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Absorption and dissolution of nitrofurantoin from different experimental formulations

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Summary

The general applicability of the polyvinylpyrrolidone, polyethylene glycol, mannitol and sorbitol solid dispersion and co-precipitation technique as a method for enhancing the gastrointestinal absorption of orally administered hydrophobic drugs was explored with the urinary antiseptic nitrofurantoin. The in vivo absorption patterns of pure nitrofurantoin and the test preparations were compared by following the cumulative amount of nitrofurantoin excreted in the urine as a function of time. The results of these urinary excretion studies demonstrated that the absorption of nitrofurantoin in man from the test systems was significantly enhanced and was present in the body at much higher levels than when equivalent doses of either the drug alone or as physical mixture were orally administered. A correlation was found between the in vitro dissolution rates of these test systems at 37°C and their in vivo absorption data.

Introduction

Among the techniques that can potentially enhance the dissolution rate and, hence, the rate and/or extent of absorption of hydrophobic drugs is the formation of solid dispersions or co-precipitates with various pharmacologically inert carriers. This physicochemical drug modification offers the advantage of enabling one to administer the drug orally in a form, in which it is most available for gastrointestinal (GI) absorption. In theory, an enhancement in the dissolution rate of a drug should

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facilitate its GI absorption rate if the absorption process is dissolution rate-limited. Although the in vitro dissolution properties of some co-precipitate systems have been characterized in some detail (Goldberg et al., 1966; Bates, 1969; Allen et al., 1978), little information is available in the literature related to the in vivo absorption characteristics of these systems.

In a previously published report from this laboratory (Genedi et al., 1978), polyethlene glycol in the form of solid dispersion with nitrofurantoin was shown to enhance markedly the rate of solution of this water-insoluble drug. In contrast, the co-precipitate of nitrofurantoin with polyvinylpyrrolidone was found to reduce the dissolution rate of the drug.

The purpose of the present investigation was to characterize and compare the in vivo absorption patterns of pure nitrofurantoin, a 1 : 4 w/w nitrofurantoin–polyvinylpyrrolidone physical mixture, a 1 : 4 w/w nitrofurantoin –polyvinylpyrrolidone co-precipitate, 1 : 4 w/w nitrofurantoin–polyethylene glycol solid dispersion, and a 1 : 10 w/w nitrofurantoin–mannitol solid dispersion in man. The dissolution behaviour of these systems was also examined.

Materials and Methods

The materials used include nitrofurantoin (Eaton Laboratories, Norwich, New York, U.S.A.); polyethylene glycol 6000 (Hoechst, West Germany); polyvinylpyrrolidone 25,000 (General Aniline and Film, New York); dimethyl formamide, reagent grade (BDH Chemicals, Poole, U.K.); hyamine hydroxide (Sigma Chemicals, Poole, U.K.); and nitromethane (Riedel-Dehaven AG, F.R.G.). All other chemicals used were reagent grade and were used as received.

Test preparation

Solid dispersions with polyethylene glycol, mannitol and sorbitol were prepared by the fusion method as previously described (Genedi et al., 1978). The 1 : 1, 1 : 2 and 1 : 4 nitrofurantoin–polyethylene glycol solid dispersions, a 1 : 10 w/w nitrofurantoin–mannitol solid dispersion and a 1 : 10 drug–sorbitol solid dispersions were prepared.

Co-precipitates of nitrofurantoin and polyvinylpyrrolidone in 1 : 1, 1 : 2 and 1 : 4 w/w ratios were prepared by dispersing accurately weighed quantities of nitrofurantoin in chloroform; the dispersion was then mixed with a solution of the polymer in chloroform and the organic solvent was subsequently evaporated in vacuo. The residue was then dried to a constant weight in vacuo and screened. The 1 : 4 w/w nitrofurantoin physical mixture with polyethylene glycol and polyvinylpyrrolidone and the 1 : 10 w/w physical mixture with mannitol and sorbitol were prepared by gently triturating appropriate quantities of each drug and polymer in a glass mortar. The various drug–polymer weight ratios were analytically confirmed. The gross particle size of the test systems was 125–180 μm. The pure drug possessing the same particle size range served as a control.

Stability of test preparations

Chemical stability of nitrofurantoin during the preparation of the various dispersion systems was studied by thin-layer chromatography and infra-red spectroscopy as previously described (Genedi et al., 1978).

Dissolution rate studies

The dissolution rate studies were performed in the manner previously described (Genedi et al., 1978). The test preparations were loosely filled into capsules, each containing a quantity equivalent to 100 mg or 50 mg drug. Capsules containing the following drug–polymer ratios were investigated. Capsules A, B and C containing nitrofurantoin–polyethylene glycol solid dispersion in the 1 : 1, 1 : 2, and 1 : 4 w/w ratios, respectively; capsule D, containing the 1 : 4 w/w nitrofurantoin–polyethylene glycol physical mixture; capsule E, containing a 1 : 10 w/w nitrofurantoin–mannitol solid dispersion, capsule F, containing a 1 : 10 w/w nitrofurantoin–mannitol physical mixture; capsule G, containing 1 : 10 w/w nitrofurantoin–sorbitol solid dispersion; and capsule H containing a 1 : 10 w/w nitrofurantoin–sorbitol physical mixture. The 1 : 1, 1 : 2, and 1 : 4 w/w nitrofurantoin–polyvinylpyrrolidone co-precipitate systems were contained in capsules J, K and L, respectively. The 1 : 4 nitrofurantoin–polyvinylpyrrolidone physical mixture was contained in capsule M. The commercial Furadantin tablet (R) and Macrodantin capsule (S) were also included in the study as control preparations.

The contents of these capsules were confirmed analytically. All dissolution rate experiments were performed in triplicate in N/10 HCl and pH 7.4 dissolution media.

Absorption rate studies

The studies were carried out on 6 healthy male volunteers (average age and body weight were 25 years and 68 kg, respectively). The volunteers did not take any drug a week before or during the trials. They were required to fast overnight and not to eat for 4 h post-medication. Each subject received 5 representative test preparations and Furadantin commercial tablet (Eaton Laboratories) in a random cross-over fashion allowing at least a one week interval between preparations. The dose of nitrofurantoin was equivalent to 100 mg drug taken with 200 ml water. Urine samples were collected immediately before administration and at 1, 2, 3, 4, 6, 8 and 12 h after drug administration. The volunteers were advised to drink water after each urine collection. The volume and pH of each urine sample were immediately recorded and an aliquot was frozen until assayed in duplicate.

Results and Discussion

Dissolution rate studies

The results of the dissolution studies are shown in Table 1. It may be seen from the table that the dissolution rate of the drug alone increased considerably in pH 7.4 buffer solution when compared with the release in pH 1.2. There was about a 2-fold

TABLE 1

DISSOLUTION STUDIES ON VARIOUS NITROFURANTOIN TEST PREPARATIONS IN pH 1.2 AND pH 7.4 AT 37 ± 0.5°C

Sample [b]	Mean percent dose dissolved					
	30 min		60 min		90 min	
	1.2	7.4	1.2	7.4	1.2	7.4
Pure drug	4.20	7.70	5.30	13.20	6.40	14.10
A	5.80	10.50	10.50	25.30	13.30	26.20
B	8.80	16.50	15.60	29.80	18.20	35.30
C	14.00	25.10	24.60	47.50	27.80	58.90
D	5.00	8.00	6.50	15.90	7.30	16.00
E	9.30	16.40	18.10	28.10	19.00	30.00
F	8.00	10.40	8.60	16.00	9.00	15.40
G	9.50	14.20	17.00	25.60	20.30	27.10
H	7.01	9.40	8.10	13.80	8.50	14.40
J	6.30	13.40	10.40	20.80	10.60	25.90
K	9.50	12.50	13.70	26.90	14.10	30.80
L	15.00	22.40	21.60	40.40	23.10	44.00
M	6.10	9.30	7.50	16.40	8.00	17.60
R	12.30	23.10	19.20	45.50	20.30	50.00
S	6.00	10.20	11.20	23.40	12.10	24.80

[a] Mean of triplicate runs.

[b] Refer to text for description of sample.

increase at any time interval as compared with its release in the acidic medium. It is important, however, to examine dissolution rate profiles of nitrofurantoin preparations under pH conditions simulating both gastric and intestinal fluids. This probably improves the in vitro–in vivo correlation and hence prediction of absorption characteristics and toxicity of the drug from these products.

Table 1 shows that the percentage of nitrofurantoin from all test preparations increased significantly when compared with pure drug or physical mixtures at any time interval. In addition there was a progressive increase in the percentage release of the drug corresponding to the increased weight fraction of the polymer. Comparison of the dissolution rates (at either dissolution medium) of the 1 : 1 w/w nitrofurantoin–polyethylene glycol solid dispersion (sample, A) and the commercial Macrodantin capsule (sample S) indicates that the test preparation has almost identical release profiles as the commercial capsule. This similarity in the dissolution rates of the two preparations is of interest. It has been demonstrated that the Macrodantin commercial capsule produced less nausea and vomiting than the Furadantin commercial tablet, and this reduction of side-effect was assumed to be due to the lower dissolution rate and absorption of the former commercial capsule (Paul et al., 1967; Conklin and Hailey, 1969). A preparation that provides a dissolution profile that is superimposible on the data of the product Macrodantin may also have reduced side-effects. It seems that one of the advantages of solid

dispersion technique is that the dissolution rate of the test preparation can be controlled by adjusting the drug–polymer ratio.

The enhanced dissolution rates of polyethylene glycol–nitrofurantoin solid dispersions are in good agreement with our previous results (Genedi et al., 1978). In contrast to the previous results, however, nitrofurantoin–polyvinylpyrrolidone coprecipitate systems also showed significant increase in the percentage release when compared with the capsule containing this drug alone. The discrepancy between the former study and the present work is difficult to explain, but it may be ascribed to the difference in the source of the polymer in the two studies. However, the present dissolution determination is supported by the in vivo absorption study which is discussed later in this work.

Stability of test preparations

None of nitrofurantoin preparations demonstrated any decomposition products after being subjected to the formulation of solid dispersion systems according to the analytical method used. TLC revealed no additional spots, and there was good correspondence with the reference samples. IR spectral analysis showed that the band characteristics of nitrofurantoin were not affected in the drug–polymer systems studied. There was no evidence of interaction between the drug and any of the polymers. It may be concluded that the chemical stability of nitrofurantoin was not affected after being exposed to the preparation of the dispersion systems.

Absorption rate studies

It has been demonstrated that a relationship exists in man between the blood levels of nitrofurantoin and its rate of urinary excretion (Mannisto, 1978). Furthermore, since the urinary tract is the site of therapeutic activity, and as much as 30% of the drug is excreted in urine unchanged after oral administration in humans (McGilveray et al., 1971), urinary excretion data were employed to reflect bioavailability. The urine analysis was carried out in duplicate by the method of Conklin and Hollifield (1965). Nitrofurantoin is a weakly acidic drug, so its urinary excretion in man can be significantly affected by variation in urinary pH (Schirmeister et al., 1965). Therefore, the urinary pH was determined at the time of each sample collection, and the values ranged from 5.4 to 6.2. For a given subject, the pH fluctuation did not exceed 0.5 pH unit. The similarity of these pH values for all test samples indicates that the slight variation in urinary pH would not affect the interpretation of the results of the in vivo study. The excretion rate and the cumulative amounts excreted were determined and plotted for each subject. From these data, the percent of the orally administered dose excreted in the urine and the time of the maximum excretion rate were determined for each subject. Data for each individual are not given to conserve space. The cumulative amount of unchanged nitrofurantoin excreted by each of the six subjects, during 8 h period, for each test sample and the commercial Furadantin tablet is summarized in Table 2. Also recorded in Table 2 are the mean cumulative excretion of unchanged drug (expressed as percent of dose) and standard error of the mean for each test sample. The

TABLE 2

MEAN CUMULATIVE PERCENT EXCRETION OF NITROFURANTOIN IN 8 h AFTER ORAL ADMINISTRATION OF VARIOUS NITROFURANTOIN EXPERIMENTAL FORMULATIONS

Subject	Formulation [a]					
	Pure drug	M	L	E	R	C
1	11.35	22.93	28.85	20.51	26.26	24.72
2	19.85	10.73	29.85	20.35	31.70	43.20
3	10.47	20.98	24.18	27.35	41.09	25.00
4	14.50	16.30	28.10	22.20	47.40	33.30
5	11.65	15.10	27.32	22.36	14.84	27.80
6	19.43	13.50	31.27	21.50	23.02	34.72
Mean	14.55	16.64	28.25	22.42	27.36	33.16
(±S.E.) [b]	(±2.08)	(±2.29)	(±1.79)	(±1.28)	(±4.37)	(±3.20)
	N.S.			N.S.	N.S. [c]	
		$P < 0.02$		N.S.		
			$P < 0.02$			

[a] Refer to text for description of samples.
[b] Standard error.
[c] Not significant $P > 0.05$.

significance of the difference between the means in Table 2 was calculated using the paired *t*-test.

Fig. 1 shows the mean cumulative amount of nitrofurantoin excreted as a function of time for each test preparation.

Table 3 lists the maximum excretion rates for each of the 6 subjects. Also reported in Table 3 is the mean excretion rate (±S.E.) for each test preparation and the results of the paired *t*-test. The time of occurrence of the peak excretion rate for the various products administered to each individual subject are reported in Table 4.

An examination of the mean cumulative amount of unchanged nitrofurantoin excreted by the subjects (Table 2) reveals that about twice as much drug was excreted from the 1:4 w/w nitrofurantoin–polyvinylpyrrolidone co-precipitate (sample L) as from either the physical mixture (sample M) or the pure drug. The control Furadantin commercial tablet (sample R) gave virtually the same amount of unchanged drug as the 1:4 co-precipitate material. The difference between the physical mixture and the pure drug is not significant. The data suggest that it would take only one-half of the dose in the form 1:4 w/w co-precipitate with polyvinylpyrrolidone to obtain the same extent of absorption as that observed with the pure drug. Plots of the mean cumulative amount of drug excreted versus time (Fig. 1) reveal that all the plots tend to reach a plateau between 6 and 7 h after administration, indicating that the excretion of nitrofurantoin is essentially over by 8 h and that the cumulative amount excreted in urine in 12 h is a valid estimate of the extent of absorption or availability of the drug from the test preparations.

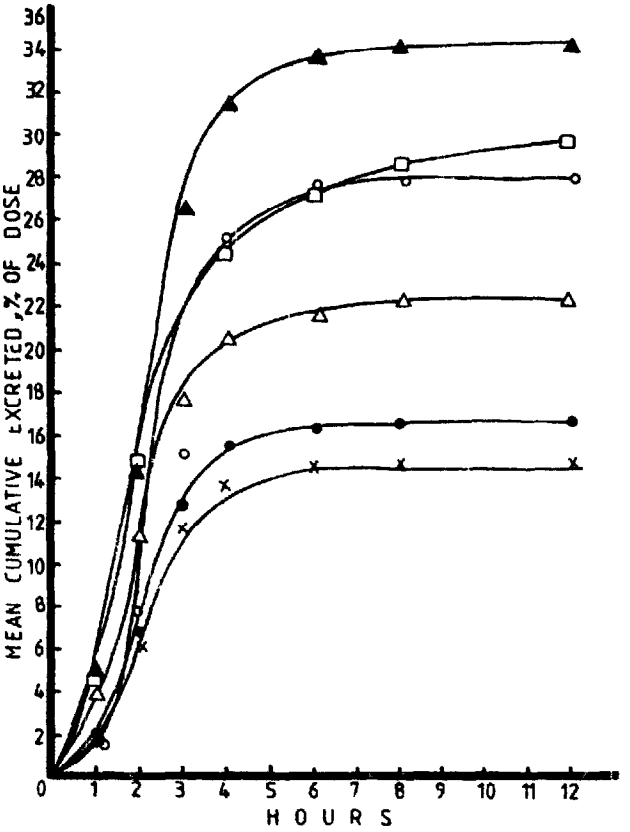

Fig. 1. Mean cumulative urinary excretion of nitrofurantoin after oral administration of 6 nitrofurantoin formulations. Each point represents the mean of 6 subjects. Key: ×, drug alone; ●, formulation M; △, formulation E; ○, formulation L; ▲, formulation C; □, Furadantin tablet (R).

The peak excretion rates for the various nitrofurantoin samples administered orally to each subject (Table 3) illustrate significant peak height differences between the co-precipitate system (sample L) and the other two systems (sample M and drug alone), but the peak excretion rate occurs at approximately the same times, the difference being insignificant. The results are consistent with those of Elliot et al. (1972) and Stoll et al. (1973). The former authors found that the absorption of reserpine was significantly enhanced when the drug was given at 1 : 5 w/w co-precipitate with polyvinylpyrrolidone. Thus, the differences in the maximum excretion rate of reserpine co-precipitate material is significantly higher than the pure or the 1 : 5 w/w physical mixture, but the time of occurrence of the peak is approximately the same. Stoll et al. studied the absorption characteristics of various nitrofurantoin and nitrofurantoin–deoxycholic acid preparations. The 1 : 5 w/w nitrofurantoin–deoxycholic acid co-precipitate showed significant increases in both rate and extent of absorption when compared with nitrofurantoin alone or the physical mixture.

A comparison of the dissolution and absorption data of nitrofurantoin as the pure drug and as a 1 : 4 w/w physical mixture with polyvinylpyrrolidone shows them to be almost identical. This observation eliminates the possibility that polyvinylpyr-

TABLE 3

MAXIMUM EXCRETION RATES OF NITROFURANTOIN (mg·h) AFTER ORAL ADMINISTRATION OF VARIOUS EXPERIMENTAL FORMULATIONS

Subject	Formulation [a]					
	Pure drug	M	L	E	R	C
1	3.85	6.72	11.70	6.00	10.12	12.00
2	9.00	3.74	12.24	5.72	11.50	15.58
3	6.30	6.42	11.49	7.42	9.53	11.88
4	6.03	8.56	9.52	10.80	9.20	15.00
5	5.64	4.48	11.60	7.84	4.80	7.70
6	7.94	8.40	12.50	6.60	11.50	9.50
Mean (±S.E.) [b]	6.50 (±0.96)	6.45 (±0.95)	11.52 (±0.48)	7.39 (±0.92)	9.4 (±1.20)	11.92 (±1.39)
	$P < 0.05$			N.S.	N.S. [c]	
		$P < 0.05$				
	N.S.		N.S.			

[a] Refer to text for description of samples.
[b] Standard error.
[c] Not significant ($P > 0.05$).

rolidone in the co-precipitate system acts by increasing the bulk solubility of nitrofurantoin in the fluids of the GI tract or by increasing the rate of dissolution by lowering the interfacial tension between the drug and these biological fluids. Also

TABLE 4

TIME OF OCCURRENCE OF THE MAXIMUM EXCRETION RATE (h) OF NITROFURANTOIN AFTER ORAL ADMINISTRATION OF NITROFURANTOIN EXPERIMENTAL FORMULATIONS

Subjects	Formulation [a]					
	Pure drug	M	L	E	R	C
1	2.50	2.50	2.50	2.50	2.50	2.50
2	2.50	2.50	1.50	1.50	1.50	2.50
3	2.10	2.10	1.90	1.70	1.90	2.10
4	1.50	1.50	1.50	1.50	1.50	1.50
5	1.50	1.50	1.50	1.50	2.50	1.50
6	2.50	2.50	1.50	1.50	1.50	2.50
Mean (±S.E.) [b]	2.10 (±0.24)	2.10 (±0.24)	1.90 (±0.24)	1.70 (±0.19)	1.90 (±0.24)	2.10 (±0.24)
				N.S.	N.S. [c]	
		N.S.		N.S.		
	N.S.					

[a] Refer to text for description of samples.
[b] Standard error.
[c] Not significant ($P > 0.05$).

physiological effects such as gastric emptying and GI motility can be ruled out, since it is reasonable to assume that these changes would be the same for the physical mixture and the co-precipitate. A possible explanation is that the two components of the co-precipitate system are more intimately associated with one another than they are in the physical mixture and this probably resulted in the formation of very fine particles which readily go into solution in the GI tract.

The absorption of nitrofurantoin was also significantly enhanced when the drug was given as a 1 : 4 w/w solid dispersion with polyethylene glycol 6000 (sample C, Fig. 1 and Table 2). The data indicate that it would take less than half of the dose of nitrofurantoin in the form of solid dispersion with polyethylene glycol to obtain the same extent of absorption as that observed with the pure drug. Thus, the bioavailability of the 1 : 4 w/w test preparation was 239% and 126% relative to the pure drug and the commercial Furadantin tablet, respectively. The differences in the maximum excretion rates of the nitrofurantoin solid dispersion material is significantly higher than the pure drug (Table 3), but once again, there are no significant differences in the time of occurrence of the excretion peak (Table 4). The potential of pharmaceutical application of solid dispersion technique was demonstrated early in human studies of the griseofulvin–PEG 6000 system (Chiou and Riegelman, 1970). The griseofulvin dispersion in PEG 6000 was found to be almost completely absorbed while only 43% of the pure was absorbed. The rapid and complete absorption of the insoluble antibiotic in man was mainly attributed to molecular and colloidal dispersion of the drug in the highly water-soluble carrier.

The use of sugars in solid dispersion systems is advantageous over other dispersion carriers because they are non-toxic, inexpensive and physicologically acceptable (Allen et al., 1978). A preliminary study indicated that mannitol is better than sorbitol since it forms stable, non-hygroscopic free-flowing powder with very slight discolouration. Therefore, the dispersion of nitrofurantoin in mannitol was chosen for the in vivo study. Inspection of Fig. 1 shows that the 1 : 10 w/w nitrofurantoin–mannitol solid dispersion (sample E) was excreted in the urine, and therefore absorbed to a greater extent than the pure drug; absorption is slightly inferior when compared with the other test samples. By analyzing the total excretion of the unchanged drug in 12 h, it was found that approximately 23% of the dispersed nitrofurantoin, 15% of pure nitrofurantoin and 28% of the commercial tablet were excreted (Table 2). Thus, the availability of the 1 : 10 w/w nitrofurantoin–mannitol dispersion was 150% and 80% relative to the drug alone and the control tablet, respectively.

In vitro–in vivo correlations

The correlations tested were between the mean cumulative index of unchanged drug excreted in the urine after 30 and 90 min in both dissolution media. A linear correlation was found between the amount of nitrofurantoin dissolved in the acidic medium after 30 and 90 min and the cumulative amount of unchanged drug excreted after 12 h. In both cases the correlation coefficients are greater than 0.97. Similar

correlations were found when the phosphate buffer was used as the dissolution medium. The good in vitro–in vivo correlation strongly suggests that the dissolution rate is the controlling factor in the amount of nitrofurantoin absorbed from the GI tract and subsequently excreted.

In conclusion, the present study demonstrated that the dissolution and absorption of nitrofurantoin could be markedly enhanced when dispersed in polyvinylpyrrolidone, polyethylene glycol or mannitol and that these in vivo increases can be correlated with in vitro dissolution rates. The results suggest that these techniques may play an important role in increasing dissolution, absorption and therapeutic efficacy of poorly water-soluble drugs in future dosage forms.

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