AN INVESTIGATION ON THE DISSOLUTION
OF NITROFURANTOIN

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The problem of the existence of inter-lot and inter-tablet variation in the dissolution rates of nitrofurantoin (NFT) marketed tablets attracts the attention for investigating the microcrystalline NFT powder used in formulating the marketed tablet products. The x-ray diffractometry and the differential scanning calorimetry of five microcrystalline NFT powders obtained from different manufacturers revealed that this drug is not exhibiting polymorphism. NFT hydrates of large particle size were observed to be formed when the drug was to be in contact with water with the pH values in the acidic range. The unexpected dissolution–pH profile of stored NFT suspensions prepared by precipitation at pH 5.4 from alkaline solution may be illustrated by the possibility of tautomeric transformations in the drug. This was more revealed by the observed reversible shift of the λ maxima on changing the pH of its solutions.

Nitrofurantoin, a urinary tract antibacterial agent, possesses relatively low aqueous solubility characteristics at pH values normally encountered in the various segments of the gastrointestinal tract. As a result, it is not surprising that the drug displays a particle size dependence in its dissolution rate and hence the rate and extent of its bioavailability in man.

Newton and Razzo found that the solubility of nitrofurantoin is the major factor for controlling the drug release from capsules. Frigerio and Venier found a good correlation between the bioavailability of commercial tablet products and both the tablet hardness and disintegration time. Mendes et al.
in an investigation for the bioequivalency of nitrofurantoin, found that neither processing methods nor compression force would significantly affect the dissolution rate of the tablets. The results of another study done by the same authors\(^9\) indicate the presence of a good rank order correlation between one hour cumulative dissolution of some formulations and their three hours cumulative excretion. They stated that, all formulations in which at least 25% of the drug is dissolved within one hour were bioequivalent.

The USP XIX\(^{10}\) nitrofurantoin monograph specifies that the time required for 60% of the labelled amount to dissolve is not less than one hour. In the light of the findings of Bates et al.\(^1\), it was stated that, the rationale underlying the official dissolution rate specification for nitrofurantoin tablets appear quite arbitrary and inconsistent with the dissolution profile and potential toxicity of the official suspension dosage form. Many authors\(^{11-13}\) found that, although the tested commercial nitrofurantoin tablet products met the USP XIII specifications, significant differences were observed in their availability. In a recent report, Groning\(^{14}\) stated that the USP XIX dissolution test does not reflect the differences between dosage forms of nitrofurantoin.

Mattok et al.\(^{15}\) and Hossie and Mc Gilveray\(^{16}\) reported the existence of inter-lot and inter-tablet variation in the dissolution rates of commercial nitrofurantoin products and these variations could make the correlation with absorption parameters difficult.

However, numerous reports\(^{11-13}, 15-18\) about nitrofurantoin provide support for the contention that not all commercially available products meeting compendial requirements necessarily exhibit equivalent bioavailability.

Concerning the effect of the pH of the dissolution medium on the dissolution profile of nitrofurantoin products,
Bates et al.\textsuperscript{19} found that the pH 7.2 phosphate buffer medium suggested by the USP was unable to discern inherent particle size dependent differences in the rate of solution from tablets and capsules. They claim for the modification of the official USP dissolution specification for products of this drug. Moreover, Suttan et al.\textsuperscript{20} stated that the dissolution rate of nitrofurantoin tablets is highly brand-individualized and complex and the effect of pH of the dissolution medium on a particulate formulation is unpredictable. Also, they concluded that the value of any in-vitro procedure to predict bioavailability for nitrofurantoin is questionable.

The aim of this study was directed to investigate the dissolution rate behaviour of NFT solid dosage forms available from the local market. A collection of five microcrystalline NFT powders used in formulating the drug was obtained from different manufacturers and subjected to thorough investigations.

**EXPERIMENTAL**

1- Materials:

1- Commercial formulation products:
- Four batches of nitrofurantoin tablets supplied by manufacturer I.
- One batch of nitrofurantoin tablets supplied by manufacturer II.
- One batch of nitrofurantoin capsules supplied by manufacturer III.

2- Nitrofurantoin powders:—
Five samples supplied by Marsing(Denmark), Smith Kline & French(England) and Kahira Pharm. & Chem. Ind. Co. (Egypt).
II- Reagents:-

Dimethyl formamide, Glacial acetic acid, Sod. acetate, Hydrochloric acid, Ammonium hydroxide, Acetone, Ethanol, Methanol; all reagents are of analytical grade.

III- Equipment:-

- Spectrophotometer, type Specktromom 204.
- X-Ray Diffractometer, type Philips PW 1050.
- Differential Scanning Colorimeter, type perkin-Elmer Model DSC-IB.
- Rotational apparatus for solubility study N.F XI26.
- The apparatus system suggested by Levy21 for dissolution rate studies.

Determination of Nitrofurantion:

The samples were assayed spectrophotometrically at $\lambda_{\text{max}}$ of 368 nm, according to the method adopted by the B.P. (1973)22.

RESULTS and DISCUSSIONS

Table (1) shows that, although the commercial tablets are within the pharmacopoeial limits for both drug content and the disintegration, their dissolution efficiency23 reveals a significant difference between the amount of nitrofurantion dissolved from the different batches of the same marketed tablet products. Figure 1 shows the inter-lot variation in the dissolution rate of nitrofurantion from the same product. An intro-tablet and capsule variation in the dissolution rates were also observed in the marketed tablet & capsule products (Fig. 2 & 3). These results are to be in agreement with many reported findings about the inter-lot and inter-tablet variation in the dissolution rates of nitrofurantion commercial solid dosage forms6,8,11-13,15,16.

The nitrofurantion microcrystalline powders used for the marketed tablet formulations were investigated to find out
the reasons for the variations in the dissolution rates of the manufactured drug products.

The X-ray diffraction patterns of the five microcrystalline nitrofurantoin powders obtained from different manufacturers of the drug showed that there is no possible existence of different crystalline configurations in these powder samples.

In the aim of preparing different crystalline structures of the drug, nitrofurantoin was crystallized from ethanol, methanol and acetone at different conditions of crystallization. The X-ray diffractometry of these crystallizes showed that they possess different crystalline structures (Fig. 5). On the other hand, an amorphous form of the drug (Fig. 4) was obtained when the drug was dissolved in sodium hydroxide and then precipitated by gradual addition of dil. HCl until the pH of the solution was dropped to 5.4. Generally, these results lead to the conclusion that nitrofurantoin can hardly suffer from the polymorphic transformations specially if we take in our consideration that this drug melts with decomposition (Fig. 5).

The dissolution rate study of the commercial drug powders revealed that these powders (of average particle size = 50 μ) have significantly different dissolution rates (Fig. 6).

On the other hand, two of the five samples under investigation showed different solubility patterns than the other samples (Fig. 7). In general, a decline in the solubility values of all the powders was observed during the first sixty minutes of the experiment.

It was found that during this period of time the crystals of the drug were enlarged five times (from 50 μ to reach 260 μ particle size) and changed from rod shaped crystals to needle shaped ones. This could be attributed to the formation of drug hydrates having lower solubility patterns (Fig. 7). Also, the solubility of one of the commercial powders was carried out at different pH values and it was found that the solubility behaviour of the drug still
showing a similar common pattern of the solubility of the drug in distilled water. Therefore, the tendency of nitrofurantoin to form hydrate in aqueous medium is still present whatever the pH values of the medium (compare Fig. 7 & 8). From figure 8, it is clear that at thirty minutes of the experiments the drug possess of more solubility values at pH 3 than that observed at the other pH values. This coincides with the observations of Chen et al. who explain this phenomenon by the electron dislocalization of the three nitrogen atoms of nitrofurantoin molecule at lower pH values. This observation was revealed when the dissolution-pH profile was carried out for nitrofurantoin suspension prepared by precipitation of the drug from its alkaline solution(Fig. 9) and stored for one month. This complicated and unexpected solubility patterns leads to the conclusion that the drug is not simply behaving as a weak acid.

A trial to investigate the possibility of the presence of a tautomeric transformation of the drug was done by tracing any change can exist in the position of three characteristic λ maxima of the drug (at 237, 270 and 370 nm.) by changing the pH of the drug solution. Table 2 showed that the three λ max of the drug were changed by changing the pH of the solution which was found to be a reversible change.

CONCLUSIONS

The inter-lot & inter-tablet variations in the dissolution rates of NFT from its commercial products are mainly attributed to the dissolution rate behaviour of the drug powders used for the formulations of the marketed solid dosage forms. These variations cannot be attributed to polymorphic transformations in the crystalline powders of the drug.
The hydrate formation and the unusual solubility and dissolution rate behaviour of the drug in different pH media attract the attention to the possibility that NFT may exhibit tautomeric transformations. This assumption was supported by the results showing that a reversible change of the three characteristic λ max of the drug occurred by changing the pH of the drug solution.
**Table I** — Weight Variation, Porenoy• Disintegration Time, Per Cent Dissolved (Product I & II) and Capsules.

After 30 Minutes, D.K. 70% of Commercial Nitrification Tablets.

<table>
<thead>
<tr>
<th>Capsules</th>
<th>1.87</th>
<th>3.26</th>
<th>14</th>
<th>51</th>
<th>50</th>
<th>1.5</th>
<th>3.99</th>
<th>357</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product I</td>
<td>92.95</td>
<td>4.68</td>
<td>15</td>
<td>71</td>
<td>100</td>
<td>2</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>Product II</td>
<td>72.95</td>
<td>3.83</td>
<td>14</td>
<td>96</td>
<td>100</td>
<td>2.5</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>Product I</td>
<td>81.52</td>
<td>4.28</td>
<td>11</td>
<td>95</td>
<td>100</td>
<td>1.25</td>
<td>159</td>
<td></td>
</tr>
<tr>
<td>Product II</td>
<td>100</td>
<td>5.31</td>
<td>12</td>
<td>86</td>
<td>100</td>
<td>3.8</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>Product I</td>
<td>2.82</td>
<td>4.64</td>
<td>12</td>
<td>95</td>
<td>100</td>
<td>2.66</td>
<td>151</td>
<td></td>
</tr>
</tbody>
</table>

Notes:

N.B.:

* Dissolution Efficiency After 30 Minutes Expressed as Per Cent.

D.K. = 30
Table 2- Effect of the solution pH on the shift of $\lambda_{\text{max}}$ of NFT.

<table>
<thead>
<tr>
<th>pH</th>
<th>Wavelength of the $\lambda_{\text{max}}$ of NFT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>237</td>
</tr>
<tr>
<td>2.2</td>
<td>226</td>
</tr>
<tr>
<td>2.4</td>
<td>237</td>
</tr>
<tr>
<td>3.4</td>
<td>236</td>
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<td>4.4</td>
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<td>234</td>
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<td>6.4</td>
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<td>7.4</td>
<td>233</td>
</tr>
<tr>
<td>8.0</td>
<td>226</td>
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</tbody>
</table>
FIG. (1) DISSOLUTION RATES OF DIFFERENT BATCHES OF NITROFURANTOIN
TABLETS PRODUCT 1 IN DISTILLED WATER AT 37°C
An Investigation On The Dissolution Of Nitrofurantoin

**Figure 2** Dissolution Rates of Five Tablets from the Same Batch of Nitrofurantoin Tablet Product 11 in Dist. Water at 37°C
(Fig. 3) Dissolution Rate of Nitrofurantoin Capsules.
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crystallize from acetone

standard sample

ethyl alcohol solvate

FIG(4) DIFRACTOGRAMS OF NITROFURANTOIN SAMPLES
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**FIG. (6) Dissolution Of Different Commercial Samples Of Nitrofurantoin In Distilled Water At 37°C.**

*Graph showing the amount dissolved (mg/200ml) over time (min) for different samples.*
FIG. 7. "Dissolution Patterns of Different Nitrofurantoin Coatings in Distilled Water at 30°C"
FIG. (9) 15-MINUTES DISSOLUTION-pH PROFILE OF NITROFURANTOIN SUSPENSIONS I AND II AT 37°C.
REFERENCES


دراسة على أداب النيتريفيوراتون
حدي السريدي ـ علي سينا ـ ميد علي إبراهيم ـ خالد علي خالد
قسم الصيدلانيات ـ كلية الصيدلة ـ جامعة أسوان
1974

يناقش هذا البحث مشكلة وجود الاختلافات الواضحة في معدلات اذابة عقار
النيتريفيوراتون من الأقراص سواء في نفس التشغيلة أو بين التشغيلات المختلفة
لنفس نوع الأقراص المحشية على العقار

وقد أثبتت نتائج حديد الأشعة السينية والتحليل الحراري الفعال لخمسة
مساحيق ذات بلورات دقيقة للعقار وتم استخدام في تصنيف الأقراص
العقاران الاختلافات الواضحة في معدلات إذابة فيهما بينما لا ترجع إلى وجود
ظاهرة التأصل البولري في العقار. كا لوحظ أن بلورات العقار يملأ حجمها خمسة
مرات وذلك عند وجود العقار كملعبي وسط مائي سواء كان حمضيا أو معتمدا،
وقد أعطت هذه البلورات ضد علاجها معدلات إذابة انتهائية بضعة متوسطة وهيجور
بلاضط على أن هذه البلورات هي بلورات مائية للعقار.

وقد أوضح دراسة معدل اذابة معلق العقار في البلايك (البحور من محلولة
العقار) بترسيبها ضد الأسدروميديي (ور) في واسطات ذات الأسدروميديي
مختلف ـ احتمال وجود تحولات تنظيمية في جزيئ العقار الذي تأيد بحسب دروت
تغيبية عكسية في طول الموجة ذات أقصى اختاصات الأشعة لحل محل العقار ضد
تغيبية الأسدروميديي للبحور.