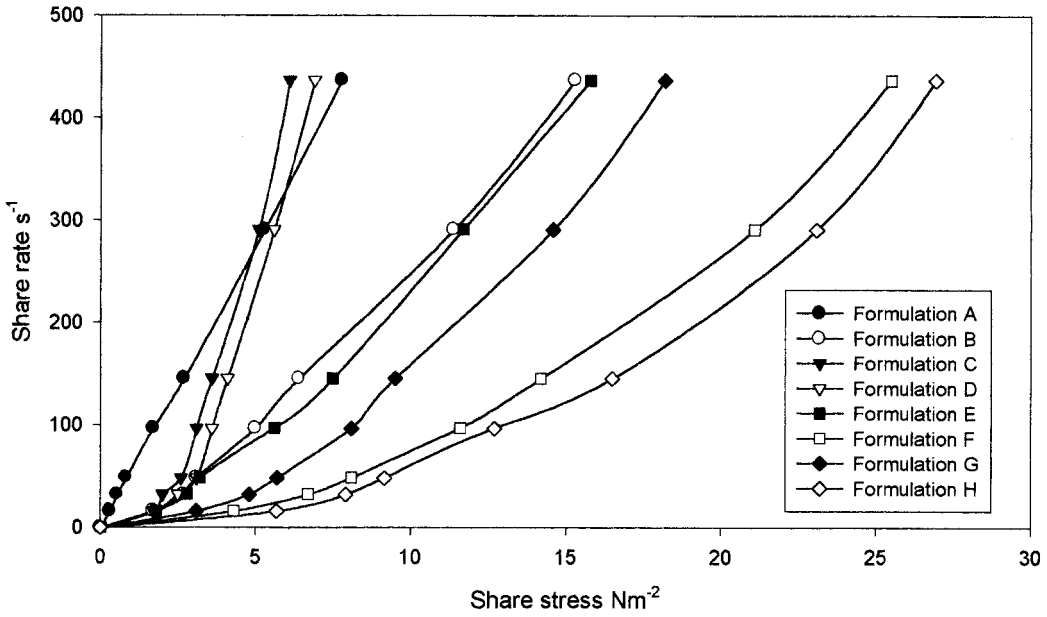

Figure 1. Rheograms of suspensions of nitrofurantoin in different oily and aqueous formulations.

dissolution rate of nitrofurantoin. The mean values of the $t_{50\%}$ are given in Table 2. Analysis of variance and multiple range tests (26) were carried out to distinguish the significance or otherwise of the differences between the mean $t_{50\%}$ values. The results are summarized as follows:

Mean values								
Of $t_{50\%}$ in rank	D	C	A	B	G	E	H	F
Order	2.4	2.5	12.3	17.2	23.5	47.3	48.4	59.9
1% level								
	D	C	A	B	G	E	H	F
5% level								

where at probability $p < 0.05$, any two means not underscored by the same line are significantly different and any two means underlined by the same line are not significantly different.

These results show that the two suspensions in aqueous vehicles C and D produced rapid release of the drug and gave very close $t_{50\%}$ values. Both vehicles contained 0.25% w/v xanthan gum, but D also contained 20% w/v sucrose. The presence of sucrose therefore appeared to have little effect on the release of nitrofurantoin from the aqueous suspensions. This is to be expected because the agitation of the dissolution medium will cause rapid dispersion and dilution of the dissolved sucrose.

The release of nitrofurantoin from the oily formulations was often poorly reproducible, and this poor reproducibility was probably associated with the behavior of the vehicles when they were placed in the dissolution medium. In addition, the variety of behaviors shown by the different vehicles was considered to be a major factor that contributed to the significant differences detected in the $t_{50\%}$ values from some of the vehicles.

In general the main difference in behaviors depended on the presence or absence of sucrose in the oily formulations. Thus, the formulations that did not contain sucrose, i.e., A and E, tended to form oily layers on the surface of the dissolution medium. Under the influence of the agitation of the aqueous medium, droplets of oil could be seen to become detached from the oily layer and then coalesce with it, particularly in the case of A. The higher viscosity of the layer formed by E reduced the tendency to form these droplets, and was probably responsible for the significant increase in the $t_{50\%}$ value for this formulation over that of A, $p < .01$. The release of

Table 2

$t_{50\%}$ Values and Percentage Nitrofurantoin Dissolved at Various Times from Different Formulations Using the Flask–Stirrer Method. Each Value Is Represented as Mean ± SD from Three Experiments

Formulation[a]	Time (min)						$t_{50\%}$[b]
	5	10	20	30	45	60	
A	20.0 ± 1.9	40.5 ± 2.1	68.1 ± 2.2	77.1 ± 1.8	82.7 ± 2.1	84.2 ± 1.4	12.3 ± 2.3
B	21.8 ± 7.8	38.7 ± 4.7	51.5 ± 3.7	65.4 ± 3.3	74.8 ± 3.5	84.1 ± 6.7	17.2 ± 4.5
C	79.8 ± 0.8	84.2 ± 0.5	86.9 ± 0.6	88.6 ± 1.3	88.6 ± 1.2	88.9 ± 1.4	2.4 ± 1.1
D	80.3 ± 1.6	86.2 ± 2.5	88.4 ± 3.1	90.1 ± 1.8	90.3 ± 3.8	90.1 ± 2.6	2.5 ± 1.3
E	11.9 ± 3.5	20.5 ± 3.5	31.5 ± 5.1	38.5 ± 4.8	49.3 ± 3.0	57.2 ± 3.1	47.3 ± 4.1
F	5.6 ± 1.7	10.4 ± 2.4	16.0 ± 4.2	26.5 ± 6.6	39.4 ± 7.9	51.2 ± 3.4	59.9 ± 5.1
G	12.6 ± 2.7	25.9 ± 3.7	46.0 ± 3.5	57.2 ± 4.6	66.5 ± 4.5	73.9 ± 5.5	23.5 ± 3.9
H	11.0 ± 3.8	19.3 ± 5.1	29.0 ± 6.9	40.0 ± 7.8	46.8 ± 5.1	55.9 ± 5.4	48.4 ± 6.4

[a]See Table 1 for formulation (vehicle) codes.
[b]Calculated from individual dissolution rate curves for each formulation.

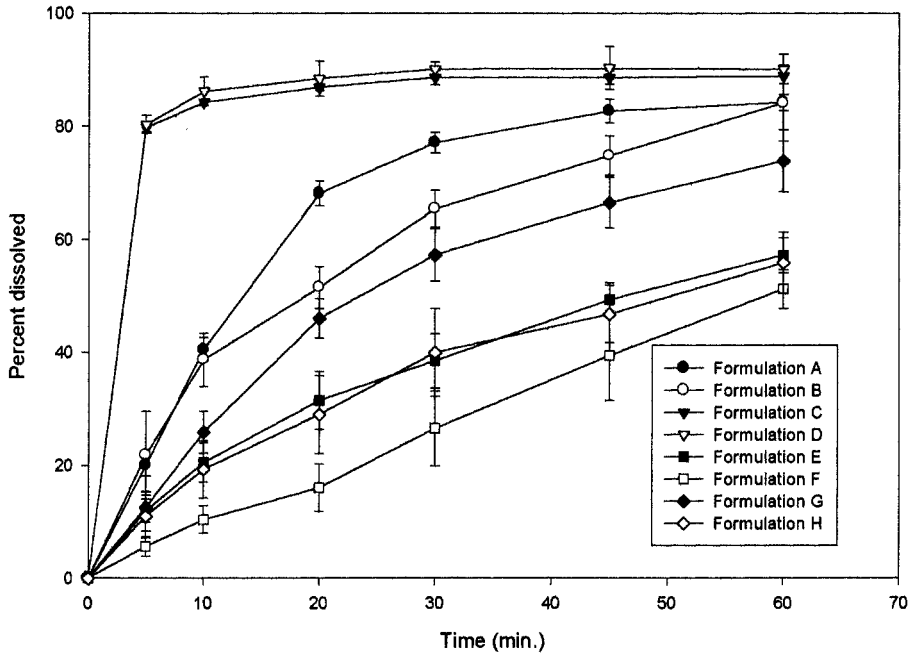

Figure 2. Percentage of nitrofurantoin dissolved vs. time for different oily and aqueous suspensions.

nitrofurantoin from the simple suspension in FCO (A) was fairly rapid, as would be expected from the low oil:0.1 M HCL partition coefficient of this drug (0.48). The mean $t_{50\%}$ value for this simple oily suspension did not differ statistically from the mean values for the aqueous suspensions C and D, $p > .05$.

In the cases of sucrose-containing formulations, i.e., B, G, H and F, the oily vehicle tended to form relatively large pear-shaped globules, in which the sucrose and other solid ingredients sedimented inside the globules, leaving a clear oily layer at the top of the globule. The sizes of these globules ranged from approximately 1 to 10 mm, and their

Table 3

Amount of Nitrofurantoin Excreted (dose%) During Different Sampling Times After Oral Administration of Nitrofurantoin Suspensions (0.1 w/v) as a Single Dose in an 8×8 Latin Square. Each Value Is Represented as Mean ± SD from Eight Experiments

	Nitrofurantoin Excreted (dose%)									
	Time (hr)									
Formulation[a]	0–4	4–8	8–24	24–27	27–30	30–32	32–34	34–36	Total	η_{app}[b] (mN s/m^2)
A	7.8 ± 2.4	2.9 ± 1.4	8.3 ± 4.6	0.6 ± 1.1	0.3 ± 0.6	0.1 ± 0.2	0.1 ± 0.2	0.05 ± 0.1	20.2 ± 3.8	17.5
B	9.1 ± 3.8	4.0 ± 1.2	9.4 ± 3.9	0.1 ± 0.2	0	—	—	—	22.6 ± 4.5	51
C	21.7 ± 4.0	8.4 ± 6.2	1.6 ± 4.4	0[c]	—	—	—	—	31.7 ± 7.5	33
D	22.8 ± 6.1	5.4 ± 4.2	3.3 ± 3.2	0	—	—	—	—	31.5 ± 4.6	38
E	7.8 ± 4.5	5.7 ± 4.5	6.6 ± 3.9	0.1 ± 0.1	0	—	—	—	20.2 ± 4.1	58
F	5.4 ± 2.8	2.9 ± 1.8	9.7 ± 6.8	0.4 ± 0.6	0.2 ± 0.5	0	—	—	18.6 ± 7.4	120
G	8.9 ± 4.3	4.3 ± 1.4	7.8 ± 5.8	0.05 ± 0.1	0	—	—	—	21.1 ± 4.2	83
H	5.1 ± 4.0	5.4 ± 1.9	9.4 ± 3.7	0.7 ± 1.2	0.3 ± 0.8	0.05 ± 0.1	0		21.0 ± 5.4	131

[a]See Table 1 for formulation (vehicle) codes.
[b]η_{app}= apparent viscosity, at shear rate of 100 sec^{-1} and temperature of 37°C.
[c]Recorded zero values indicate that mean value < 0.05.

overall densities caused them to fall to the bottom of the dissolution flask. As the sucrose was removed from the globules by dissolution into the aqueous phase, they gradually disappeared and the oil then formed a layer on the surface of the aqueous phase. The lifetimes of these globules therefore appeared to depend on the dissolution rate of sucrose, which in turn will depend on the viscosity of the oily liquid inside the globules. Thus, the lifetime of the globules formed by vehicle B (20% sucrose in FCO) was only of the order of 5 min, so that an oily layer was formed on the surface of the dissolution medium in a relatively short time. The viscosity of this layer was presumably similar to that of FCO alone, and the release of nitrofurantoin from formulation B would therefore be expected to be not much slower than from a suspension in FCO alone (A). In fact, the $t_{50\%}$ value for B was about 5 min longer than that for A, and the two values were not statistically different, $p > .05$.

The lifetimes of the globules produced by the remaining sucrose-containing formulations fell into the order G < H < F. Formulations G and H also contain Cab-o-sil in 0.3% and 1% concentrations, respectively. The resultant higher viscosities will delay the loss of sucrose from the globules and the release of nitrofurantoin not only from the globules, but also from the oily layer that is eventually produced on the surface of the dissolution medium. In fact, the globule-forming tendencies of these two formulations caused by their sucrose contents do not seem to be as important as the effect produced by including 1% Cab-o-sil, because formulations E and H gave very similar $t_{50\%}$ values (Table 2).

These two formulations both contain 1% Cab-o-sil but only H contains 20% sucrose. Although the apparent viscosities of these two vehicles are markedly different (Table 3), it is likely that the viscosity of the oily layers produced by both of them will be similar when the sucrose has been removed from H. The increase in viscosity of an oily layer produced by 0.3% Cab-o-sil does not appear to be sufficient to lead to a significant decrease in the release rate of nitrofurantoin, because the $t_{50\%}$ value of formulation G did not differ significantly from that of B, $p > .05$.

Finally, although the apparent viscosity of formulation F was less than that of H (Table 3), the lifetime of the globules was greater in F. This increase in globule lifetime appears to be responsible for the higher mean $t_{50\%}$ value for F compared to H, and the difference between these values was significant, $p < .05$.

One final point concerning the aqueous suspensions of nitrofurantoin (C and D) is that the maximum amount of drug released appeared to be about

90%, and this value remained constant over the last few sampling times. This may suggest that some nitrofurantoin remains in the oily vehicle, but the low oil:0.1 M HCL partition coefficient does not support this suggestion. The decomposition of nitrofurantoin under the influence of light offers an alternative explanation. Such a decomposition was confirmed by preliminary studies, and although the dissolution experiments were carried out in the dark as far as possible, exposure to light could not be avoided completely. Thus, some decomposition of dissolved nitrofurantoin is likely to occur and may reduce the rate of apparent dissolution of the drug, particularly in the latter stages when the concentration of nitrofurantoin in solution is high and when the rate of dissolution is decreasing.

In Vivo Bioavailability Studies

The amount of nitrofurantoin excreted during each time period, together with the cumulative amount excreted, were expressed as a percentage of the dose administered. The mean values of these percentages are shown in Table 3 and illustrated diagrammatically in Fig. 3.

The results in Table 3 and Fig. 3 indicate that nitrofurantoin is excreted in urine, and therefore absorbed, both at a faster rate and to a greater extent when administered as an aqueous rather than as an oily suspension. This statement is based on the concept that the only way the drug can get into the urine is via the blood (27).

With regard to the rate of absorption, the results show that when nitrofurantoin is administered in the two aqueous formulations C and D, 70% and 73%, respectively, of the total amount excreted appeared in the urine within 4 hr. After 8 hr the respective values were 95% and 90%. In contrast, the ranges of values obtained using the oily formulations were 24–41% after 4 hr and 45–66% after 8 hr. Statistical analysis indicated that these differences between the aqueous and oily formulations were highly significant ($p < .01$). The most likely explanation for this difference is that the delay in the gastric emptying rate (GER) brought about by the oil (28) consequently delays the appearance of the drug in the small intestine, which is regarded as the chief site for absorption of nitrofurantoin (29). These results are in agreement with those which showed that a delay in the GER, brought about by using a very high viscous aqueous suspension (12–14) or by the presence of food with a commer-

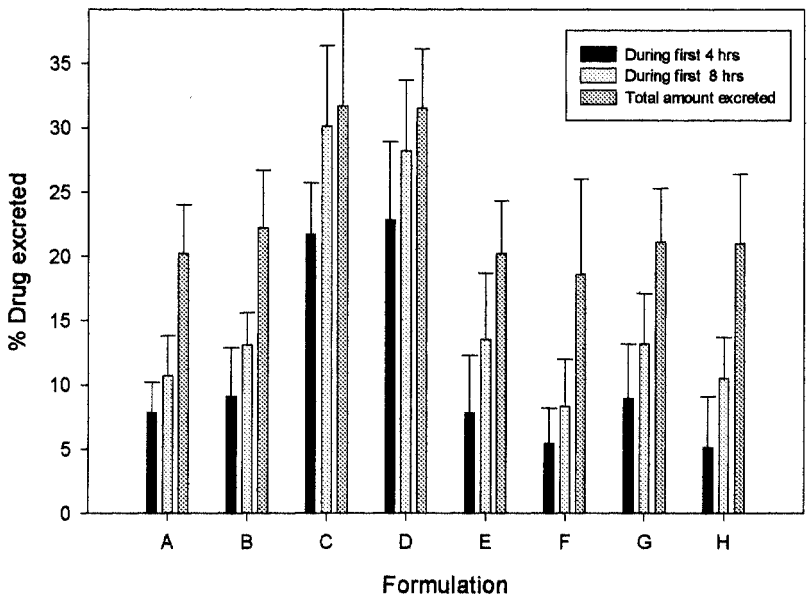

Figure 3. Amount of nitrofurantoin excreted during the first 4 hr, 8 hr, and total amount excreted (dose%) after oral administration of various suspension formulations. Results are expressed as means, with the vertical bars showing the SD of the eight experiments.

cial tablet (1), decreased the rate of nitrofurantoin absorption. The above explanation is supported by the findings which showed that a delay in GER brought about by anticholinergic drugs (30) or by oils (23) slow the absorption of paracetamol and sodium salicylates, respectively, because of the slower appearance of the drug in the small intestine.

The variations in the extent of absorption of nitrofurantoin in the different formulations are reflected by the total amounts (expressed as dose%) of nitrofurantoin that are excreted in the urine (31). Statistical analysis shows that the 1.4–1.7-fold differences in the amounts excreted after administration of the aqueous formulations, when compared with those excreted after administration of the oily products, are significant at $p < .01$.

It was found that food increased the extent of nitrofurantoin absorption from tablets containing macrocrystalline drug (1,2). This effect was ascribed to the decrease in GER brought about by the viscosity or lipid content of food. However, when nitrofurantoin was administered in a very viscous aqueous suspension, the rates of absorption and urinary excretion were slowed but the extent of absorption did not decrease (13). These results are in conflict with those reported (3,12,14) with regard to the extent of absorption. Niazi et al. (3) found that, in dogs, the absorption half-lives following tablet administration were not affected by food and atropine (a drug which delays GER). Seager (12) found that the amount of drug excreted by humans in 6 hr was reduced significantly ($p < .01$), and the biological availability of the drug was impaired by inclusion of 5% w/v methylcellulose in the suspension. Barzegar-Jalali and Richards (14) observed that nitrofurantoin excreted in the urine, expressed as a percentage of the dose administered to rats, decreased as the viscosity of the suspension medium increased. The authors ascribed this result to the delay in GER caused by the different viscosity-enhancing agents.

The results obtained in this study appeared to support those of Seager (12) and Barzegar-Jalali and Richards (14), and conflict with those of Bates et al. (1), Rosenberg and Bates (2), and Soci and Parrott (13) with regard to the extent of absorption, although they do agree with the results of Bates et al. and Soci and Parrott (1,13) with regard to the rate of absorption. However, Bates et al. (1) were unable to find any significant enhancement in the extent of absorption from a commercial tablet containing microcrystalline drug, and Rosenberg and Bates (2) could not find any significant enhancement in the case of commercial nitrofurantoin suspension and a microcrystalline tablet ($p > .05$). Furthermore, when nitrofurantoin was assessed in non-fasting subjects, these three commercial dosage forms were bioequivalent. It is suggested, therefore, that a delay in GER would have an enhancement effect only with those formulations having poor bioavailability in fasting subjects (e.g., macrocrystalline formulations), since it allows a longer time for dissolution of these dosage forms in the GI tract and consequently a better bioavailability. In the case of suspensions and well-formulated tablets (e.g., microcrystalline tablets), since dissolution of a significant fraction of the drug occurs fairly rapidly, a further delay in GER would have no effect. This suggestion is also supported by Soci and Parrott (13), who could not find any significant difference in the extent of nitrofurantoin absorption when GER was delayed using a very viscous aqueous suspension compared with a simple aqueous suspension as a reference ($p > .05$).

In addition, these investigators (1,2,13) conducted their experiments in humans, while this study was conducted in rats. It is possible, therefore, that a difference between the species could offset the similarities in the absorption. The rat differs from other species because it does not have a gall bladder (32). It is possible that some absorption of nitrofurantoin could take place in the gall bladder itself, since nitrofurantoin is excreted to some extent in the bile (33), and this could be a possible explanation of why the extent of absorption of nitrofurantoin, when administered in a suspension, did not decrease significantly when GER was delayed in humans.

It must be pointed out that enzymatic degradation of nitrofurantoin, when entering into the GI tract (29,31,34), should be taken into account when a delay in GER occurs for any reason, e.g., food, viscosity-enhancing agents, or lipids. However, this point was not taken into account in the assessment of the extent of bioavailability (1,2,13). In fact, Watari et al. (15) reported that the reduction in relative bioavailability of nitrofurantoin following oral administration is probably due to gastric degradation of the drug. It is possible that the enzymatic degradation of nitrofurantoin could provide the basis for a more detailed explanation of the different effects observed in this study and in previous ones (1–3,12).

Extending the suggestion to the present results would indicate that the oily vehicle delays the GI transit time to such an extent that, although release of nitrofurantoin into solution in the aqueous gut fluids will have time to occur, the extent of enzymatic degradation will be appreciable and consequently the degree of absorption of intact drug will be decreased when compared with that obtained using an aqueous vehicle.

There was no significant difference between any of the oily formulations, either during the first 4 and 8 hr or between the total amount excreted, except that the amount excreted during the first 8 hr post-administration of formulation F was lower than the amounts obtained using the other oily formulations ($p < .05$) (Table 3) (Fig. 3). A consideration of the viscosity of formulation F indicates that it has the second highest viscosity of all the formulations. However, these remaining formulations show no significant differences in comparison to formulation A, the simple oily suspension, although their viscosities are higher than that of A and include that of formulation H, which has a higher viscosity than F. In addition, no significant difference was observed between the extent of absorption from any of the oily formulations, including F ($p > .05$). These results suggest that the viscosity has no additional effect on the extent of absorption of nitrofurantoin from the oily vehicles used in this study, and the effect of the oil on GER is predominant.

The inclusion of sucrose in the oil (B) had no significant effect on the rate and extent of nitrofurantoin absorption ($p > .05$), thus suggesting that the delaying effect of osmotic pressure on GER had no significant effect in this study. This is supported by comparison of the results obtained with the two aqueous formulations (C and D). The lack of effect of sucrose on nitrofurantoin absorption differs from the situation observed with salicylate in the previous work (23), where osmotic pressure appeared to cause a significant effect on bioavailability. This latter effect was explained on the basis of the high oil:0.1 M HCL partition coefficient of salicylate (38.6). In case of nitrofurantoin this partition coefficient is only 0.48 (see text). It is suggested, therefore, that the role of the osmotic effect of sucrose in minimizing the uptake of water by the GI membrane, and hence maintaining a large volume of available water in the GI tract, is not as important as in the case of drugs with oil:HCL partition coefficients of more than unity, i.e., salicylate.

A comparison of formulations A, B, E, G, and H (Table 3) suggests that neither 0.3% nor 1% Cab-o-sil has any significant effect ($p > .05$) on the bioavailability of nitrofurantoin in the oily vehicle. The higher concentration, i.e., 1% w/v, nullified the increasing effect of sucrose on the bioavailability of sodium salicylate (23), when given in the formulation which corresponds to formulation H in this study, and the difference was significant ($p < .05$). It was suggested that this effect was possibly due to adsorption of salicylate onto the large surface area of the Cab-o-sil by hydrogen bonding, and in vitro studies have confirmed this possibility (23). However, the absorption of nitrofurantoin is not altered by the inclusion of the Cab-o-sil. Neither the viscosity (as mentioned above) nor the adsorption would seem to have an effect in this study. In fact, in vitro adsorption studies did not detect any appreciable adsorption of nitrofurantoin onto Cab-o-sil.

Relation Between In Vivo and In Vitro Parameters

Apparent Viscosity of Vehicle (η_{app})

Analysis of the results given in Table 3 supports the suggestion made earlier, that the viscosity played an insignificant role in the results obtained in vivo, by showing poor correlations between viscosity and either the amount of drug excreted (dose%) during the first 4 and 8 hr periods or the total amount excreted, as indicated by Eqs. (1)–(3), respectively:

$$\%\text{dose excreted (4 hr)} = 17.746 - 0.1006\,\eta_{app} \quad r = -0.5907, \quad p > .1 \tag{1}$$

$$\%\text{dose excreted (8 hr)} = 23.238 - 0.1009\,\eta_{app} \quad r = -0.5453, \quad p > .1 \tag{2}$$

$$\%\text{dose excreted (total)} = 27.62 - 0.0642\,\eta_{app} \quad r = -0.5105, \quad p > .1 \tag{3}$$

However, viscosity appears to play a significant role in the in vitro dissolution studies, as indicated by the existence of a correlation between $t_{50\%}$ and viscosity [Eq. (4)]:

$$t_{50\%} = -2.7560 + 0.444\,\eta_{app} \qquad r = 0.8244, \quad p < .02 \tag{4}$$

Drug Release In Vitro

In addition, $t_{50\%}$ showed reasonable degrees of correlation with the in vivo parameters, as indicated by Eqs. (5)–(7):

$$\%\text{dose excreted (4 hr)} = 17.627 - 0.2455 t_{50\%} \qquad r = -0.776, \quad p < .05 \tag{5}$$

$$\%\text{dose excreted (8 hr)} = 23.244 - 0.2733 t_{50\%} \qquad r = -0.7302, \quad p < .05 \tag{6}$$

$$\%\text{dose excreted (total)} = 28.071 - 0.1764 t_{50\%} \qquad r = -0.7556, \quad p < .05 \tag{7}$$

These correlations are perhaps surprising in view of the previous comments that the in vivo parameters do not show any relationship to viscosity, whereas the in vitro parameter, $t_{50\%}$, does show some correlation with viscosity. The only explanation that can be suggested to account for this apparent contradiction is that dissolution, whether in vivo or in vitro, is influenced not only by the viscosity of the formulation but also by additional factors. For example, possible effects of the formulation components on the solubility of nitrofurantoin, adsorption of nitrofurantoin onto sucrose particles in the oily formulations, or complexation with sucrose in solution in the aqueous phase. The correlation between the in vitro dissolution rate and the in vivo parameters is supported by the work of a number of investigators (5,35). Groning (35) studied the bioavailability of nitrofurantoin after oral administration of dosage forms with different onsets of release. The author found that a delay in the release of merely a few hours leads to a statistically significant reduction in the bioavailability of active ingredients. After administration of coated tablets, where release was delayed for up to 5 hr, only 8.3% of the dose was excreted in urine, whereas with rapidly disintegrating tablets, 34.5% of the dose underwent renal elimination. The author indicated that nitrofurantoin is only optimally available from the GI tract over a limited period, and that with dosage forms of nitrofurantoin, which are subject to passage through the GI tract, only that part of the active ingredient which is released from the preparation within the first few hours of administration is optimally absorbed and eliminated in urine. These findings are in good agreement with the present results.

CONCLUSIONS

The results in this study show that in rats the rate and extent of absorption of nitrofurantoin are decreased significantly when the drug is administered as a suspension in fractionated coconut oil compared with aqueous suspensions. In addition, enhanced osmotic pressure and increased viscosity did not produce any significant effects on the absorption. It is therefore suggested that the decreased bioavailability is caused by the delaying effect of the oil on the GER, and this effect predominates in all the oily formulations used in this study. This suggestion is supported by the poor correlation between the viscosity and the in vivo parameters. However, viscosity appears to play a significant role in the in vitro dissolution release studies, as indicated by the existence of a correlation between the in vitro release rate and viscosity.

Finally, reasonable degrees of correlation between in vitro release and in vivo parameters suggest that dissolution, whether in vivo or in vitro, is influenced not only by the viscosity of the formulation but also by additional factors.

It is recommended that nitrofurantoin is not given in a formulation or dosage form or in any situation where the rate of gastric emptying is reduced, e.g., in a very viscous suspension, oily vehicle, or after a fatty meal. Otherwise, the absorption is dissolution rate-limited, in which case a delay in intestinal transit time favors better dissolution, and consequently better bioavailability, of the drug.

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