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# Effect of storage on nitrofurantoin solid dosage forms

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Storage under adverse conditions of temperature and humidity is not uncommon in many parts of the world. Packages used for the dispensing of medications are often less than adequate. These conditions may adversely affect the quality of pharmaceutical preparations (Gouda et al., 1980; York, 1977). While changes in the chemical stability of drugs in their dosage forms are usually easily detected, changes in biopharmaceutical properties may pass unnoticed. Nitrofurantoin, a urinary tract antibacterial drug, has a potential for bioavailability problems. Formulation factors, mainly particle size, affect dissolution rate, bioavailability in humans and incidence of side-effects (Cadwallader et al., 1975). The USP XX monograph for nitrofurantoin tablets requires not less than 25% of the labeled amount of drug to dissolve in 60 min in a pH 7.2 phosphate buffer. The objectives of the present study are to determine the effect of storage on the dissolution of nitrofurantoin tablets and capsules and to assess any bioavailability changes associated with storage.

Two brands of nitrofurantoin capsules containing macro- or microcrystals and a tablet were stored in original blister packs, in child-proof vials and in plastic bags. The storage conditions adopted were 40°C/79% relative humidity (R.H.), 25°C/79% R.H. and 40°C/31% R.H. Samples were taken at various time intervals and the drug content, weight variation and dissolution at 37°C in a pH 7.2 phosphate buffer (USP XX) were determined.

A limited bioavailability study based on determination of urinary excretion of unchanged drug was also carried out. Administration of stored (in plastic bags for 10 weeks at 40°C/79% R.H.) and unstored capsules under non-fasting conditions (Bates et al., 1974) to two healthy volunteers was performed in a cross-over design. Urine samples were collected at various time intervals and analyzed for nitrofurantoin (Conklin and Hollifield, 1965).

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Results have shown no change in weight variation and content uniformity of nitrofurantoin dosage forms upon storage under various conditions. Nitrofurantoin capsules containing microcrystals, as expected, dissolved at a considerably faster rate. Storage did not markedly alter the dissolution pattern of nitrofurantoin tablets or microcrystal capsules. The dissolution of nitrofurantoin from macrocrystal capsules was, however, markedly decreased (Tables 1, 2 and 3). While all preparations complied before storage with the USP XX dissolution requirements for tablets, the capsules containing macrocrystals just failed to comply with these requirements when stored in plastic bags for 2 weeks at 40°C/79% R.H. (Table 1). Macrocrystal capsules stored for 10 weeks in various containers at these conditions all failed to comply with the USP XX dissolution requirement for tablets. Urinary excretion data have shown that storage of macrocrystal capsules resulted in delaying the time of

TABLE 1

EFFECT OF STORAGE AT 40°C/79% R.H. IN PLASTIC BAGS ON DISSOLUTION OF NITROFURANTOIN SOLID DOSAGE FORMS

| Dosage form | % dissolved after 60 min | |
|---|---|---|
| | Unstored | Stored (2 weeks) |
| Macrocrystal capsules | 63 | 22 |
| Microcrystal capsules | 100 | 93 |
| Tablets | 58 | 65 |

TABLE 2

EFFECT OF STORAGE CONDITIONS ON DISSOLUTION OF MACROCRYSTAL CAPSULES STORED IN PLASTIC BAGS

| Storage conditions | % dissolved after 60 min | |
|---|---|---|
| | Unstored | Stored (2 weeks) |
| 40°C/79% R.H. | 63 | 22 |
| 25°C/79% R.H. | 63 | 50 |
| 40°C/31% R.H. | 63 | 63 |

TABLE 3

EFFECT OF STORAGE AT 40°C/79% R.H. ON THE DISSOLUTION OF MACROCRYSTAL CAPSULES IN VARIOUS CONTAINERS

| Container | % dissolved after 60 min | | |
|---|---|---|---|
| | Unstored | Stored (2 weeks) | Stored (10 weeks) |
| Blister pack | 63 | 49 | 6 |
| Childproof vials | 63 | 49 | 5 |
| Plastic bags | 63 | 22 | 3 |

maximum excretion of nitrofurantoin from 2.5 to 3.5 h. However, the extent of absorption as measured by the cumulative amount of drug excreted in 12 h was about the same (38–40% of the dose). The storage of microcrystal capsules did not significantly affect its bioavailability.

The decrease in nitrofurantoin dissolution from macrocrystal capsules upon storage (Table 1), as compared to microcrystal capsules or tablets is probably due to a physical change involving agglomeration of the particles and may be due to the dissolution conditions adopted. In the absence of knowledge of the additives included in the formulation, it would be difficult to identify the exact mechanism responsible for this change. Table 2 shows that humidity is a more important factor in retarding dissolution upon storage. Plastic bags, as expected, afforded the least protection for the capsules (Table 3). In spite of the marked decrease in dissolution of the macrocrystal capsules, bioavailability data did not show a parallel decrease. The lack of correlation between in vivo bioavailability and dissolution characteristics observed for nitrofurantoin, in the present investigation, confirm the findings of previous reports (Meyer et al., 1974) and would suggest that the use of dissolution parameters for bioavailability prediction is not satisfactory for nitrofurantoin.

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