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# The compaction properties of nitrofurantoin samples crystallised from different solvents

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## Summary

The compaction properties of samples of nitrofurantoin crystallised from formic acid (FI) and formic acid/water (2 : 1) (NFIII) have been investigated using a fully instrumented single punch tablet machine. Compaction data analysed by means of the Heckel equation, both during compression and after ejection, revealed a greater degree of densification for NFI compared with NFIII. This was attributed to widely dissimilar crystal habits. Yield pressure values calculated from both Heckel plots demonstrated an increased ability of NFI to undergo plastic deformation compared with NFIII. Increased elastic deformation occurred with NFIII as shown by the greater extent of total axial recovery of the compacts compared with those of NFI. The differing degrees of elastic and plastic deformation of these two samples were attributed to their different solid-state properties but it was not possible to distinguish between the effects of the different solvents or the additional drying of NFIII. It was observed that while all the compacts of NFI failed in tension when subjected to a diametral compression test, only a limited number of compacts of NFIII failed in this manner. The different stress distributions within the two sets of compacts leading to this behaviour were attributed to a number of factors including the relative occurrence of groups of different polarity in the crystal faces influencing the bonding mechanisms of the two samples, and different abilities to deform elastically and plastically.

## Introduction

The majority of drugs used in tablets are produced by crystallisation from solution. It has been demonstrated that the use of alternative crystallisation solvents can produce crystals with altered properties, especially the crystal habit (Mullin, 1972; Davey, 1982). Pharmaceutical examples of solvent induced crystal habit modifications include nitrofurantoin (Garti and Tibika, 1980), ibuprofen (Gordon and Amin, 1984) and hexamethylmelamine (Gonda et al., 1985). Whilst the findings of these studies implicated different processing properties for the crystals, few were actually demonstrated.

In a previous study (Marshall and York, 1989) nitrofurantoin was crystallised from formic acid and formic acid/water (2 : 1). Differences in the solid-state and particulate properties of these two

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samples were observed and were primarily attributed to differences in the interactions between nitrofurantoin and the solvent systems during crystallisation. In the present study the compaction properties of the two samples are investigated with an attempt to relate any differences to the properties of the crystals.

## Materials and Methods

*Materials*

Nitrofurantoin was crystallised from both formic acid (NFI) and formic acid/water (2:1) (NFII) as described previously (Marshall and York, 1989). As NFII was shown to be a monohydrate, the water of crystallisation was removed by heating to produce NFIII and allow direct comparison with NFI. The 125–250 $\mu$m fractions of NFI and NFIII were investigated.

*Compaction procedure*

Compaction of crystalline samples was carried out using an instrumented single punch tablet machine (Type E2, Manesty Machines Ltd, Speke, U.K.), fitted with 12.7 mm diameter flat faced punches. Piezo-electric load transducers (Type 901A, Kistler Instruments Ltd, Switzerland) positioned in both the upper and lower punch holders were used to monitor punch pressures. The displacements of both punches were followed by means of linear variable differential transducers (LVDTs) (Type D5/1000 for the upper punch and Type D5/500 for the lower punch; RDP Electronics, Wolverhampton, U.K.). The complete system used for powder compaction including the interfacing of the tablet machine to a microcomputer for the capture and analysis of compaction data, has been described previously (Marshall, 1987). The elastic deformation of the punches under load was determined and was used to correct the compact heights under load.

550 mg of powder were manually transferred into the unlubricated die. This procedure was used to overcome compact weight variability due to the poor flow characteristics of the powders. The powders were compressed at a series of applied loads by adjustment of the eccentric cam. At least four compacts were produced at each load. The compacts were stored for 24 h at 20°C and 40 ± 5% relative humidity prior to testing.

*True density*

The true density of powder samples were determined using an air comparison pycnometer (Model 930, Beckman Instruments Ltd, Fife, U.K.).

*Heckel analysis of compaction data*

From the outputs of the upper punch load transducers and both the upper and lower punch LVDTs, it was possible to calculate the thickness of the compact during a single compression event as a function of the pressure applied by the upper punch. From compact weight and powder true density, data were analysed by the following equation (Heckel, 1961a,b):

$$\ln \frac{1}{1-D} = kP + A \qquad (1)$$

where $D$ is the relative density, the ratio of the compact density, at an applied pressure $P$, to the true density of the powder, and $k$ and $A$ are constants. Heckel plots were constructed for each of the samples compressed to the maximum upper punch pressure applied. Values of $k$ and $A$ were obtained from regression analysis of the linear portion of the plots obtained over the upper punch range of 35–100 MPa. The yield pressure, from the reciprocal of the gradient, $k$, of the linear portion of the plots (Hersey and Rees, 1972) and the extrapolated intercept on the ordinate axis, $A$, were calculated. From $A$, the total densification occurring prior to appreciable interparticle loading, $D_A$, was obtained. The value of $D_0$, the initial densification occurring due to filling of the die, was obtained from the relative density of the powder bed when a pressure was first applied by the upper punch. The densification due to particle slippage and rearrangement, $D_B$, was calculated by subtracting $D_0$ from $D_A$ (Fell and Newton, 1971).

The density of each compact was also determined 24 h after its ejection from its dimensions and weight and these data were analysed by

Eqn 1 to construct Heckel plots after ejection of the compacts. Although only a limited number of data points were obtained, linear portions of these Heckel plots indicated by regression analysis, occurred over upper punch pressure ranges of approx. 52–102 and 63–102 MPa for NFI and NFIII, respectively. The values of the yield pressure, $D_A$ and $D_B$ were calculated as described above. The values of $D_0$ obtained from the plots during the compression of the two samples were also used for the Heckel plots constructed after ejection.

*Analysis following the recovery of compacts*

The heights of each of the compacts of the two samples under the maximum upper punch pressure applied were calculated from the outputs of the two LVDTs. 24 h after their ejection, the heights of the compacts were measured using a micrometer gauge. The total axial recovery of each ejected compact, which is dominated by the elastic component of postcompression material relaxation, was calculated by the following equation (Armstrong and Haines-Nutt, 1972):

$$\text{Percentage total axial recovery} = \frac{H - H_c}{H_c} \times 100 \quad (2)$$

where $H_c$ and $H$ are the heights of the compact under pressure and after ejection, respectively. The mean value of the percentage total axial recovery at each of the pressures applied was calculated and plotted against the maximum upper punch pressure.

*Analysis of the compact tensile strength*

Compact crushing strengths were determined by means of a diametral compression test, 24 h after ejection. The device used for this purpose has been previously described in detail (Marshall, 1987). It consisted essentially of a motor that was able to drive a ram downwards at a constant rate of 1 mm/min and a load transducer (Type 903A, Kistler Instruments Ltd, Switzerland). The load transducer was interfaced to a microcomputer to capture and analyse the data. All the compacts of NFI split into two halves along the loaded diameter during the test, indicating tensile failure (Rudnick et al., 1963; Fell and Newton, 1970) thus permitting calculation of tensile strengths using the following equation (Rudnick et al., 1963; Fell and Newton, 1970):

$$\text{Tensile strength} = \frac{2P}{\pi D t} \quad (3)$$

where $P$ is the applied load and $D$ and $t$ are the compact diameter and thickness, respectively. Only a limited number of compacts of NFIII failed in tension. Plots of tensile strength versus maximum upper punch pressure and porosity were drawn, using mean data for NFI and individual data points for NFIII.

## Results and Discussion

Representative Heckel plots obtained during the compression of NFI and NFIII are illustrated in Fig. 1. The form of the two plots is very similar. Initial curved portions are attributed to densification of the powder bed occurring by particle movement and rearrangement (Heckel, 1961a,b; York and Pilpel, 1973), while above an upper punch pressure of 35 MPa the linear plots indicate deformation of the particles. These trends have been observed in other studies which have used the Heckel equation to analyse compaction data

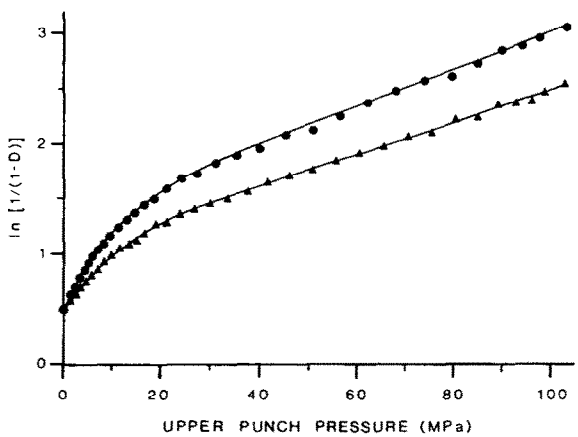


Fig. 1. Representative Heckel plots obtained during compression of nitrofurantoin samples. (●) NFI, (▲) NF III.

(e.g. Heckel, 1961a,b; York and Pilpel, 1973; Duberg and Nystrom, 1986), and the derived values from the Heckel plots are listed in Table 1. Fig. 1 also demonstrates that the degree of densification that occurred during compression was greater for NFI as compared to NFIII at all pressures. This is attributed to the markedly different crystal habits of these two samples (Marshall and York, 1989). The plate-like crystals of NFI with correspondingly low aspect ratios would have been able to achieve a greater degree of packing than the needle-like crystals of NFIII which possessed higher aspect ratio. This was due to the particles of NFI overcoming interparticulate frictional forces to a greater extent.

Despite the relatively low value obtained for the correlation coefficient of the linear portion of the Heckel plot, $r$, for NFI (see Table 1), the yield pressures for the two samples were shown to be significantly different ($p < 0.001$) by means of a Student's $t$-test. It is unlikely that the dissimilar crystal habits of these two samples influenced the yield pressures since the ability of a material to deform plastically is thought to be dependent upon molecular rather than particulate properties. The observed differences in the yield pressures are attributed to the dissimilar solid-state properties of these samples discussed previously (Marshall and York, 1989). However, it is not possible at present to specify whether the effect on the solid-state properties due to the different solvents employed or the additional drying and subsequent internal restructuring of NFIII, or a combination of the two processes, was the primary cause of the difference in yield pressure.

As discussed previously (Marshall and York, 1989) there were differences in the interactions between the solvent and solute molecules at the various crystal/solution interfaces during the crystallisation of these two samples. This would be expected to alter the pattern and distribution of defects within the crystals and, as a result, the crystals would exhibit different abilities to deform with variation in their yield pressures.

TABLE 1

*Data calculated from Heckel plots obtained during the compression of nitrofurantoin samples NFI and NFIII*

| Sample | Yield pressure (MPa) | $D_A$ | $D_0$ | $D_B$ | $r$ |
|---|---|---|---|---|---|
| NFI | 59.3 | 0.737 | 0.389 | 0.348 | 0.9746 |
| NFIII | 69.4 | 0.650 | 0.380 | 0.270 | 0.9940 |

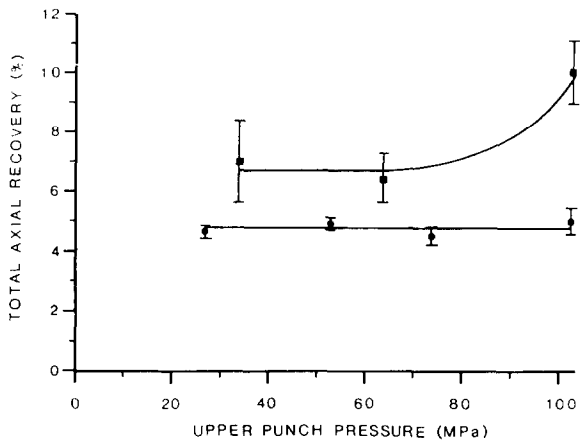


Fig. 2. Percentage total axial recovery versus upper punch pressure for nitrofurantoin samples. (●) NFI, (■) NF III.

It has been claimed that the drying of materials improves their compression properties due to an increase in the level of crystalline disorder (Huttenrauch, 1982, 1983). However, it has also been demonstrated that the thermal dehydration of hydrates causes a transition in their compaction behaviour to a more brittle nature as reflected by an increase in the yield pressure of dehydrated dextrose monohydrate (Armstrong and Patel, 1986) and a different pore distribution of compacts of dehydrated lactose monohydrate (Lerk, 1984). Thus, the rearrangement of the crystal structure associated with the removal of water of crystallisation, reflected by the 4% difference in the true densities and differences in the X-ray powder diffraction spectra of NFI and NFIII (Marshall and York, 1989), may have been responsible for the increased resistance of NFIII to deform.

In Fig. 2 the degree of axial recovery for both nitrofurantoin samples following compression, is shown with NFIII exhibiting a higher recovery at all pressures. As discussed above when interpreting yield pressures, it seems unlikely that dissimilar crystal habits are responsible for the increased total axial recovery of NFIII. However, it is again

not possible to distinguish between the effect on the solid-state properties of the different crystallisation solvents, or the additional drying of NFII or both processes as the causative factor. As a result of the different interactions discussed above and the modified growth rates of certain crystal faces, the relative abundance of planes within the crystal in any given direction would have been altered. The environment for intermolecular bonding within crystals would also have been changed, which in turn could have affected the relative abilities of these bonds to recover and be re-established following the removal of pressure.

The increased ability of NFIII, which had undergone thermal dehydration, to recover axially, is consistent with published data for anhydrous dextrose prepared from a monohydrate form (Armstrong and Patel, 1986). The process leading to the removal of water of crystallisation and the associated restructuring of the crystal causes an increase in the axial recovery, and therefore the inherent elastic properties, for these materials.

The pattern of total axial recovery with increasing pressure was also influenced by the solvent of crystallisation (see Fig. 2). For NFI the degree of recovery was independent of the maximum upper punch pressure over the range investigated. This trend was unexpected, as in previous studies employing Eqn 2 increases in the total axial recovery with increasing pressure were observed (e.g. Krycer et al., 1982a,b). Thus data in Fig. 2 indicate that a limiting total axial recovery was attained with a continuously decreasing proportion of the energy of compression utilised in elastic deformation. Initially NFIII displayed a recovery pattern that was similar to that of NFI but at increased pressures a greater proportion of the compressional energy was utilised in elastic deformation.

The Heckel plots obtained after the ejection of the compacts of these two samples (Fig. 3) were similar in form to those obtained during the compression process, as was the greater degree of densification exhibited by the compacts of NFI compared to those for NFIII. The different crystal habits of these two samples, discussed above, again appears to play a major role in these processes. However, an additional factor, the ability of the compacts to recover axially following their ejection, also influenced the final density of the compacts. As expected, axial recovery caused the density of the ejected compacts of both samples to be lower at all pressures investigated than those during the compression process.

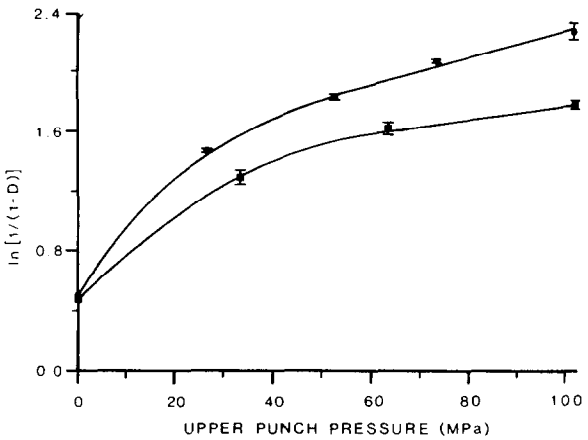


Fig. 3. Heckel plots obtained after ejection of the compacts of nitrofurantoin samples. (●) NFI, (■) NF III.

The yield pressures for the two samples calculated from the Heckel plots constructed after compact ejection (Table 2) clearly indicate different deformation characteristics for the two samples. The factors discussed above for the Heckel plots obtained during compression again played a major role but as with the degree of densification that occurred, the axial recovery of the compacts also influenced the yield pressures obtained. Since the yield pressures determined from Heckel plots obtained after compact ejection reflect the permanent deformation undergone by a material due to plastic deformation (Krycer et al., 1982c; Paronen and Juslin, 1983), the extent of consolidation due to this mechanism for NFI and NFIII is markedly

TABLE 2

*Data calculated from Heckel plots obtained after ejection of the compacts of nitrofurantoin samples NFI and NFIII*

| Sample | Yield pressure (MPa) | $D_A$ | $D_0$ | $D_B$ | $r$ |
|---|---|---|---|---|---|
| NFI | 113.6 | 0.748 | 0.389 | 0.359 | 0.9898 |
| NFIII | 255.1 | 0.743 | 0.380 | 0.363 | ND |

ND, not determined.

different. Thus the yield pressure value obtained from NFIII during compression is falsely low as has been observed in other studies (e.g. Fell and Newton, 1971; York, 1979) and reflects its total ability to deform, a large extent of which is due to an elastic component.

As shown by Fig. 4 a linear relationship between compact tensile strength and maximum upper punch pressure was obtained for NFI. However, a limited number of NFIII compacts failed in tension during the diametral compression test with the others failing along the axis perpendicular to the loaded diameter. Tensile strength values did not appear to follow a pattern with increasing upper punch pressure but were typically higher than those obtained at the same pressure for NFI.

A number of factors may have contributed to the different stress distributions within the compacts. The dissimilar crystal habits of these two samples may have had a role to play. As discussed previously (Marshall and York, 1989), NFI would have contained larger non-polar crystal faces than NFIII, where polar faces would have predominated due to the less polar formic acid interacting more strongly with non-polar faces during crystallisation. As a consequence, the difference in the relative abundance of non-polar and polar groups in the faces of these two samples may have affected the mechanisms, frequency and magnitude of bonding that occurred during compression, leading to dissimilar stress distributions within the two sets of compacts. As discussed above, the relative ability of these two samples to deform was different, with NFIII displaying a higher degree of axial recovery following compact ejection compared to NFI. Thus bonding of NFIII that took place during compression, would have been more prone to the disruptive effects of this recovery process than that which occurred with NFI.

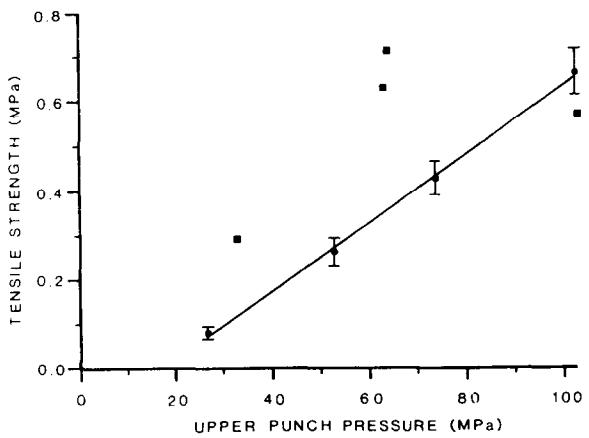


Fig. 4. Compact tensile strength versus upper punch pressure for nitrofurantoin samples. (●) NFI, (■) NF III.

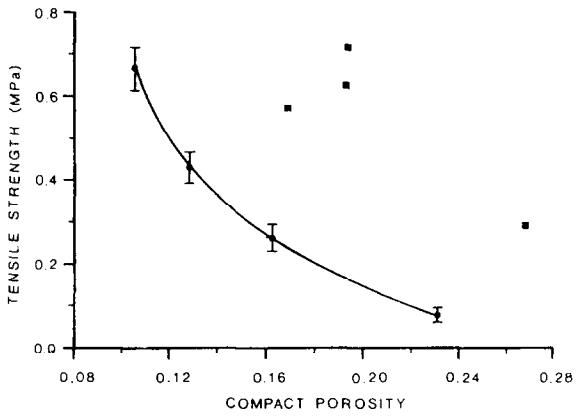


Fig. 5. Compact tensile strength versus compact porosity for nitrofurantoin samples. (●) NFI, (■) NF III.

An increase in compact tensile strength occurred for NFI as compact porosity decreased (Fig. 5). The decrease in porosity was a result of particle deformation producing bonding which gave strength to the compacts. The strength of the compacts of NFIII that failed in tension was generally higher than that of NFI at similar porosities.

Owing to the limited number of compacts of NFIII that failed in tension, it is not possible to state whether the higher tensile strengths observed represent an increased bonding ability compared to NFI. The absence or presence of tensile failure in the compacts of NFIII demonstrated that the overall bonding that occurred was not reproducible. When tensile failure did not occur the disruptive influences discussed above predominated. However, when it did occur, the tensile strength of the compact was increased, compared to similar compacts of NFI, due to an as yet unrecognised mechanism.

## Conclusions

The compaction properties of samples of nitrofurantoin crystallised from formic acid (NFI) and formic acid/water (2 : 1), (NFIII) were found to be different. As one of the samples, NFIII, had undergone additional drying it was necessary to consider both the effects of this process and the alternative crystallisation solvent on the solid-state properties of the two samples when examining the different compaction behaviour of these samples. Heckel plots constructed both during compression and after ejection revealed a greater degree of plastic deformation for NFI compared with NFIII. However, the compacts of NFIII demonstrated a greater ability to recover axially following load removal, compared with those of NFI. During diametral compression testing all the compacts of NFI, but only a limited number of NFIII, failed in tension.

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