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Analysis of Factors affecting Dissolution of Digoxin from Tablets[1)]

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Factors affecting dissolution of digoxin from the tablets were investigated on the basis of the measurement on physical characteristics and the amount of digoxin released from 10 lots of tablets prepared by different procedures and formulations. While the hardness, friability and basket disintegration time (by U. S. P. dissolution apparatus) were influenced by the content of magnesium stearate, the disintegration time (by J. P. disintegration test method) was neither affected by the content of magnesium stearate nor the preparative procedure. Concerning the dissolution test by the U. S. P. dissolution apparatus, it was found that the dissolution rate had a tendency to increase with an increase in the rotation speed of basket. The dissolution of the tablets prepared by the powder dilution method was influenced significantly by the difference in mean particle size of digoxin powders, while the release of digoxin from the tablets produced by solvent deposition method showed a fast dissolution profile compared with the case by powder dilution method without depending on the difference in batch. Therefore, it was found that one of the predominant factors affecting the release of digoxin from digoxin tablets was either the formulation or the preparative procedure. Additionally, it was proposed that the dissolution test should be necessary for a quality test of digoxin tablets because the present J. P. disintegration test alone could not guarantee the quality of the tablets.

Keywords——tablets; digoxin; dissolution; linear regression analysis; powder dilution method; solvent deposition method; J. P. disintegration test; U. S. P. dissolution test; magnesium stearate content

It is well known that the blood level of digoxin is much influenced by differences in brand and in lot of digoxin tablets when administered orally.[3–5)] In this connection, it has been reported that the bioavailability of digoxin in oral dosage form is closely related to its dissolution from the preparation, and the therapeutic effectiveness may be presumed to some extent on the basis of *in vitro* dissolution data.[6,7)] Dissolution of digoxin depends on the physical property of powdered material of digoxin itself, particularly on the particle size of the powder.[8)] Additionally, the crystal structure of digoxin powder particle seems important, which may be changed by grounding,[9)] resulting in a remarkable enhancement of the dissolution rate.[10)]

Recently, it has been attempted to determine the best formula by analyzing statistically the factors affecting physical properties of the preparation.[11,12)] This kind of approach seems

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significant also for producing qualified preparations of digoxin. In the present study, therefore, an investigation was made into the correlation between the physical characteristics and the dissolution property of digoxin tablets under different preparative procedures.

Experimental

Materials——Two different lots of digoxin (lot No. 411449, 416778) produced by Boehringer Mannheim were employed in this study. Lactose, corn starch and magnesium stearate used were of J.P. IX grade. The other reagents used for quantitative analysis were of reagent grade.

Preparative Procedures for Digoxin Tablets——a) Powder Dilution Method: The formula of digoxin tablets was shown in Table I. Digoxin was mixed with lactose to make 10% and then diluted to 1%. To this mixture, the rest of lactose and corn starch were added, and granulated with addition of 10% corn starch paste following a conventional granulation method. The granules were blended with corn starch and magnesium stearate, finally compressed to tablets of 7 mm diameter and 120 mg weight by a Kimura-KM2 single punch tablet machine.

Table I. Formula of Digoxin Tablets

		Lot				
		A, F	B, G	C, H	D, I	E, J
Digoxin	(mg)	0.25	0.25	0.25	0.25	0.25
Lactose	(mg)	78.40	78.40	78.40	78.40	78.40
Corn starch	(mg)	41.23	40.75	40.15	37.75	35.35
Magnesium stearate	(mg)	0.12	0.60	1.20	3.60	6.00

b) Solvent Deposition Method: The formula was the same as above. Digoxin was dissolved to make 2% in equivolume mixture of methyl alcohol and chloroform. This solution was poured into the mixture of lactose and corn starch, mixed thoroughly and granulated with addition of 10% corn starch paste in the same way as mentioned above. The tablets were made of the granules also in the same way as mentioned above.

Determination of Mean Weight——Twenty tablets were used.

J.P. Disintegration Time and Basket Disintegration Time——J.P. disintegration time was determined by the testing method described in J.P. IX. Additionally, the basket disintegration time, which is defined in this study as the time when the tablet disintegrates and passes through the net of the basket of the U.S.P. XIX dissolution apparatus, was also determined.

Thickness, Hardness and Friability——Thickness was measured using a dial gauge, and the hardness was determined using a Heberlein hardness tester. The tablet friability was obtained from the decrease in weight of 60 tablets after 100 rotations using a Kayagaki Irikakogyo friabilator at 25 rpm.

Determination of the Content of Digoxin——The content of digoxin of each tablet was determined using a Hitachi 204 fluorometer.[13]

Dissolution Test——The procedure and apparatus described for digoxin tablets in U.S.P. XIX were applied. Under the rotation speeds of basket of 25, 50, 100 or 150 rpm at 37°, 10 ml of samples were withdrawn at appropriate intervals and immediately the equivolume of the test medium was supplied.

Measurement of Particle Size of Digoxin Powder——The distribution of particle size of digoxin powder was determined by a Seishin SKN-500 phototransmittance particle size determination apparatus, using benzene as the dispersing solvent.

Powder X-ray Diffractometry of Digoxin——Two kind of samples were prepared. One was physical mixture of equal weight of digoxin powders and corn starch. And the other sample was prepared as follows: digoxin was dissolved in equivolume mixture of methyl alcohol and chloroform, and to this solution corn starch was added and solvent was evaporated under mixing. Powder X-ray diffraction patterns were obtained by a Rigaku Denki Geigerflex Model D-2 diffractometer by Ni-filtered Cu-Kα radition.

Results and Discussion

The content of magnesium stearate had no relation to the thickness, weight, content of digoxin and J. P. disintegration time of the tablets made by both preparative procedures,

13) U.S.P. XIX, Mack Publishing Co., Easton, Pa. 18042, 1975, p. 149.

as shown in Table II and III. On the other hand, the hardness of tablets decreased with an increase in the content of magnesium stearate. The friability increased with an increase in the content of magnesium stearate, especially remarkably in the range of 1 to 3%. J. P. disintegration time was little affected by the content of magnesium stearate, while the basket disintegration time, as shown in Table IV, was much affected. As was shown in lots A, B, C, D and E, the basket disintegration time was affected extensively by both the basket rotation speed and the magnesium stearate content, and the critical rotation speed was found to be 50 or 100 rpm for all the contents of magnesium stearate. The results obtained by a linear

Table II. Physical Characteristics of Digoxin Tablets Produced by Powder Dilution Method

		Lot				
		A	B	C	D	E
Content of magnesium stearate	(%)	0.1	0.5	1.0	3.0	5.0
Thickness[a]	(mm)	2.44	2.38	2.43	2.40	2.43
Hardness[a]	(kg)	4.7	4.6	4.4	2.8	2.5
Friability	(%)	0.255	0.290	0.218	0.448	0.461
Weight	(mg)	121.1	120.1	119.9	119.3	119.0
Content of digoxin regarding the formula[b]	(%)	107.4	101.9	109.5	104.2	103.5
J. P. Disintegration time	(sec)	49.8	56.4	51.0	51.0	48.6

a) Mean of twenty determinations.
b) Mean of ten determinations.

Table III. Physical Characteristics of Digoxin Tablets Produced by Solvent Deposition Method

		Lot				
		F	G	H	I	J
Content of magnesium stearate	(%)	0.1	0.5	1.0	3.0	5.0
Thickness[a]	(mm)	2.40	2.42	2.40	2.41	2.40
Hardness[a]	(kg)	4.6	3.6	4.5	2.6	2.3
Friability	(%)	0.298	0.301	0.288	0.449	0.476
Weight	(mg)	120.0	120.0	121.1	119.0	120.2
Content of digoxin regarding the formula[b]	(%)	100.0	99.2	100.0	99.8	100.4
J. P. Disintegration time	(sec)	49.2	37.2	48.0	52.8	55.2

a) Mean of twenty determinations.
b) Mean of ten determinations.

Table IV. Effect of Rotation Speed on Digoxin Tablets Disintegration (min, U. S. P. Dissolution Apparatus at 37°)

Basket rotation speed	Lot				
	A	B	C	D	E
25 rpm	8.96	8.39	21.00	25.00	52.17
50 rpm	1.94	3.16	5.16	5.56	25.24
100 rpm	0.94	1.04	1.12	2.06	6.02
150 rpm	0.66	0.97	0.52	1.17	3.12

regression method utilizing IBM 370 program package BMD are shown in Table V and VI. In both the powder dilution method and solvent deposition method, the hardness and friability were correlated well with the magnesium stearate content, while the weight, thickness, content

Table V. Analysis of Effect of Magnesium Stearate Content on Physicochemical Properties of Digoxin Tablets by Linear Regression Method

Dependent variable	Method	n	r
Weight	I+II	10	−0.55
	I	5	−0.88
	II	5	−0.12
Thickness	I+II	10	0.0087
	I	5	0.099
	II	5	−0.240
Hardness	I+II	10	−0.919
	I	5	−0.966
	II	5	−0.892
J. P. Disintegration time	I+II	10	0.302
	I	5	−0.525
	II	5	0.713
Friability	I+II	8	0.944
	I	4	0.949
	II	4	0.940
Drug content	I+II	10	−0.121
	I	5	−0.379
	II	5	0.599
$t_{1/2}$	I+II	10	0.0912
	I	5	0.221
	II	5	0.842
Amount dissolved	I+II	10	0.029
	I	5	0.133
	II	5	0.034

I: powder dilution method.
II: solvent deposition method.
n: number of variables.
r: correlation coefficient.

Table VI. Analysis of Effect of Magnesium Stearate Content on Basket Disintegration Time (U. S. P. Dissolution Apparatus) of Digoxin Tablets by Linear Regression Method

Rotation speed	n	r
25 rpm	5	0.961
50 rpm	5	0.898
100 rpm	5	0.933
150 rpm	5	0.899

n : number of variables.
r : correlation coefficient.

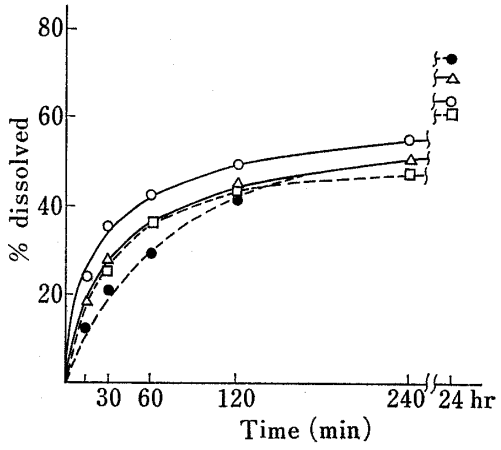

Fig. 1. Effect of Rotation Speed on Dissolution of Digoxin Tablets (lot B, magnesium stearate content 0.5%)

—●—: 25 rpm.
—△—: 50 rpm.
—□—: 100 rpm.
—○—: 150 rpm.

of digoxin, amount dissolved and J. P. disintegration time had no relation to the content of magnesium stearate. The fifty percent dissolution time, $t_{1/2}$, was correlated with the content of magnesium stearate in the case of solvent deposition method, while not so well in the case of powder dilution method. The basket disintegration time was correlated well with the magnesium stearate content at all the rotation speeds, while J. P. disintegration time was not. Therefore, it was suggested that J. P. disintegration test might be an unsatisfactory testing method to guarantee the release of a drug from pharmaceutical solid preparations because of the failure to reflect such a variation as coming from a difference in formulation. Therefore, it may be said that a dissolution test is more suitable for the quality control of tablets than the conventional disintegration test.

In Fig. 1 and 2 the effect of the basket rotation speed on the dissolution of digoxin tablets is shown both for comparatively lower concentration and higher concentration of magnesium stearate. At the higher concentration of the lubricant the dissolution of digoxin was much retarded with a decrease in the rotation speed. However, under the higher basket rotation speed, even under the 5% of magnesium stearate content, effect of the content of the lubricant on the dissolution of digoxin was little as shown in Fig. 3. These results may indicate

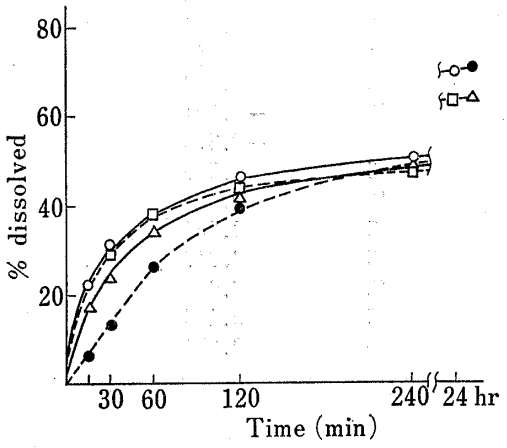

Fig. 2. Effect of Rotation Speed on Dissolution of Digoxin Tablets (lot E, magnesium stearate content 5.0%)

—●—: 25 rpm.
—△—: 50 rpm.
—□—: 100 rpm.
—○—: 150 rpm.

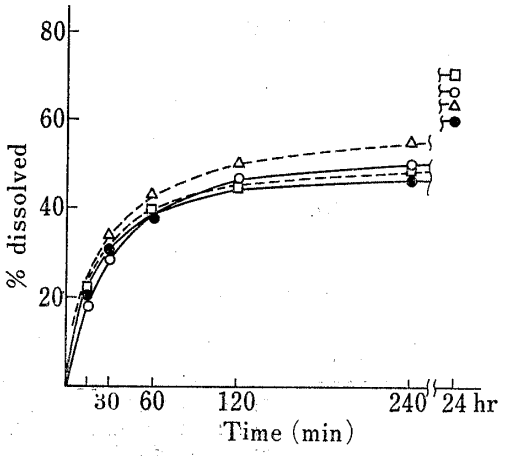

Fig. 3. Effect of Content of Lubricant on Dissolution of Digoxin Tablets (U. S. P. dissolution apparatus, 150 rpm, at 37°)

—●—: lot A (magnesium stearate content 0.1%).
—△—: lot B (magnesium stearate content 0.5%).
—○—: lot D (magnesium stearate content 3.0%).
—□—: lot E (magnesium stearate content 5.0%).

Table VII. Correlation Coefficient of Linear Regression Analysis of Dissolution of Digoxin

	Rotation speed	Basket disintegration time	Amount dissolved at 30 min
Rotation speed	I 1.000 II 1.000		
Basket disintegration time	I −0.833 II −0.904	I 1.000 II 1.000	
Amount dissolved at 30 min	I 0.612 II 0.929	I −0.653 II −0.981	I 1.000 II 1.000

I: magnesium stearate content 0.5% (lot B).
II: magnesium stearate content 5.0% (lot E).

that the dissolution of digoxin from tablets is much influenced not only by the formulation but by the dissolution conditions, therefore suitable optimal experimental conditions to reveal the dissolution property should be required for a quality test of digoxin tablets. For further investigation of interrelation of these factors, the amount dissolved at 30 min, rotation speed of the basket, and basket disintegration time of lot B and E were analyzed by a linear regression method and correlation coefficients were calculated as shown in Table VII. It was confirmed for both lot B and E that there was a correlation between the rotation speed of basket and the basket disintegration time while not between the amount dissolved at 30 min and the rotation speed of the basket or basket disintegration time for the tablets of lower lubricant content (lot B). This result may support that the penetration of the test solution into the tablets is increasingly disturbed with an increase in the concentration of magnesium stearate resulting in a retardation of the tablet disintegration.[14,15] Based on the above results, it was suggested that the disintegration process might perform the rate-determining step of the dissolution of digoxin from the tablets of lot E in the basket of U. S. P. dissolution apparatus, while the dissolution process of digoxin crystal itself might do for lot B. In this connection, if the dissolution test of digoxin tablets were carried out only by the J. P. disintegration apparatus, a difference in dissolution property would not be observed because both lot B and E had almost the same disintegration time, as shown in Table II. Therefore, the dissolution test employing the U. S. P. dissolution apparatus was considered to reflect better the differences in dissolution property among digoxin tablets which come from the differences in formulation factor.

As shown in Fig. 4, the dissolution was influenced directly by the particle size of digoxin crystals in the case of the powder dilution method. The amount of digoxin released from the tablets of large particle size of digoxin (50.0 μ) was only 50% even after 24 hr, while the tablets of smaller particle size of digoxin (25.5 μ) released 80% of the content in the same period. These results indicated that a different particle size of digoxin brought a different dissolution profile. It has been reported that such the difference in dissolution profile may

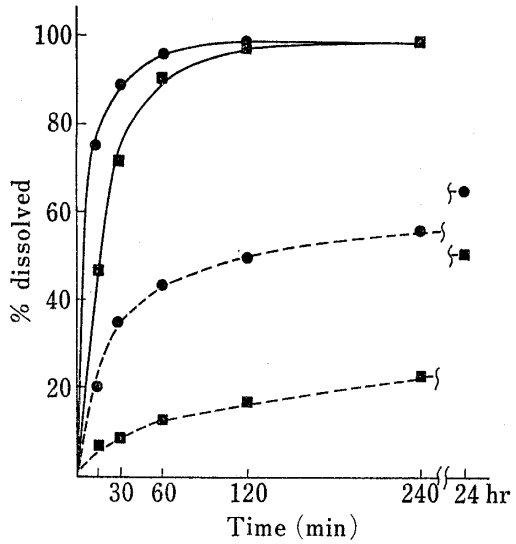

Fig. 4. Effect of Preparative Procedure on Dissolution of Digoxin Tablets

——: solvent deposition method.
– – –: powder dilution method.
● : particle size 25.5 μ.
■ : particle size 50.0 μ.

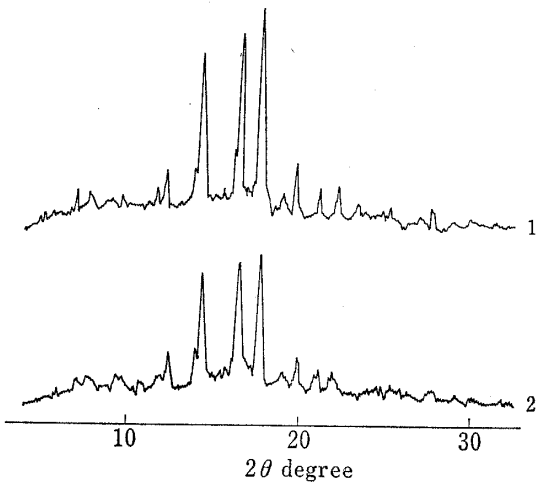

Fig. 5. Powder X-ray Diffraction Patterns of Digoxin-diluent (corn starch) Mixture (1 : 1)

1: physical mixture.
2: solvent deposition mixture.

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result in variation of the bioavailability of digoxin tablets.[16] It was found that tablets prepared by solvent deposition method showed a good release of digoxin compared with the powder dilution method and the dissolution profiles of the respective batches became almost identical. Considering the suggestion of Florence, *et al.*, that a freely soluble amorphous layer may exist on the surface of ground digoxin crystals,[10] the above result might be due to an amorphous property of the particles of digoxin produced by the solvent deposition method. However, as shown by the powder X-ray diffraction patterns of digoxin in Fig. 5, only a little decrease in intensity was observed for the sample prepared by the solvent deposition method with the equivolume mixture of methyl alcohol and chloroform, and no significant difference in crystallinity of digoxin was found. This suggested that the surface area effective for the dissolution increased but no crystal conversion took place by the solvent deposition method. From the facts described above, it was suggested that the solvent deposition method afforded a good dissolution property for the digoxin tablets compared with the powder dilution method. In this connection, Ampolsuk, *et al.* reported that the solvent deposited trituration method was not effective to enhance the dissolution rate of the digoxin-lactose blends, which was some different from the digoxin-lactose-starch blends in this study, giving such an explanation that a binding of the drug with the diluents took place in a molecular state.[17] Therefore, it was concluded that the preparative procedure of digoxin tablets was one of the most important factors affecting the dissolution property of the preparations.

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