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STUDIES ON FUROSEMIDE TABLETS I
DISSOLUTIONS OF COMMERCIAL PRODUCTS AND DIFFERENT FORMULATIONS

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ABSTRACT

Tablet properties of 3 different commercial brands of furosemide tablets from different manufacturers have been investigated. Their dissolution characteristics were determined by using USP rotating basket method and two different pH degrees as the test medium. At pH 4.6 a large variation in the dissolution rate of these brands was observed. The release rate differed from one lot to another.

The effect of methods of tablet processing on furosemide release was also studied. A poor dissolution profile was observed with the tablet prepared by direct compression. The best

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result was obtained with the wet-granulation and the further study is extended on this process.

INTRODUCTION

Furosemide is a widely used diuretic drug with a rapid action for the treatment of edematous states of hepatic, cardiac and renal origin. It can be used in clinical circumstances where a prumpt diuresis is need. But, recently diuretic ineffectiveness of some of the furosemide tablet products have been reported (1-6). In the U.S.A. a generic furosemide tablet was recalled by the FDA because of its therapeutic failure (7). However there is no information about commercial furosemide tablets in our market.

On the other hand, very little works have been published on the pharmaceutical factors which affect the furosemide tablet dissolution (8-12).

Since furosemide is a poorly water-soluble drug, dissolution may be a rate-limiting step in drug absorption. It was noted that different formulation variables such as the type of disintegrant, binder, lubricant were effective at the dissolution of furosemide from tablets. Recently, correlation between in vitro dissolution rate and drug bioavailability of furosemide was reported (13-14).

The present study was undertaken to investigate in vitro dissolution characteristics of furosemide commercial tablets available on the market and the secondly, to research the effect of formulation factors and process variables on the dissolution of furosemide tablets.

EXPERIMENTAL

Materials

Furosemide (hoechst A.G. Frankfurt), anhydrous lactose (Sheffield Chem. New Jersey 07 071), Avicel PH 101. (FMC Corp. Marcus Hook.Philadelphia), magnesium stearate (E.Meck, Darmstadt). Starch, gelatin and talc were pharmaceutical grade.

The following buffers were used: pH 4.6 (acetate) (15), pH 7.4 (phosphate) (USP XX).

Three lots of furosemide-40 mg tablets manufactured by 3 different manufacturers were investigated and the preparations were labeled according to the date of manufacture; L_1, L_2, L_3, D_1, D_2, D_3, K_1, K_2, K_3, respectively.

Apparatus

Tablet machine (Korsch EK-0 Berlin), hardness tester (Monsanto), disintegration tester (Denel Fizik), friabilator (Roche), dissolution tester USP, spectrophotometer (Varian, Techtron Series 634).

Methods

Studies on the commercial Furosemide Tablets

Different lots of furosemide tablets were tested as follows;

Disintegration, weight variation and content uniformity tests were carried out according to USP XX. and coefficient of variation (cv) was calculated for weight variation.

Hardness of at least six tablets was determined and a mean value was obtained.

Dissolution test; the rotating basket method of USP XX was used. At 37 ± 0.5^{o}, 1000 ml of buffer was used as a medium. Dissolution test was carried out with two different buffer systems; pH 4.6. acetate and pH 7.4 phosphate buffers. The rotating rate was 75 rpm. The amount of substance dissolved in unit time was determined spectrophotometrically at 272 nm. The results are the mean of six determinations. By TLC under the experimental conditions no degradation was found.

Formulation Studies

Different furosemide tablets were prepared with the formulations; shown in Table I, by using the manufacturing processes given below:

Formulation prepared by slugging (F-I)

All the ingredients were dried at 60^{o}/2 hrs and sieved. Furosemid in 100-mesh size was used. Powders were mixed in a plastic bag for 5 min and then compressed. The briquettes so formed were broken up gradually in a mortar before passing through a 25 mesh

TABLE 1
Tablet Formulations

Ingredients (mg)	Formulations				
	F-I	F-II	F-III	F-IV	F-V
Furosemide	40	40	40	40	40
Lactose	150	80	80	-	100
Cornstarch	50	-	-	150	50
Avicel PH 101	-	80	40	-	-
Gelatine	-	-	-	2.8	2.8
Talc	5.7	6	4.3	8.1	8.1
Magnesium stearate	3.8	4	3.2	5.4	5.4

screen. Lubricant was added and compressed on a single-punch tablet machine using 8.1 mm flat-faced punches.

Formulation prepared by direct compression (F-II, F-III).

Dried ingredients were sieved and mixed in a plastic bag for 5 min then tablets were compressed as mentionned above.

Formulation prepared by wet granulation (F-IV, F-V).

The powders were mixed and binder solution was added. The total wet-mixing time was 10 minutes. The mass was discharged through an ossillating granulator. fitted with 16 mesh screen. The granules were dried for 20 min at 60^{o} and the lubricant incorporated by mixing in a plastic bag for 5 min after sieving

through a 25-mesh screen. The tablets were compressed as mentionned above.

For each formulation, tablet properties such as weight variation, hardness, friability, disintegration time, content uniformity and dissolution were determined as described above.

RESULTS and DISCUSSION

Studies on Commercial Tablets

Tablet properties of 3 brands of commercial furosemide tablets produced by different manufacturers are shown in Table 2.

As it is seen in Table 2, these commercial tablets met the USP XX. requirements for weight variations and disintegration times. Except Lots D_1 and D_3, furosemide content of these tablets were within the limits of USP XX. Therefore it can be said that these tablets are chemically equivalent. On the other hand, except lots D_2, D_3, K_2, and K_3 furosemide tablets had a satisfactory mechanical strength. Only in Brand D handness values changed between 1.6-3.0 kg.

Since there is no dissoliton specification for furosemide tablet in the pharmacopeia and pH of the medium is very important for furosemide, dissolution mediums having 2 different pH degrees (4.6 and 7.4) were tested. As observed in Table 2, except lot D_3 all the tablets showed a rapid and similar drug release. The t_{50} values changed between 5-8.30 min in Brand L and 5-10 min in Brand K while in Brand D varied between 4-24 min. It can be said that at pH 7.4 - except lot D_3 - all the commercial furosemide tablets had a rapid dissolution profiles.

Prasad et al (7) noted that differences in dissolution profiles of furosemide tablets were disappeared at pH 7.4, based on this information, dissolution studies were repeated at pH 4.6. Indeed, at pH 4.6 significant variations in vitro dissolution rates of commercial tablets were found (Table 2). Our findings are in accordance with Rubinstein et al (8) and Prasad et al (7) that the dissolution medium with pH between 4.0-5.0 is very convenient to differentiate good and poor furosemide formulation.

TABLE 2
Physical Properties of Commercial Furosemide Tablets

Lots	Hardness (kg)	Disintegration time (s)	Weight var. (g,cv)	Drug cont. % label claim	Dissolution Parameters		
					pH 7.4	pH 4.6	
					t_{50} (min)	t_{50} (min)	A_{30} (%)
L_1	3.80	98	0.1610 (1.75)	96.87	< 5	> 60	25.00
L_2	4.40	106	0.1660 (3.27)	100.00	7.30	> 60	24.37
L_3	4.47	125	0.1629 (5.46)	100.00	8.30	45	41.87
D_1	3.00	92	0.1953 (1.90)	88.12	4.00	16.30	65.00
D_2	1.60	120	0.1987 (2.56)	96.25	4.30	> 60	21.87
D_3	2.08	150	0.1938 (2.44)	92.50	24.00	30.00	50.62
K_1	2.58	236	0.2005 (2.85)	100.62	< 5	> 60	16.25
K_2	2.86	261	0.2040 (2.63)	100.00	9.30	27	51.87
K_3	3.45	370	0.2014 (2.65)	98.11	10.00	60	41.25

Furosemide tablets having a good dissolution characteristic in pH 7.4, lots L_1, L_2, D_2, K_1, and K_3, indicated a very long dissolution half-life at pH 4.6. However a rapid dissolution was obtained with the lots L_3, D_1, D_3, and K_2, .Slow dissolution rates observed in tablet lots L_1, L_2, D_2, and K_1, can be attributed to the aggregates remained in the basket during the test. As the furosemide contents of these tablets met the compedial limits, this, slow drug release pointed out inter-batch variations of commercial preparations.

Furthermore, Kingsford et al (14) have demonstrated that percentage of drug dissolution in 30 min (A_{30}) at pH 5 is a convenient parameter for prediction of furosemide bioavailability. When A_{30} values were compared with each other a similarity with t_{50} values were observed. Since there is a problem of bioinequivalance of commercial furosemide tablets, our data may be beneficial to explain the variations in therapeutic effectiveness of this drug.

Formulation Studies

Effect of Manufacturing Process

By using different manufacturing processes such as direct compression, slugging and wet granulation, tablets were prepared and the results were compared.

As it is given in Table 3 tablets complied with the USP XX requirements for disintegration time and weight variation.

Since Avicel PH 101 concentration in F-III is lower than F-II, this formulation (F-III) could not be tabletted and therefore it was not shown in Table 3. This result indicated that lactose-avicel ratio is important for the preparation of furosemide tablets by direct compression. On the otherhand, as it is seen in Table 3 avicel adversely affected furosemide release when avicel lactose was used in a ratio of (1:1).

Tablets made by slugging and wet granulation exhibited similar drug release patterns (t_{50} 9.30 min), however a very slow dissolution rate was found with tablets prepared by direct compression (t_{50} 47.30 min). The best drug release was obtained with the formulation F-IV prepared by wet granulation.

TABLE 3

Physical Properties of Furosemide Tablets Prepared by Different Processes

Formulas	Disintegration time (s)	Hardness (k,cv)	Friability (%)	Weight	Drug cont. % claimed	Dissolution Parameters		
						t_{50} (min)	A_{30} (%)	k (min^{-1})
F-I	95	3.16 (8.40)	0.47	0.2073 (2.48)	85.62	9.30	68.38	0.0745
F-II	60	5.38 (5.62)	0.15	0.1966 (3.48)	90.62	47.30	32.43	0.0146
F-IV	310	5.02 (2.73)	0.25	0.2115 (2.10)	91.87	9.30	77.00	0.0745
F-V	260	4.33 (6.97)	0.20	0.2043 (1.38)	95.62	5.00	87.58	0.1386

When the disintegration times of these tablets are compared a longer disintegration time was obtained with the tablets produced by wet granulation, but the granulation process only affected the tablet disintegration. On the otherhand there is also a poor correlation between the disintegration time and dissolution rate (t_{50}) (r=0.592) of furosemide tablets as contrary to previous report (8).

As the disintegration times of formulations F-IV and F-V are compared, it is seen that differences between them are directly due to variations in their formulations.

As a conclusion our data brought forward the variations in in-vitro drug release from commercial furosemide tablets and the importance of medium pH to show this release. And when furosemide tablets manufacturing processes were compared best tablet properties were obtained with wet granulation technique.

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