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Pharmaceutical availability of digoxin tablets

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Summary

Pharmaceutical availability of two similar formulations of digoxin tablets was compared. A marked difference in drug dissolution rate was found; it was shown that the principal causes of this behaviour come from particle size, crystallinity of active principle and influence of some excipients.

Introduction

The bioavailability of digoxin has been widely studied and several cases of bioinequivalence among commercial tablet dosage forms have been reported (Binnion and McDermott, 1972; Lindenbaum et al., 1971; Wagner et al., 1973).

Furthermore, several investigations have demonstrated that the bioavailability from capsules was greater than that from tablets (Astorri et al., 1979; Mallis et al., 1975; Ghirardi et al., 1977); in addition the capsule dosage form produced less intra- and inter-subject variability in absorption than did the tablet form (Johnson et al., 1976). These problems of bioavailability from tablets are particularly important for such a sparingly soluble drug such as digoxin which has such a narrow therapeutic index. Therefore much attention should be paid to the investigation of all factors affecting release of digoxin from this pharmaceutical dosage form.

The purpose of this study was to compare the pharmaceutical availability of two similar formulations of tablets containing the same declared amount of digoxin. The tablets were tested for drug uniformity content and dissolution rate; in addition, the chemical–physical characteristics of the respective pure active principles and the influence of the various excipients of two formulations were also examined.

Materials and Methods

Reagents and chemicals

The samples of digoxin supplied by Fluka (Switzerland) (F), and two pharmaceutical industries (A and B) were used as obtained, without further purification.

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TABLE 1

Composition of digoxin tablets

Ingredients	Tablet 1	Tablet 2 *
digoxin A (mg)	0.25	–
digoxin B (mg)	–	0.25
lactose (mg)	97.25	74.75
maize starch (mg)	14.00	–
magnesium stearate (mg)	0.50	–
talc (mg)	–	5.00
polyvinylpyrrolidone (mg)	–	20.00

* No longer available on the market.

The composition of the two brands of tablets examined is given in Table 1.

All other chemicals were of analytical reagent grade.

Uniformity of content

Single tablet assays were performed on 6 samples of each brand. The means of the results are reported.

Disintegration time

This was done according to the USP.

Dissolution test

The F.U.I. IX Ed. dissolution apparatus was used to determine the dissolution of digoxin from tablets. The dissolution medium (500 ml of 0.6% HCl) was stirred with a teflon paddle rotated at 60 rpm and thermostated at 37 ± 0.5 °C. After the introduction of the tablet, samples were removed by syringe-filter (0.45 μm) from the dissolution medium at 30 and 60 min and digoxin concentration was assayed. The results are the mean of 10 separate assays.

Solubility studies

The solubility of the 3 digoxin samples in water at 37 °C was determined. Excess drug (as received, without previous grinding or sifting) was placed in a beaker along with 50 ml of water. The beaker was immersed in a constant-temperature water-bath and stirred with a magnetic stirrer. Samples were withdrawn through a syringe-filter (0.45 μm) at 120 and 240 min and assayed for drug content. Each experiment was effected at least in triplicate, and mean values were reported.

Diffusion studies

Diffusion tests were carried out with the Sartorius apparatus model S.M. 16750, according to Stricker (Stricker, 1971, 1973). Phase I (100 ml) consisted of artificial gastric juice (1 N HCl 94 g; NaCl 0.35 g; glycine 0.5 g at 1 liter with double-distilled water). Phase II (artificial plasma) was composed of 100 ml of $Na_2HPO_4 \cdot 12H_2O$–KH_2PO_4 buffer at pH 7.5 according to Sörensen. The apparatus was thermostated at 37 ± 0.5 °C.

One mg of digoxin, alone or with the appropriate amount of excipient, was added to Phase I; Phase I and Phase II were connected to the diffusion cell containing the artificial lipid barrier (Sartorius M1; area 40 cm^2). Then 6 serial 3-ml samples were collected from Phase II every 15 min, and digoxin concentration was assayed. All concentrations were corrected for volume changes occurring in Phase II. All reported values of digoxin concentration are the mean of at least four experiments. The coefficient of variation was always less than 2%.

Assay of digoxin concentrations

Digoxin concentrations were measured with a fluorometric method described by Fraser et al. (1973). The intensity of fluorescence was measured on a Perkin Elmer Mod. 650-10S Fluorimeter at an excitation wavelength of 354 nm and an emission wavelength of 483 nm. The reproducibility of method was verified and coefficient of variation was less than 2%. The tablet excipients did not appear to interfere with the assay.

Infrared absorption spectrometry

The KBr spectra were obtained with a Perkin Elmer Mod. 1710 FTIR spectrophotometer, a polystyrene filter being used to check the calibration. The instrument was internally calibrated with a laser.

Differential thermal analysis

DTA thermograms were carried out using a scanning rate of 10 °C/min on a Mettler TA 2000 Mod. thermal analyser. Nitrogen was used as purge gas. Sensitivity was 200 μV/f.s., chart speed 2 cm/min.

Nuclear magnetic resonance

C-NMR spectra were recorded on a Perkin Elmer EM-360 spectrometer (60 MHz), using dimethylsulphoxide as solvent, and tetramethylsilane as reference.

Microscopic analysis

A Nikon Mod. Optiphot microscope was used to examine the 3 digoxin powder samples.

Results and Discussion

Uniformity of content

Single tablet assays were performed on 6 samples of each brand since variation in digoxin content from tablet to tablet is to be expected in a formulation with such a small amount of active substance.

The results for the uniformity of content are reported in Table 2. The drug content was seen to be in excess of the labelled amount for both brands, even if a difference of about 8% was found between them.

Disintegration studies

All samples disintegrated within 10 min, and therefore passed the test.

Dissolution studies

The results of the dissolution test (Table 3) showed that whereas tablet 1 gave 85.7% release of digoxin just after 30 min, tablet 2 instead was less than 40% dissolved even after 60 min. This marked difference in dissolution rate and pharmaceutical availability between the two brands of tablets may cause their bioinequivalence. Several reports have in fact demonstrated a correlation between digoxin in vitro dissolution rate and its in vivo absorption (Fraser et al., 1973; Lindenbaum et al., 1973; Johnson et al., 1973).

The reasons for this behavioural difference between the two brands of tablets might be due to differences in the characteristics of the respective active principles (% crystallinity, presence of impurities, particle size, etc.) or else to the influence of the excipients of the formulations.

TABLE 2

Individual tablet assay

Sample	Mean digoxin per tablet (μg $\pm$ S.D.)	% of labelled content $\pm$ S.D.
Tablet 1	294 $\pm$ 4.1	117.85 $\pm$ 1.6
Tablet 2	272 $\pm$ 3.7	108.80 $\pm$ 1.4

TABLE 3

Dissolution test results

Sample	% dissolved after 30′ $\pm$ S.D.	% dissolved after 60′ $\pm$ S.D.
Tablet 1	85.72 $\pm$ 3.90	87.41 $\pm$ 2.87
Tablet 2	24.80 $\pm$ 3.29	38.99 $\pm$ 5.17

Comparison of digoxin samples

The actual identity of samples A and B and of reference sample F was verified by the comparison of their respective IR and NMR spectra and of thermal profiles.

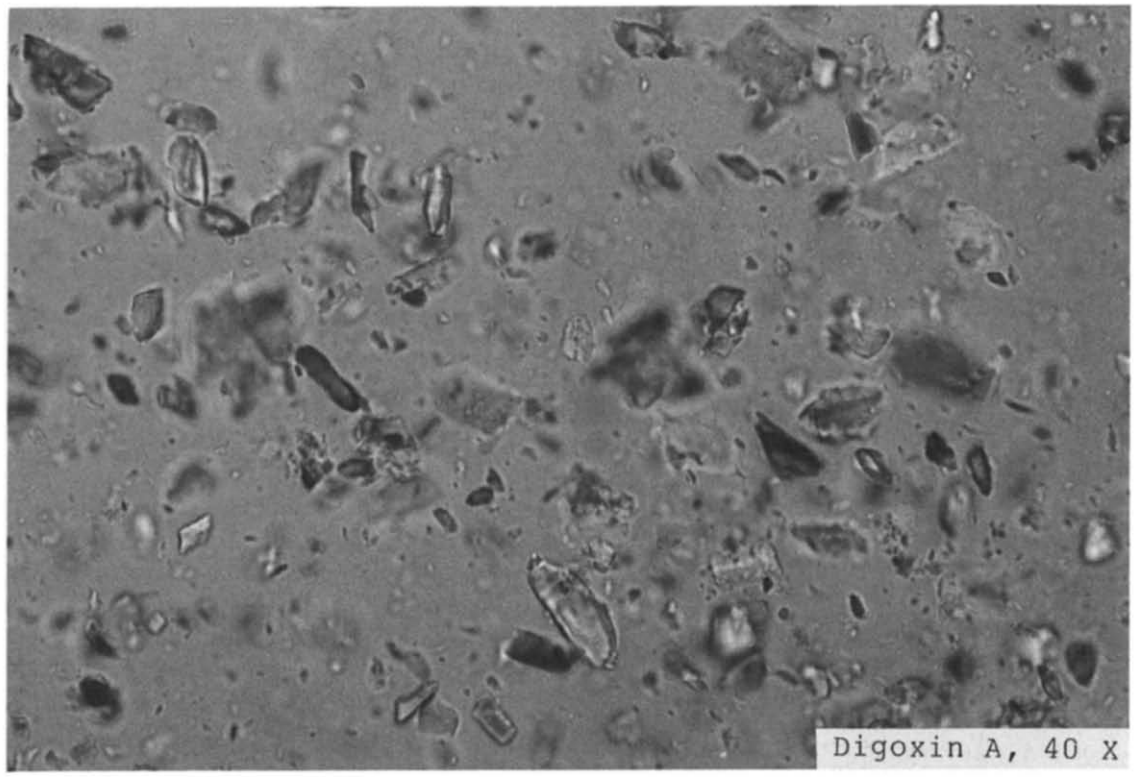
All these were perfectly comparable.

Microscopic analysis

Microscopic analysis of the 3 digoxin samples revealed that digoxin F and A were prevalently amorphous powders with similar granulometric distribution and particle size ranging from 12.5 $\times$ 12.5 to 80 $\times$ 30 μm. Digoxin B instead was a powder with a high percentage of prismatic crystals from 45 $\times$ 10 to 200 $\times$ 60 μm in size (see Fig. 1).

Solubility studies

The results of the solubility studies are presented in Table 4. Sample B showed a 15% lower solubility than samples A and F. This may be due to differences in particle size and in crystallinity (as observed in the microscopic analysis) that also influenced dissolution experiments. Several reports have in fact shown the increased dissolution rate of digoxin after grinding (Jounela et al., 1975; Florence et al., 1974).



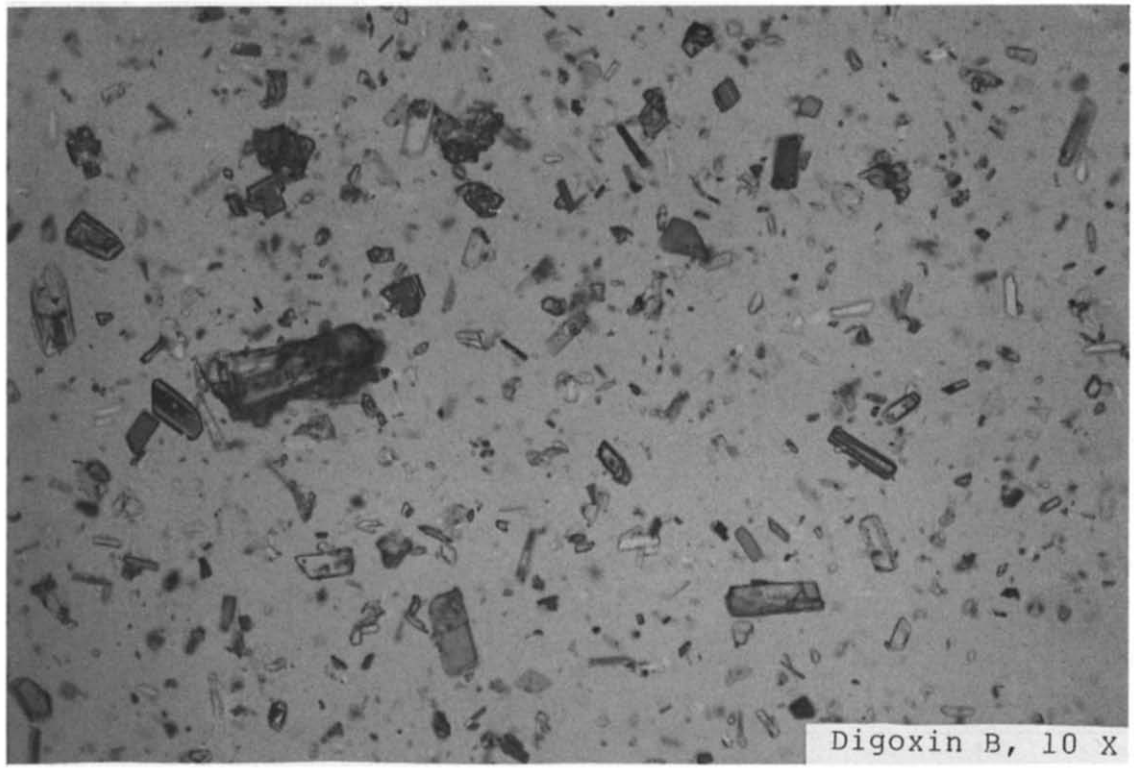


Fig. 1. Photomicrographs of digoxin samples A (40 ×) and B (10 ×).

TABLE 4

Solubility study results

Sample	Concentration (μg/ml $\pm$ S.D.) after 2 h	Concentration (μg/ml $\pm$ S.D.) after 4 h
A	29.64 $\pm$ 1.6	31.91 $\pm$ 1.8
B	23.54 $\pm$ 1.4	28.65 $\pm$ 1.6
C	28.55 $\pm$ 1.5	31.71 $\pm$ 1.7

Diffusion studies

The results of diffusion tests for the drug alone or with the various excipients are illustrated in Figs. 2, 3 and 4.

The experiments of drug diffusion in the presence of the excipients were always effected using sample F so as to eliminate possible differences due to active principle characteristics. Digoxin sample B showed a lower appearance rate in Phase II than samples A and F, reaching about a 16.5% lower concentration than those after 90 min (Fig. 2). This result is similar to that previously obtained in solubility studies.

Moreover, from these diffusion experiments the presence of the excipients appears to increase the appearance rate of active principle in Phase II, with the exception of PVP. This caused a lowering of appearance rate and the active principle concentration in Phase II after 90 min was 24% lower than for the active principle alone and about 38% lower than the active principle with the other

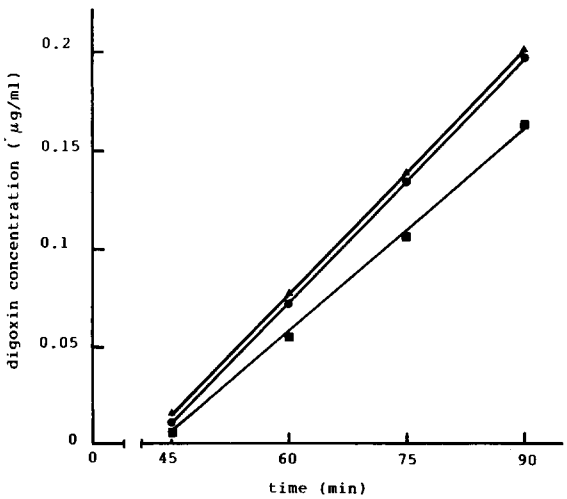


Fig. 2. Drug diffused concentrations vs time. Key: ●, digoxin F; ▲, digoxin A; ■, digoxin B.

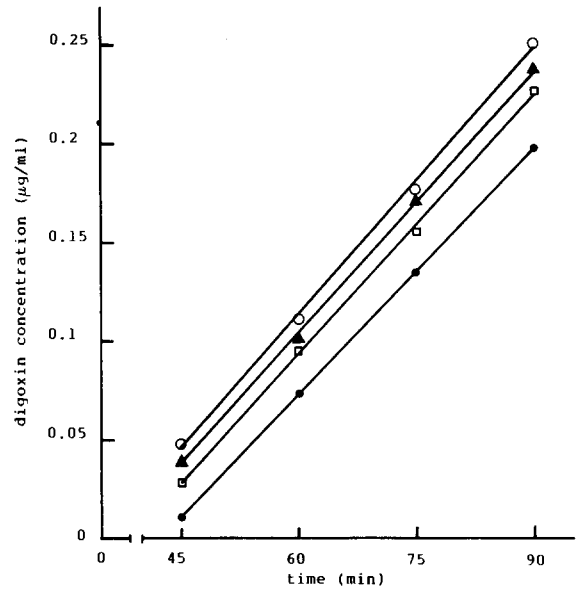


Fig. 3. Drug diffused concentrations vs time. Key: ●, digoxin F; ○, F + lactose; ▲, F + maize starch; □, F + magnesium stearate.

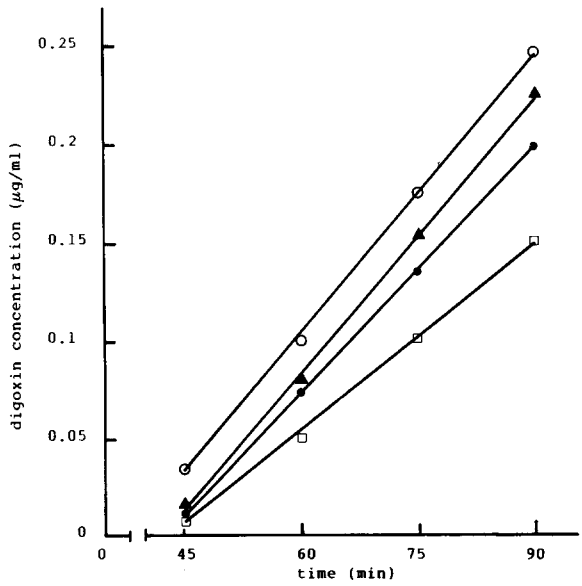


Fig. 4. Drug diffused concentrations vs time. Key: ●, digoxin F; ○, F + lactose; ▲, F + talc; □, F + PVP.

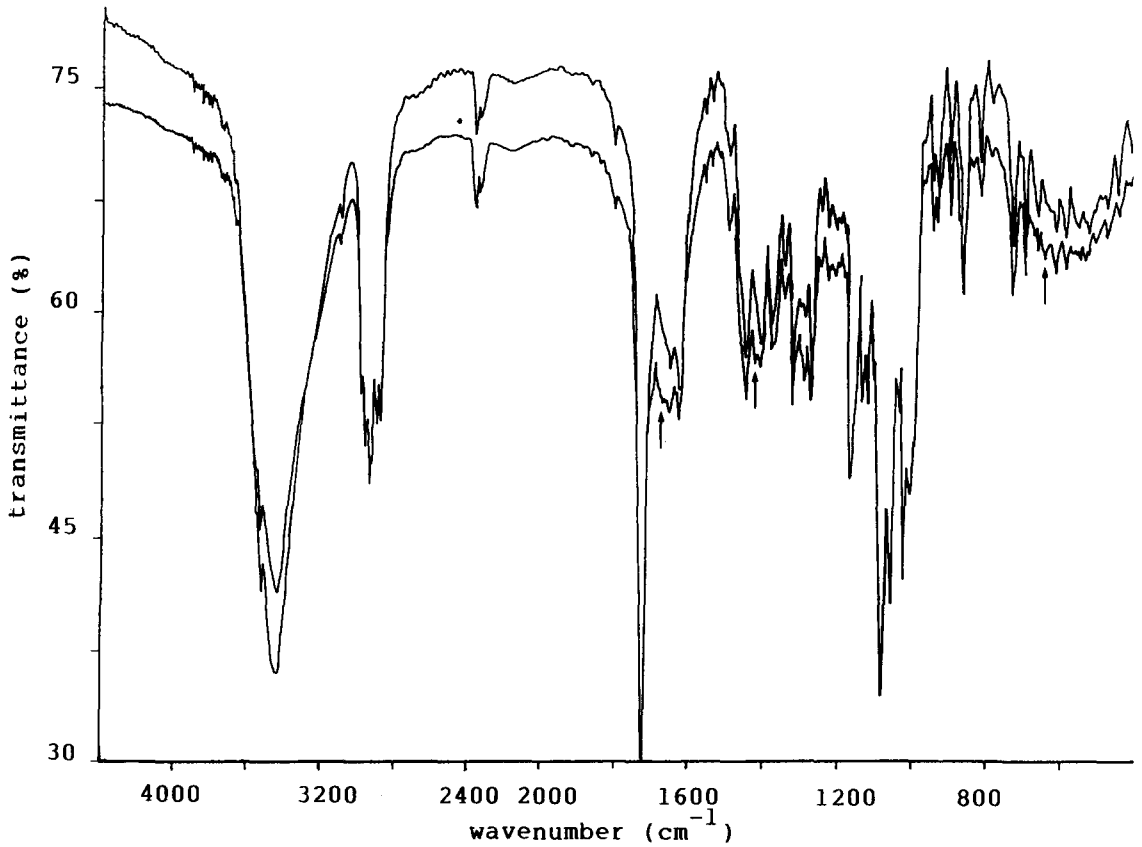


Fig. 5. FTIR spectra of mathematical sum of the pure digoxin and PVP spectra (top) and their 1/1 mix (bottom). Arrows indicate principal found differences.

excipients examined. This finding was in keeping with those of Ritschel et al. (1982) and Concheiro et al. (1986), who reported a deficient release of the active principle from digoxin tablets containing crosslinked PVP.

The effect of PVP might be attributed to the formation of a physicochemical combination with the drug, from which the drug is slowly released. The complexing tendency of PVP is well-known. PVP appears to form water-soluble complexes with a number of drugs, but also to hold certain drugs and release them slowly, retarding their pharmacological action (Higuchi and Kuramoto, 1954). In an attempt to show the effective existence of a digoxin–PVP interaction, the FTIR technique was used. The spectrum of 0.01/1 w/w digoxin–PVP mix (which is the ratio used in tablets) was of no use because strong polymer absorption completely covered the digoxin bands. The spectrum of 1/1 drug–PVP mix was therefore recorded.

The spectrum obtained by the mathematical addition of the pure component spectra was compared with the spectrum of their 1/1 mix. The observed differences (Fig. 5) could be attributed to a drug–polymer interaction that should become more evident as the PVP–digoxin ratio is increased as is in tablets.

Further investigations will be carried out to determine the type and grade of this interaction. In any case these first results seem to support our previous hypothesis that the retarding action of PVP on digoxin dissolution and diffusion rates can reasonably be attributed to its physicochemical combination with the drug.

Conclusions

The two digoxin tablet brands examined showed a marked difference in dissolution rates.

This result was found to be due either to differences in the chemical–physical characteristics of the respective active principles (e.g. particle size and % crystallinity) or to the influence of some excipients (e.g. interaction with PVP).

This study shows the need for more strictly-controlled investigations of all parameters influencing the pharmaceutical availability of digoxin from tablet dosage form. There clearly appears to be a need for a specification for digoxin pharmaceutical formulations which not only controls particle size and crystal properties of the drug but also verifies in a preformulation study the lack of influence of used excipients on dissolution and diffusion behaviour of the drug.

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