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STUDIES OF FUROSEMIDE TABLETS II
INFLUENCE OF WET-MIXING TIME, BINDER VOLUME AND BATCH VARIATION ON DISSOLUTION RATE

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ABSTRACT

The effect of wet-mixing time and the volume of granulating solution on furosemide tablet quality and in vitro dissolution rate were studied. The wet-mixing time has shown an effect on the in vitro dissolution of furosemide tablet formulation. Small variations in wet-mixing time can be important and effective on the tablet dissolution. A decrease in the dissolution rate was observed when the time of wet-mixing increased.

Changes in the volume of granulating solution, when the amount of gelatin was constant, did not alter the tablet dissolution.

Moreover, the effect of batch variation on tablet formulation was also investigated. There was no significant differences in the dissolution of the different batch of furosemide bulk powder.

INTRODUCTION

It is known that some of the generic furosemide tablets might not be therapeutically interchangable (1). Recent reports have suggested that drug availability and dissolution of these commer - cial preparations are variable, especially when the products of

different manufacturers are compared (2,3,4) and a good correlation between in vitro dissolution and in vivo parameters for furosemide tablets has been established (4).

Our previous work indicated that some of the commercial furosemide tablets dissolved slowly and tablet manufacturing methods affected furosemide dissolution. The best results were obtained with the wet-granulation process (5). Therefore a study of the wet-mixing time, volume of granulating solution and batch variation on furosemide tablet properties were undertaken in this part of study.

EXPERIMENTAL

Materials

Furosemide (Hoechst AG, Frankfurt), anhydrous lactose (Sheffield Chem. New Jersey 07071), magnesium stearate (E.Merck, Darmstadt). Starch, gelatin and talc were pharmaceutical grade. pH 4.6 acetate buffer (6) was used.

Apparatus

Tablet machine (Korsch EK-0, Berlin), hardness tester (Monsanto), spectrophotometer (Varian, Techtron Series 634).

Methods

The standard tablet formulation was: Furosemide 40 mg, lactose 100 mg, corn starch 50 mg, gelatin solution (5 % w/v) 30 % v/w, talc 8.1 mg, magnesium stearate 5.4 mg per tablet.

Effect of Wet- Mixing Time

All the ingredients were dried at 60^{o}/2 hrs and sieved. Furosemide in 100 - mesh size was used. Powders were mixed in a plastic bag for 5 min and granulated under standard conditions using 5, 10 and 30 min wet-mixing time. The mass was discharged through an oscillating granulator fitted with a 20 mesh. The granules were dried for 1 hr at 60^{o} and the lubricant was incorporated by mixing in a plastic bag before using a 25 mesh screen. The tablets were compressed on a single-punch tablet machine using 8.1 mm flat-faced punches.

Effect of Variations in Binder Volume

Tablets were prepared by the addition of 20 %, 25 % and 30 % v/w of hot gelatin solution (5 %). Powders were granulated under standard conditions using 5, 10 and 30 min wet-mixing time.

Effect of Batch Variation

40 mg of furosemid obtained from 2 different manufacturers was directly filled into size 0 gelatin capsules. Furosemide tablets were also prepared from 2 different batches designed as I and II.

Tablet properties;

For each formulation tablet properties such as weight variation, hardness, friability, disintegration time, content uniformity and dissolution rate were determined as previously described in our report (5).

RESULTS and DISCUSSION

Influence of Wet-Mixing Time

As indicated in Table I tablet formulations prepared in various wet- mixing times showed good tablet properties such as hardness, friability, disintegration time, weight variation and content uniformity. But an optimum time is needed for mixing the moistened mass, and prolongation of this period changes the consistency of the mass which looks like quite a thick suspension. While the amount of granulating solution is constant, the difference in moistened mass consistency is directly propotianal to the wet-mixing time. The prolongation of wet-mixing time, during the granulation process, had a consolidation effect on bulk powder.

When a constant compression force (A) was applied to the granules, prepared as mentionned above, an increase in tablet hardness related to the wet-mixing time was observed (Table I, Fig.1)

There was apoor correlation between wet-mixing time and tablet hardness ($r=0.488$) but no correlation was observed between disintegration time and dissolution rate ($r=0.715$). When tablets

TABLE I

Effect of Wet-Mixing Time on the Properties of Furosemide Tablets Compressed under the same Pressure

Mixing Time (min)	Hardness (kg,cv)	Disintegration (s)	Friability (%)	Weight (g,cv)	Drug Content % claimed	Dissolution Parameters		
						t_{50} (min)	A_{30} (%)	k (min^{-1})
5	4.65 (5.73)	200	0.23	0.2041 (2.19)	97.50	5.30	89.74	0.1307
10	5.85 (5.48)	220	0.23	0.2038 (2.37)	99.37	11.00	71.25	0.0630
30	8.20 (7.93)	200	0.15	0.2204 (1.96)	103.75	9.00	77.71	0.0770

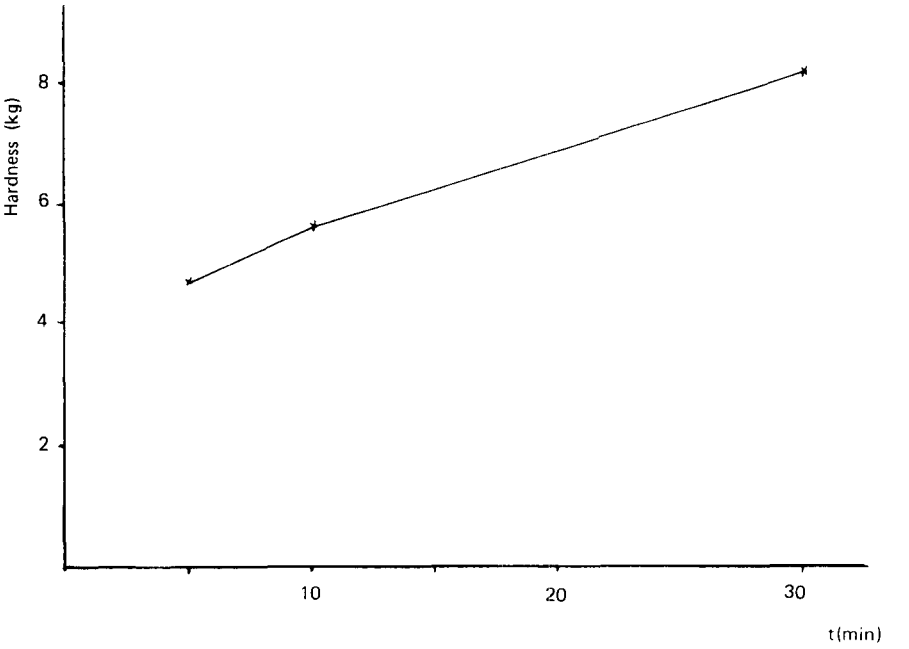

Figure 1. Wet-mixing time and hardness correlation of furosemide tablets

were compressed with granules prepared with different wet-mixing times but of almost equal hardness (B) prolongation of disintegration times were observed (Table 2). Wet-mixing time affects the dissolution rate. t50 values were 5.30 and 11.00 min for 5 min and 10 min mixed tablet formulations respectively. Dissolution rate of tablet was related with the time that a change began to appear in the cosistence of the moistened mass. After this stage the prolongation of mixing time had no effect on the dissolution parameters. 5 min wet-mixing time was found as an optimum period. Our data on the importance of wet-mixing time is in accordance with the previous reports (8,9).

Influence of Binding Solution Volume

Physical properties of furosemide tablets prepared by using different volumes of granulating solution at a fixed gelatin concen-

TABLE 2

Effect of Wet-Mixing Time on the Properties of Furosemide Tablets Having the same Mechanical Strength

Mixing Time (min)	Hardness (kg,cv)	Disintegration (s)	Friability (%)	Weight (g,cv)	Drug Content % claimed	Dissolution Parameters		
						t_{50} (min)	A_{30} (%)	k (min^{-1})
5	4.65 (5.73)	200	0.23	0.2041 (2.19)	97.50	5.30	89.74	0.1307
10	4.31 (8.17)	255	0.19	0.2091 (3.44)	98.12	11.30	73.88	0.0613
30	4.47 (8.24)	230	0.08	0.2188 (4.18)	103.12	12.30	67.87	0.0563

TABLE 3

Effect of varying Volume of Granulating Solution on the Properties of Furosemide Tablets Compressed under the same Pressure

Binder volume % v/w	Mixing Time (min)	Disintegration time (s)	Hardness (kg,cv)	Friability (%)	Weight (g,cv)	Drug Content % claimed
20	5	170	3.92 (3.79)	0.18	0.1952 (0.68)	91.25
	10	198	5.32 (3.72)	0.08	0.1997 (0.52)	95.00
	30	180	5.48 (3.70)	0.07	0.2061 (0.44)	100.62
30	5	200	4.65 (5.73)	0.23	0.2041 (2.19)	97.50
	10	220	5.85 (5.48)	0.23	0.2038 (2.37)	99.37
	30	200	8.20 (7.93)	0.15	0.2204 (1.96)	103.75
25	30	197	10.32 (2.91)	0.073	0.2328 (0.69)	110.62

TABLE 4

Effect of Varying Volume of Granulating Solution on the Properties of Furosemide Tablets having the same Mechanical Strength

Binder volume % v/w	Mixing time time (min)	Disintegration time (s)	Hardness (kg,cv)	Friability (%)	Weight (g,cv)	Drug content % claimed
20	5	170	3.92 (3.79)	0.18	0.1952 (0.68)	91.25
	10	225	3.75 (4.48)	0.38	0.1911 (4.72)	90.00
	30	230	4.68 (7.81)	0.19	0.1900 (3.60)	93.12
30	5	200	4.65 (5.73)	0.23	0.2041 (2.19)	97.50
	10	255	4.31 (8.17)	0.19	0.2091 (3.44)	98.12
	30	230	4.47 (18.24)	0.08	0.2188 (4.18)	103.12
25	30	300	4.06 (4.92)	0.41	0.2027 (4.10)	95.62

TABLE 5

Effect of varying Volume of Granulating Solution on the Dissolution Parameters of Furosemide Tablets

Binder volume volume (% v/w)	Mixing time (min)	A^x			B^{xx}		
		t_{50} (min)	A_{30} (%)	k (min^{-1})	t_{50} (min)	A_{30} (%)	k (min^{-1})
20	5	5.00	91.21	0.1386	5.00	91.21	0.1386
	10	9.00	77.63	0.0770	12.00	78.05	0.0577
	30	11.30	78.75	0.0613	20.00	62.66	0.0345
30	5	5.30	89.74	0.1307	5.30	89.74	0.1307
	10	11.00	71.25	0.0630	11.30	73.88	0.0613
	30	9.00	77.71	0.0770	12.30	67.87	0.0563
25	30	17.30	69.49	0.0400	30.00	49.35	0.0231

A^x - Tablets compressed under the same pressure, B^{xx}- Tablets having the same mechanical strength.

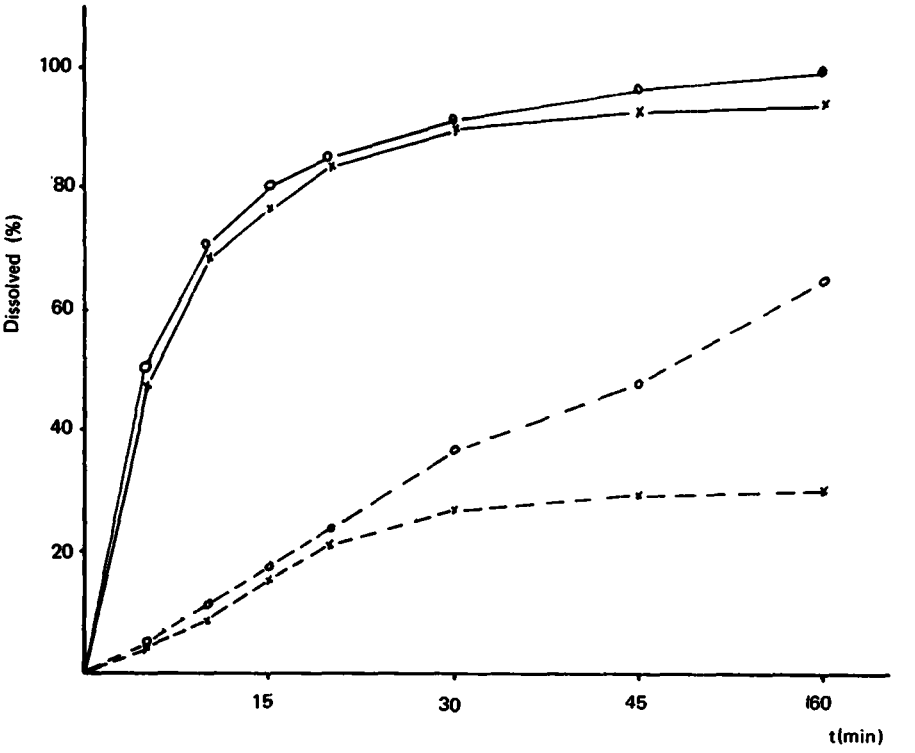

Figure 2. Comparison of dissolution profiles of furosemide capsules and tablets prepared with batch (I) and batch (II).
Key: Furosemide bulk powders (- - -)
Furosemide tablet (————)
Batch I (x————x), Batch II (o————o)

tration, were given in Table 3 and 4. Mixing the mass at different periods with 30 % binding solution caused dissolution differences. To examine the importance of binding solution volume 20 %, 25 % and 30 % ratios were investigated. However there was not any significant effect of these volumes on dissolution times. As shown in Table 5 when 20 % binding solution was applied t_{50} were 5.00 min and 11.30 min for the mixing times of 5 min and 30 min respectively.

Difference Related to Batch Variations

Dissolution profiles of capsules prepared from two different batches of furosemide are shown in Fig.2. Dissolution profiles of these batches were found quite different from each other (t_{50} was more than 60 min for Batch I, and t_{50} was 48 min for Batch II) and the contents of the capsules remained as aggregates at the end of dissolution test. Whereas tablets prepared from different batches were unaffected and exhibited almost similar profiles. A_{30} values were found 71 % and 79.41 % for batches I and II respectively. The results are summarized in Fig.2. Slow dissolution of capsule content was not traced to the tablets, as it was reported previously (1,2), especially granultaion process and compression affected furosemide dissolution.

Results confirm the opinion that during wet granulation process of furosemide tablet formulation, wet-mixing time of moistened mass has a prime importance from the point of tablet dissolution. An optimum period in wet-mixing process is needed and these findings can be important in controlling industrial granulations. But dissolution was unaffected by the volume differences of binding solution. The data suggests the need for standardization of process factors for production of furosemide tablets in order to be able to correlate dissolution with bioavailability. The contrary, these brand-to-brand and batch-to-batch differences will cause therapeutic failures.

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REFERENCES

1- V.K. Prasad, R.S. Rapaka, P.W. Knight and B.E. Cabana, Int. J. Pharm. 11, 81 (1982)

2- M.A.F. Gadalla and A.A. Ismail, Pharmazie 36, 553 (1981)

3- W. Stüber , E. Mutschler and D. Steinbach, Arzneim Forsch. 32, 693 (1982)

4- M. Kingsford, N.J. Eggers, G. Soteros, T.J.B. Maling and R.J. Shirkey, J. Pharm. Pharmac. 36, 536 (1984)

5- J. Akbuğa and A.Gürsoy, submitted for press

6- Documents Geigy VII th Edition, Published by Ciba-Geigy, Basel, 1973, p.280

7- M.H. Rubinstein and E.J. Price, J. Pharm. Pharmac. Supl. 29 5P (1977)

8- G. Banker, in "Sprowls' American Pharmacy " VII th Edition L.W. Dittert, eds., J.B. Lippincott Comp. Philadelphia, 1974, p. 362

9- D. Ganderton and B.M. Hunter, J. Pharm. Pharmac. 23 Suppl. IS (1971)