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COMMUNICATION

# Nitrofurantoin: Particle Size and Dissolution

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**ABSTRACT**

*Tablets manufactured from micronized anhydrous nitrofurantoin exhibited unsatisfactory dissolution properties, whereas excellent results were obtained with unmilled drug material having fine particle size.*

## INTRODUCTION

Nitrofurantoin is a drug entity of low aqueous solubility as substantiated in the reported values of 174, 154, and 374 mg/l in water, at pH 1.1, and pH 7.2, respectively, at 37°C (1). Numerous investigations on the dissolution and/or bioavailability of nitrofurantoin in solid dosage forms have been published (2). The present communication describes an unexpected result of the influence of the drug's particle size on dissolution.

## MATERIALS AND METHODS

All raw materials were of pharmacopeial (EP) quality. Milling of nitrofurantoin was carried out in an impact comminuting mill (Apex Ltd., UK). The tablet formulation was according to the Nordic Pharmacopeia (3). Granulations were performed in an intensive mixer (Gral-25, Collette, Belgium) and tablet compression in a rotary tableting machine (Manesty B3B, Manesty, UK). Particle size analysis of micronized nitrofurantoin was done by dispersion using compressed air, gold coating, and examination in a Cambridge Instruments Stereoscan S240 scanning electron microscope followed by electronic image analysis. X-ray powder diffractograms were taken at ambient temperature with a Philips PW instrument: target Cu, filter Ni, voltage 40 kV, current 20 mA, receiving slit 0.1 mm.

## EXPERIMENTAL

Anhydrous nitrofurantoin was milled by passing it three times through a 0.25-mm screen using hammers at 4600 rpm followed by one pass through a 0.15-mm sieve under the same conditions. This material was found to have a mean Feret's diameter of 1.2 μm, range $<$1–10 μm and 90% below 2.2 μm (based on particle number) and is designated as micronized nitrofurantoin. X-ray diffraction analysis in the region 5–30° (2θ) proved it to be the unaltered, crystalline, and anhydrous form by comparison with a published diffractogram (4). The unmilled nitrofurantoin was used as received and had the following particle size characteristics: 47% below 48 μm, 87% be-

low 96 μm, and 99% below 200 μm (based on mass by sieving as reported by the manufacturer).

Two 5-kg wet granulations using gelatin solution (4% w/w, ca. 40 mg per tablet) were prepared followed by drying, sizing, mixing with lubricant (magnesium stearate and talc, 1 + 9, w/w, 10 mg per tablet), and compaction to a target tablet mass of 181.6 mg and nominal strength of 50 mg. The composition of the two batches (A and B) was identical except that batch A contained unmilled and batch B micronized nitrofurantoin. The remaining ingredients were lactose monohydrate and potato starch (60 mg of each per tablet) (3). The two tablet batches were analyzed for hardness ($n = 10$; Schleuniger tester), disintegration ($n = 6$; Erweka tester with discs), and dissolution ($n = 6$) (5).

## RESULTS

The hardness, disintegration, and dissolution values (% of label claim) for the two batches were as follows: A (unmilled): hardness 3.8 kg (CV 16.1%), disintegration 2:20 min, dissolution at 60 min 99.5% (CV 1.2%), and dissolution at 120 min 100.4% (c.v. 0.9%), B (micronized): hardness 3.8 kg (CV 9.0%), disintegration 3: 45 min, dissolution at 60 min 46.1% (CV 45.7%), and dissolution at 120 min 57.1% (CV 28.1%).

## DISCUSSION AND CONCLUSIONS

The dissolution limits specified by USP for nitrofurantoin tablets are not less than 25% after 60 min and not less than 85% of label claim after 120 min. The tablets manufactured from the unmilled drug material exhibit complete dissolution already after 60 min. By contrast, unexpectedly, the tablets containing the micronized nitrofurantoin fail on dissolution after 120 min, and the variation in the data is large. Although both batches have short disintegration times in the disintegration test apparatus (water, disc), the tablets from batch B did not disintegrate in the dissolution test instrument (pH 7.2 phosphate buffer, basket, 100 rpm). Instead they swelled, and one of them split radially into two halves. It is proposed that the micronized, cohesive, and hydrophobic (6) nitrofurantoin acts as an agglomerated barrier impairing access of the aqueous medium to the ingredients in the tablets under the relatively mild agitating conditions in the dissolution test apparatus. The results of this study are still another illustration of the importance of the physical attributes of raw materials concerning the functionality of the finished products (7).

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