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OPTIMIZATION OF DIGOXIN TABLETS

Zeinab A. El Gholmy, L.K. El-Khordagui and

Y. Hammouda

Department of Pharmaceutics, Faculty of Pharmacy,

University of Alexandria, Alexandria, Egypt.

ABSTRACT

Four digoxin tablets have been formulated using potassium chloride and urea as water soluble directly compressible fillers. Simple blending and solvent deposition techniques were used for drug incorporation. The physical characteristics and content uniformity of the formulated tablets were comparable to those of two commercial brands of digoxin tablets. However, the dissolution rate of digoxin from tablets prepared by solvent deposition either on potassium chloride or urea (% dissolution after 1 h was 94 and 83 respectively) was higher than that from tablets made by simple blending (39 and 45% respectively)and superior to that of the two commercial brands (75.5% for both).

INTRODUCTION

The bioavailability of digoxin from tablets was reported to vary significantly among brands and lots of the same brand (1-4). This led the FDA in 1975 to announce the requirement for in vivo testing of digoxin tablets (5). Variation in digoxin bioavailability has been attributed mainly to differences in dissolution rate since excellent correlations were found to exist between the two parameters (6-8). Particle size of digoxin has also been revealed as an important determinant of digoxin bioavailability (9-11). More recently, several investigators (12-14) pointed out the importance of hydrolysis of digoxin in the acidic gastric juice, as a potential source of bioinequivalence among different digoxin formulations (12-14). This implies that immediate release tablets containing fast dissolving digoxin would provide greater assurance of more bioavailable and more bioequivalent formulations.

Several attempts have been made to enhance the dissolution rate of digoxin either via the formation of more soluble complexes (15,16) or by particle size reduction using solid dispersion(17,18),ball milling(11) and solvent deposition techniques (19-21). The objective of the present study was to prepare immediate release fast dissolving digoxin tablets using directly compressible

water soluble fillers. Solvent deposition and simple blending were used as drug incorporation techniques. The characteristics of the formulated tablets were compared to those of two commercial brands of digoxin tablets.

MATERIALS AND METHODS

Preparation of drug triturations for compression

Two formulations of digoxin tablets with either potassium chloride[1] or urea[2] as directly compressible fillers were prepared using the following techniques:

A. Simple blending or solid-solid mixing (S-S)

An amount of digoxin powder[3] sufficient to make two hundred 0.25 mg tablets was mixed with the appropriate amount of either potassium chloride or urea (particle size range 0.20-0.25 um) by the conventional geometric dilution method. The blending was carried out in a porcelain crucible using a flat knife. Maize starch was then added to potassium chloride and urea triturations as disintegrant in the ratio of 5 and 10% respectively. The final drug filler ratio was 1:400.

B. Solvent deposition or liquid-solid mixing (L-S)

A solution of digoxin in a mixture of equal volumes of methanol[4] and chloroform[5] was used to uniformly wet a 400-fold excess of either potassium chloride or urea (same particle size range as above) so as to provide

triturations containing 0.25 mg of digoxin per 100 mg. The solvents were evaporated at room temperature with continuous stirring. The triturations were passed through a 60-mesh screen (0.25 mm) to break up any agglomerates. Starch was added as previously mentioned. The final drug-filler ratio was 1:400.

Compaction - The four triturations prepared were compressed on an Erweka single-punch tablet machine using a flat-faced bevelled edge punches into 100 mg, 6 mm diameter tablets. Besides, two commercial brands of digoxin tablets were used for comparison:

Brand A; Lanoxin tablets 0.25 mg Wellcome, England, Batch No 0057, Feb. 1983, expiring Feb. 1988.

Brand B; Digoxin tablets 0.25 mg B.P. 80, The Alexandria Co. for Pharmaceuticals and Chemical Ind., Egypt.

Quality control tests

Hardness - Erweka hardness tester type TB 24 was used to evaluate the tablet hardness.

Disintegration test - This was carried out according to the B.P. 1980.

Uniformity of weight - Twenty tablets were randomly selected during the compression process and weighed individually.

Uniformity of content - Single tablet assays (22) were

performed on ten tablets of each of the four formulations under study, Brand A and Brand B. One tablet was placed in a 25-ml volumetric flask. 2.5 millilitres of distilled water was added and the flask was swirled for 2-3 min. Exactly 8.5 ml of methanol was added and the mixture was mechanically shaken for 15 min. The suspension was brought to volume with distilled water and thoroughly mixed. An aliquot of the mixture was filtered through a 0.2 um millipore filter. Samples of the filtrate were assayed using the fluorometric B.P. (23) and HPLC methods (22) described below.

Dissolution rate - The dissolution profiles of the four types of tablets under study were determined over 15-90 min and compared to those of the commercial brands using the U.S.P. rotating basket apparatus[6] at 37°C. The equivalent of 0.5 mg digoxin (2 tablets) was placed in each of the baskets rotating at 100 r.p.m. in 500 ml distilled water as the dissolution medium. Sink conditions were maintained throughout the dissolution test since concentration at 100% dissolution (0.1 mg/100) is much lower than the equilibrium solubility of digoxin at 37°C (3.47 mg/100 ml) (17). The samples, withdrawn and filtered automatically, were assayed according to the fluorometric B.P. (23) method. The data presented are the averagesof five determinations. The HPLC method adopted in the present investigation could

not be used in the dissolution study due to the large sample volume, to be injected on the column, imposed by the low drug concentration in the dissolution medium. This led to interference of some impurities, present in the dissolution medium, with the digoxin peak at 220 nm.

Assay procedures

A. Spectrofluorometric method - The procedure adopted was essentially that described in the B.P. 1980 for the determination of digoxin in the dissolution test of tablets. To 1 ml of the filtrate in a 10 ml volumetric flask was added 3 ml of ascorbic acid solution 0.1% w/v in methanol and 0.2 ml of hydrogen peroxide solution (0.009M) and the volume was completed with hydrochloric acid. All reagents were analytical reagent grade. The fluorescence of the solutions was measured after exactly 2 h at an excitation wave length of 360 nm and emission wave length of 470 nm using a Perkin-Elmer model 204 fluorescence spectrophotometer.

B. HPLC method - Digoxin content of the various tablets was determined by an HPLC method reported by Desta and McErlane (22). The mobile phase, consisting of a mixture of water-methanol-isopropanol-methylene chloride (47:40:9:4), was pumped through a column[8] (25 x 0.46 cm) at a flow rate of 1 ml/min. The eluent was monitored at 220 nm. Under these conditions, digoxin retention time was 6 min. Peak heights were directly proportional to

Table 1 - Disintegration time, hardness and uniformity of weight.

Formulation	Disintegration time, min.	Hardness, Kg	Tablet weight, mg	
			mean	C.V %
KCl (S-S)	1	6.0	101.9	3.7
KCl (L-S)	1	5.0	106.3	2.7
Urea (S-S)	2	4.5	99.9	1.4
Urea (L-S)	1	4.0	100.9	2.5
Brand A	2	4.9	114.9	0.8
Brand B	3	3.5	101.9	4.6

the amount of digoxin injected. Peak heights were reproducible and no internal standard was used.

RESULTS AND DISCUSSION

Table 1 shows the data related to the physical characteristics of the four types of tablets under study and the two commercial brands of digoxin tablets. All tablets complied with the B.P. test for disintegration. Hardness and uniformity of weight of the formulated tablets proved satisfactory and comparable to those of the commercial brands.

This implies that the binding capacity and good flow properties of the directly compressible potassium chloride (24) and urea (25) were not adversely affected by

Table 2 - Uniformity of content

Formulation	HPLC mean content ug	C.V. %	B.P. Method mean content ug	C.V.%
KCl (S-S)	250.1	(6.5)	261.6	(2.8)
KCl (L-S)	257.0	(5.4)	261.4	(5.5)
Urea (S-S)	252.4	(8.0)	260.5	(2.8)
Urea (L-S)	244.2	(1.4)	243.6	(4.0)
Brand A	258.4	(4.2)	266.5	(2.2)
Brand B	253.0	(6.4)	261.7	(6.4)

the addition of digoxin since the drug filler ratio was considerably small (1:400).

The uniformity of drug content was assessed by replicate determinations of digoxin content of ten tablets using the fluorometric B.P. method (23) and HPLC (22). The application of the two procedures provided the data in table 2. The respective mean assay values compared quite favorably and fell within 80-120% of the mean (Fig. 1), thus complying with the B.P. standards. However, the HPLC method proved more rapid and sufficiently senstive compared to the lengthy procedure for content uniformity of digoxin tablets outlined in the B.P. monograph. The HPLC method has been used successfully for the quantitation of digoxin in tablets,elixir

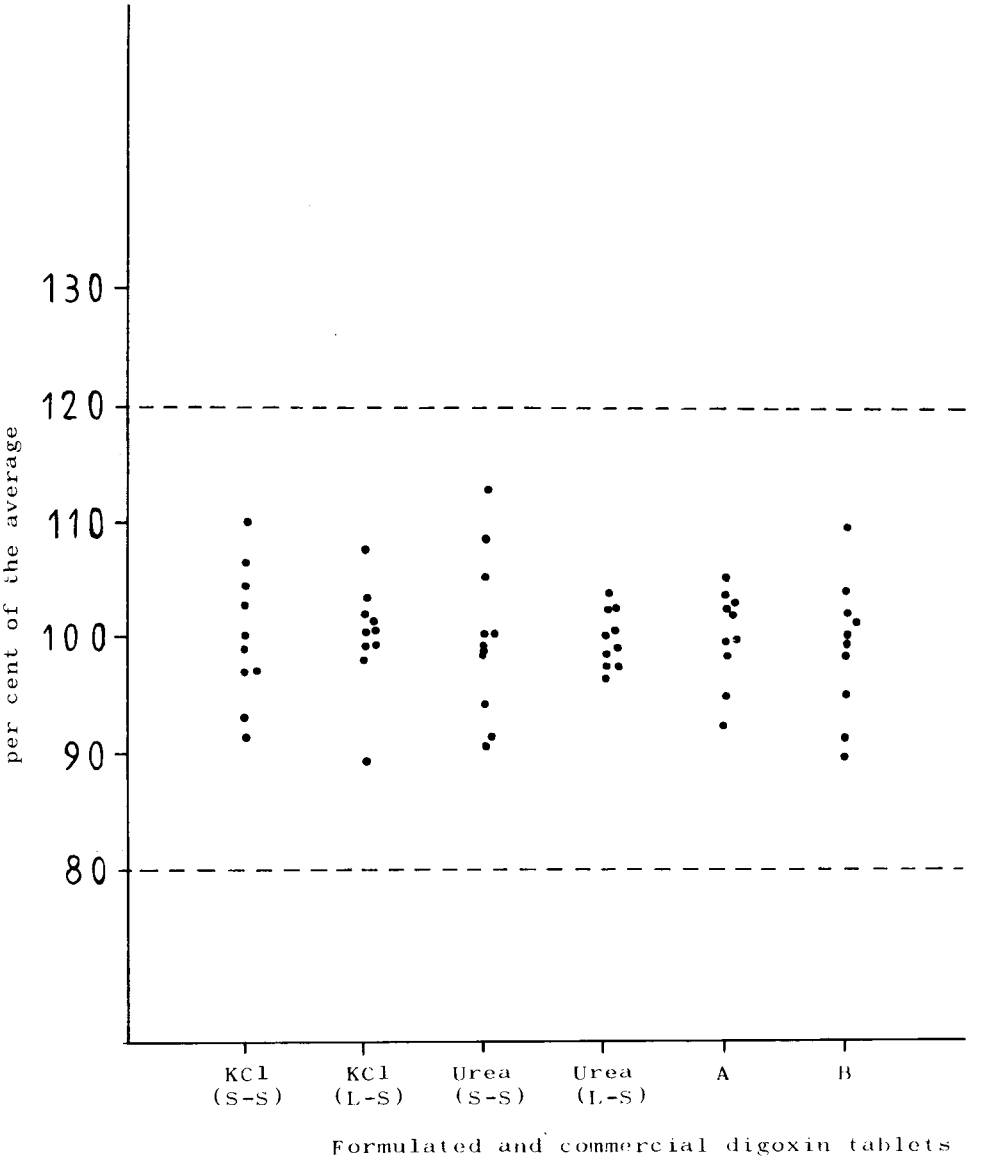

Figure 1: Content uniformity of 0.25 mg digoxin tablets. The interrupted lines represent B.P. limits.

and injections (22). Variation in drug content, in formulations with such a small amount of active ingredients (0.25%), would be expected no matter how satisfactory the trituration and tabletting processes. Nevertheless, the mean assay values, coefficients of variation (Table 2) and the scatter of percent digoxin content around the average (Fig. 1) tend to indicate uniform distribution of digoxin in the filler, the absence of segregation during compression and acceptable variation in individual tablet weights, as previously demonstrated in table 1. Besides, results of single tablet assays shown in table 2 proved that simple blending and solvent deposition techniques were almost equally efficient in providing uniform drug distribution. This is in agreement with previous findings (11,26) for tablets of small dose drugs made of triturations with these two techniques. A combination of adsorption, absorption and entrapment processes of the drug in the interstices of the filler particles (21,27) account for the efficiency of drug distribution in solvent deposition systems. On the other hand, a high degree of homogeneity could be obtained in simple blends as a result of attraction forces between the drug and filler which also minimizes segregation during compression.

The dissolution rate profiles of the four types of tablets under study as well as brands A and B are

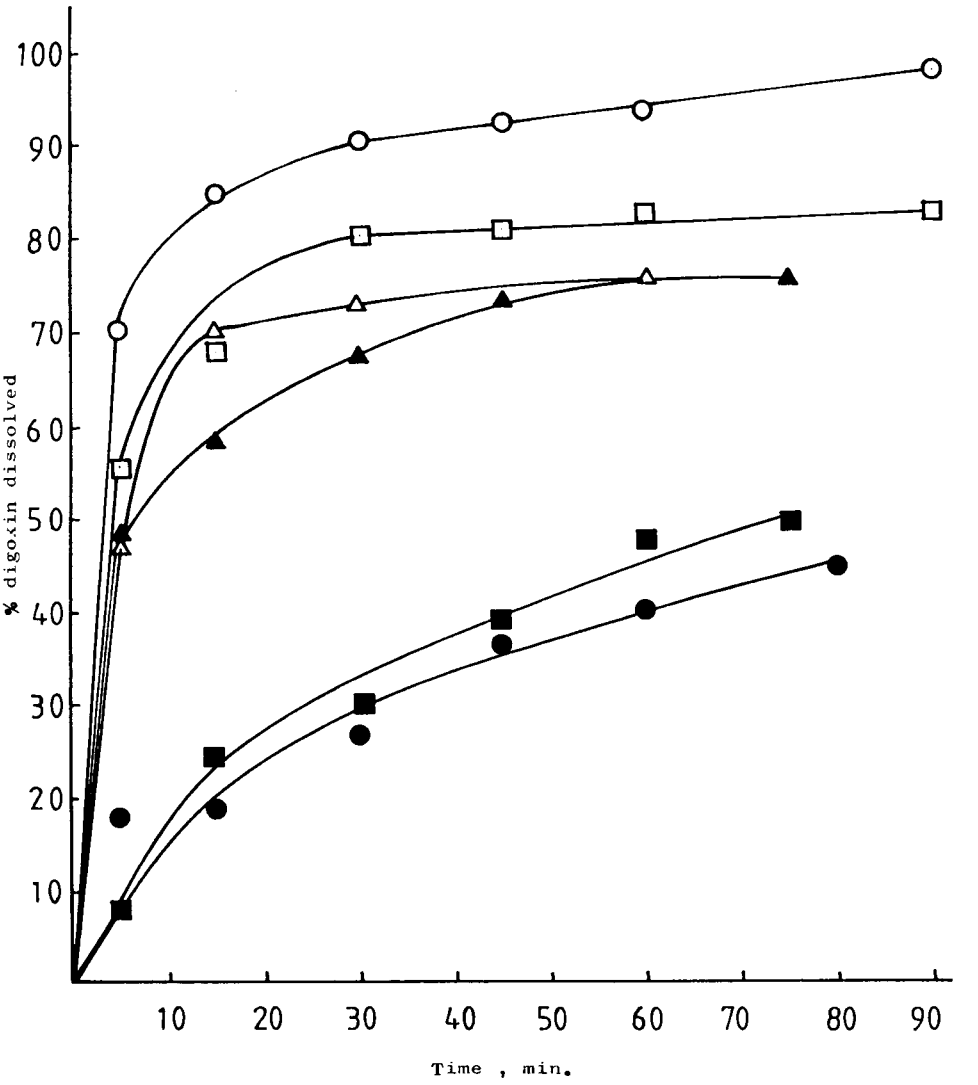

Figure 2: Dissolution rate profiles of formulated and commercial digoxin tablets (○) KCl (L-S), (□) Urea (L-S), (△) brand B, (▲) brand A (■) urea (S-S), (●) KCl (S-S).

Table 3 - Per cent dissolution after 1 h of formulated and commercial digoxin tablets.

Formulation	% dissolution after 1h
KCl (S-S)	39.0
KCl (L-S)	94.0
Urea (S-S)	45.5
Urea (L-S)	83.0
Brand A	75.5
Brand B	75.5

shown in Fig. 2. Although simple blending and solvent deposition techniques proved to be almost efficient in assuring content uniformity (Table 2), yet, dissolution of digoxin was much faster from tabletsmade using the solvent deposition technique (Table 3).

These results, though higher, are consistent with those reported for digoxin triturations with lactose, silicone dioxide and other tablet excipients (11,19,21). Tablets of digoxin,solvent deposited on potassium chloride and urea,also exhibited superior dissolution rate profiles compared to the commercial brands A & B. However, both brands presumably complied with the B.P. dissolution limit (not less than 75% dissolution after 1 h at 120 r.p.m).

Obivously, since the same lot of digoxin was used in all formulations, the great difference in the dissolution rates of the formulated tablets must be due to the method used in drug dispersion (S-S or L-S). Coupled with low drug to filler ratio, solvent deposited drugs are expected to exhibit fast dissolution as the drug undergoes molecular micronization when it is dispersed in minuscular form on a large surface area material (28). Further, digoxin appears to be among other drugs, whose particle size and crystal properties are primary determinants of dissolution behaviour (29,30) and bioavailability (9,10). This led researchers to call for the introduction of standards to ensure close control of both the particle size and crystal properties of digoxin (29,30). Such properties vary to a great extent with the type of filler, efficiency of solvent evaporation, drug-filler ratio and the method of achieving particle size reduction (19,20,28).

The use of potassium chloride and urea as carriers for the surface deposition of digoxin offers several advantages over other carriers both technical and therapeutic. Being highly soluble in water, potassium chloride and urea would allow for the prompt release of digoxin in the medium in contrast to insoluble carriers which by virtue of their adsorptive characteristics will exert certain adverse effects on the release of digoxin.

Moreover, potassium chloride would serve to compensate the depletion of potassium ion usually accompanying the use of diuretics with digoxin in case of congestive heart failure. Besides, these two fillers are expected to be compatible with body fluids since they are normal constituents of the human body.

In summary, it has been demonstrated that solvent deposition of digoxin on either potassium chloride or urea as directly compressible fillers resulted in tablets with very good content uniformity and exhibiting relatively fast dissolution rates. Apart from their high compressibility, good flow, self lubricating properties and high aqueous solubility, the use of such fillers would greatly simplify the manufacture of digoxin tablets.

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FOOTNOTES

1. Potassium chloride pure, Chemopol, Czechoslovakia.
2. Urea, pure, Veb Laborchemie, Apolda, G.D.R.
3. Digoxin B.P.Koch-light Laboratories Ltd, England.
4. Methanol, analar, BDH Chemical Ltd, Poole, England.
5. Chloroform, analar, Prolabo, Rhône-Poulenc, France.

6. 6-station dissolution tester with a sampling device, Dissoette,Model QC 72 R24-6M,Hanson Research,CA,U.S.A.
7. Perkin-Elmer Series 3B Chromatography system with an LC-75 detector and autocontrol.
8. Perkin-Elmer RP-8/10 column.

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