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IN VITRO AVAILABILITY OF NITROFURANTOIN FROM DIFFERENT TABLET BATCHES

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ABSTRACT

Four commercially available tablet preparations containing 50 mg, and on the other hand, 100 mg nitrofurantoin as well as a test preparation containing 45 mg nitrofurantoin was studied in vitro. The tested products meet USP. XIX specifiactions for drug content and weight. Statistically siginificant differences were recorded between the different preparations with regard to their in vitro availability. Two of the commercial preparations and the test preparation did not meet the USP. dissolution requirements for nitrofurantoin tablets.

INTRODUCTION

Nitrofurantoin is used as an antibacterial agent in the case of certain urinary tract infections. Gastrointestinally nitrofurantoin is a relatively difficultily soluble weak acid (pKa = 7.2). Used perorally, however, it has been found to be rapidly and almost completely absorbed (1). Its gastrointestinal dissolution rate is dependent on the particle size, and for this as well as for the aforementioned reason its rate of absorption and bioavailability can be affected by a change in the

particle size (2, 3, 4, 5). Likewise, it is possible to reduce the side-effects of nitrofurantoin *in vivo* by adjusting the particle size to a proper level (2, 3, 5, 6).

Taking into consideration the physico-chemical properties and absorption per se of nitrofurantoin, it is obvious that *in vitro* dissolution tests can give us an idea about the extent to which commercially available chemically equivalent products are similar with regard to their *in vivo* availability. For the above-stated reasons USP. XVIII and NF. XIII introduced dissolution tests for nitrofurantoin although, as has been indicated (7, 8, 9) and as has been stated in NF., the results of such tests do not necessarily indicate the effectiveness of the medicines concerned. USP. XVIII presupposes that dissolution tests be carried out also on twelve other preparations containing other drugs. However, the requirements made on nitrofurantoin tablets differ quite essentially from those made on other preparations. USP. XVIII states that the time required for 60 % of the labeled quantity of nitrofurantoin to dissolve is not less than 60 min. USP. XIX, however, states that 25 - 60 % of the labeled nitrofurantoin must be dissolved in one hour. The studies carried out by HOSSIE et al. (1973) on nitrofurantoin preparations registered in Canada showed that differences existed both within the same and between different preparations to such extent that 41 % of the cases examined according to USP.'s method did not meet the requirements of the USP. (10). According to studies of a similar kind carried out by MEYER et al. (1974), the fourteen preparations examined fullfilled the USP. requirements concerning nitrofurantoin tablets (8).

The aim of the present work is to assess the in vitro availability, content uniformity and weight variation of tablets containing nitrofurantoin which are commercially available in Finland. The study covered also one tablet type which was prepared for this very purpose.

EXPERIMENTAL

Tablet Preparations

The granules to be used in tableting were prepared from a basic mixture containing 10 % nitrofurantoin (Orion-yhtymä Oy.,028) and 90 % Macrogol 9000 (Fluka Ag, 157964102, mol. weight 9000- 10 000, melting range 333 - 336 K). Macrogol 9000 was melted in a steam bath (348 K) for about 5 min., and the nitrofurantoin was suspended into molten Macrogol. The mass was molded into a thin sheet which, after it had congealed, was disperged into granules trough a punched plate and sifted. In tableting granules having a size of 0.71 - 1.00 mm were used. Tablet compression took place in a KORSCH EK- 0 tablet machine. The diameter of the punches was 13.0 mm, and the compression force used, as measured at the lower punch, 9980 N/cm^2 (11).

Commercial Products

Table 1 gives data on the commercial preparations covered by the study. Likewise, data on the test tablets described in the foregoing are found in this table.

Assay Procedures

In the case both of the contents determinations and of dissolution tests carried out on the tablets, the samples were analyzed spectrophotometrically at pH 7 (BECKMAN DB).

Dissolution Tests

The tests were carried out in a USP. 72 B dissolution apparatus in whcich a three-blade propeller had

TABLE 1.

General data of the tablets studied. A - D = commercial preparations.M = test preparation.Number of analyses=10

Product code	Concentration Labeled	Concentration Tested	Weight	Additives
	mg	mg	mg	mg
A 181	100	99.8	398.5	298.5
B ZD2	100	95.7	479.1	379.1
C ZF06	50	46.5	868.4	818.4
D 40507	50	51.8	157.7	107.7
M	45	43.6	366.1	321.1

been attached to the shaft of the stirrer above the the tablet basket. An dissolution medium a phosphate buffer (Na_2HPO_4 x 2 H_2O + KH_2PO_4) with pH 7.1 was used in both the contents determinations and the dissolution tests. Temperature was 310 K (HETO MA 6 apparatus), and the stirring speed 100 rpm. Samples were taken for analysis at specified time intervals, and after dilution their contents were analyzed at the wavelength 369 nm.

RESULTS AND DISCUSSION

The results obtained from the content analyses (Table 1) showed that each of the preparations tested fulfilled the general minimum requirements for contents. If a total deviation of±5 % is allowed from the labeled amount, this requirement was meet by A, B, D and M tablets. The results obtained for C tablets show that preparing a homogeneous mixture is more difficult the greater the ratio between the masses of different substances to be mixed with each other. The total contents of the tablets may, however, be considered fair-

ly good because in each case of the separate analyses the extreme limits were within 10 % of the labeled amounts.

According to the results obtained from the dissolution tests (Figure 1), D tablets dissolved at a markedly more rapid rate than other tablets, although the difference was not great in comparison with the test tablets. This rapid rate of dissolution in the case of D tablets is at least partly due to their rapid disintegration, whereby the increase in the surface area of the tablets increases the rate of dissolution. Just as D tablets, C tablets, too, contain 50 mg of nitrofurantoin. The slower rate of dissolution of C tablets in comparison with that of D tablets is probably due to the compositon and the technique used in

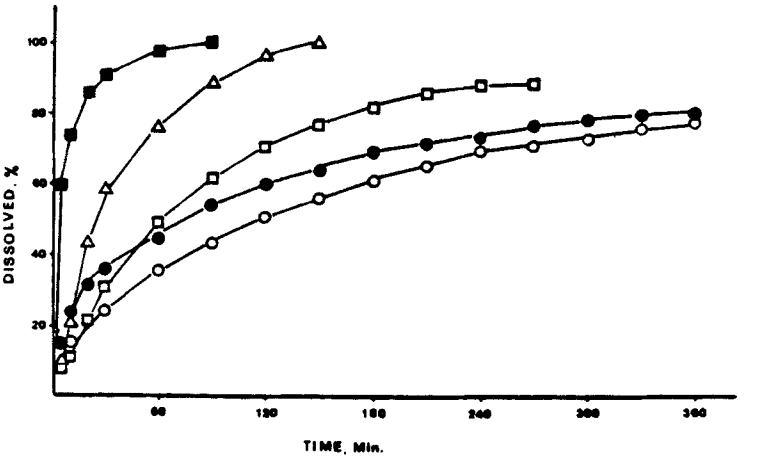

FIGURE 1.

Mean cumulative percent of nitrofurantoin dissolved from tablets. ○ = A tablets, ● = B tablets, □ = C tablets, ■ = D tablets, △ = M tablets

preparation as well as to the coating of the former. A and B tablets, which contain 100 mg of nitrofurantoin, dissolve at more or less the same rate, and slower and more evenly than the former. It is possible on the basis of the dissolution profiles to divide the tested preparations into two or three groups, and in that case the last-mentioned tablets are representative of the slowest dissolving category of tablets. None of the preparations in this group dissolved completely during the total time of the experimet, six hours. D tablets and the self-made tablets belong, on the basis of their dissolution profiles and dissolution rates, to another group, in which dissolution is more rapid than in other groups, and in which 100 % is dissolved as early as 1.5 - 2.5 hours from the beginning of the process. The dissolution profile of B tablets falls between those of the former groups, and in this case 80 % is dissolved in 5.5 hours. In all cases, on the other hand, a 30 % results is achieved in less than one hour. The greatest differences in in vitro availability are thus recorded during 3.5 - 4.0 hours of dissolution, after which they become gradually smaller.

When examination is based on the dissolution requirements of USP XVIII or XIX, it can be seen that only A, B and C tablets meet them. It must be observed, however, that the results presented in this paper are means that have been obtained from only 10 determinations, and that additional repeat tests as suggested in the USP were not carried out. On the basis of the test results the conculsion may be drawn, however, that chemically equivalent preparations, as the A and B tablets, are equivalent in this case also with regard to their in vitro availability. In the case of D and C tablets, on the other hand, irrespective on their

chemical equivalence, a difference is recorded with their in vitro availability.

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REFERENCES

1. Osol. A., Pratt, R. and M.D. Altschule, "The United States Dispensatory and Physicians Pharmacology," 26 th. Ed., J.B. Lippincott Comp., Philadelphia and London, 1967, p. 760.
2. Hailey, F.J. and H.W. Glascock, Curr. Ther. Res., 9, 600 (1967).
3. Paul, H.E., Keyon, J.H., Paul, M.F. and A.R. Borgman, J. Pharm. Sci., 56, 882 (1967).
4. Conklin, J.D., Sobers, R.J. and D.L. Wagner, Ibid., 58, 1365 (1969).
5. Stoll, R.G., Bates, R.B. and J. Swarbrick, Ibid., 62, 65 (1973).
6. Conklin, J.D. and F.J. Hailey, Clin. Pharm.Ther., 10, 534 (1969).
7. Mattok, G.L., Hossie, R.D. and I.J. Mc Gilveray, Can. J. Pharm. Sci., 7, 84 (1972).
8. Meyer, M.C., Slywka, G.W.A., Dann, R.E. and P.L. Whyatt, J. Pharm. Sci., 63, 1693 (1974).
9. Bates, R., Rosenberg, H.A. and A.V. Tembo, Ibid., 62, 2057 (1973).
10. Hossie, R.D., Mc Gileray, I.J., Mattok, G.L. and C.A. Mainville, Can. J. Pharm. Sci., 8, 37 (1973).
11. Krogerus, V.E., Kahela, P. and S.I. Malmivuori, Farm. Aikak., 78, 70 (1969).