OBSERVATIONS ON INCREASED DISINTEGRATION TIMES OF TABLETS ON STORAGE

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An attempt has been made to devise a simple and rapid method for determining whether tablets produced from a particular mass will show a significant increase in disintegration time on storage.

In the following experiments, an eight millimetre diameter punch on a single punch Comprex press was used. A sample of as soft a tablet as could possibly be handled was first made, followed by samples of tablets at gradually increasing pressures until the maximum pressure that could be applied by hand operating the machine was reached. The mass was hand filled into the die.

The "compression ratio"[1] was calculated by dividing the weight of the tablet in milligrammes by its height in millimetres. The disintegration

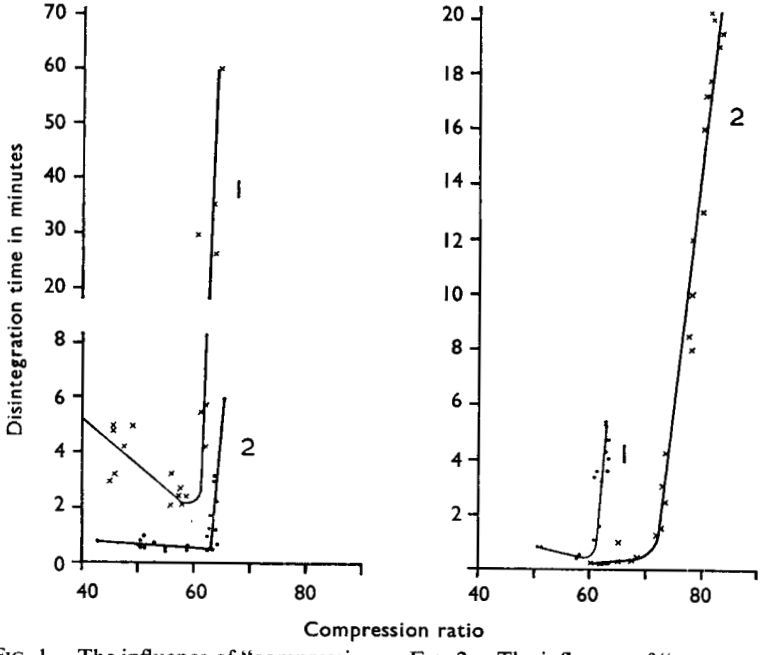

Fig. 1. The influence of "compression ratio" (weight/height) on the disintegration time of two formulations of glutethimide tablets (1) and (2), using an 8 mm. diameter punch.

Fig. 2. The influence of "compression ratio" (weight/height) on the disintegration time of calcium thiocyanate nikethamide/theophylline tablets (1) and of phenyl (α-piperidyl) acetic acid methyl ester tablets (2) using an 8 mm. diameter punch.

time of the tablet in minutes was found by the B.P. method, one tablet at a time being tested. Graphs were prepared from the "compression ratio" and the disintegration time.

The results from the tablets made from a typical sample of a glutethimide mass are shown in Figure 1 (1). This mass contained 71 per cent glutethimide with gelatin and wheat starch as binders, wheat and arrowroot starches as disintegrating agents and magnesium stearate and talc as lubricants. Normal tablets made to this formula had an original disintegration time of under three minutes but after six months storage the disintegration time approximated to thirty minutes.

A typical sample of a second glutethimide mass was then examined. This mass also contained 71 per cent glutethimide and the same binders, disintegrating agents and lubricants, but 0·25 per cent of a wetting agent was added. The results are shown in Figure 1 (2). Normal tablets using this formula and process had shown no increase in disintegration time after two years storage.

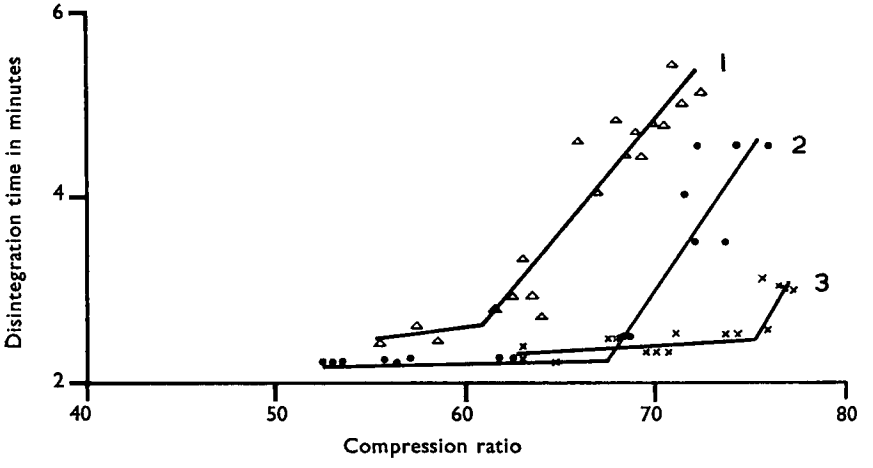

FIG. 3. The influence of "compression ratio" (weight/height) on the disintegration time of tolazoline tablets (1), of reserpine tablets (2) and of sulphathiazole tablets (3) using an 8 mm. diameter punch.

The graphs of "compression ratio" and disintegration time for freshly prepared tablets containing calcium thiocyanate, nikethamide, and theophylline, and of phenyl (α-piperidyl) acetic acid methyl ester are shown in Figure 2 (1 and 2). Normal tablets containing calcium thiocyanate, nikethamide, and theophylline gave an original disintegration time of thirty seconds which increased to fifteen minutes after three years storage, while tablets of phenyl (α-piperidyl) acetic acid methyl ester gave an original disintegration time of three minutes increasing to six minutes after three years storage.

The graphs of "compression ratio" to disintegration time for freshly prepared tablets of tolazoline hydrochloride, reserpine and sulphathiazole are shown in Figure 3 (1, 2 and 3). Normal tablets of these products gave no increase in disintegration time after three years storage.

For each tablet mass tested there exists a critical tabletting pressure. When this pressure is exceeded, the disintegration time of the tablets is increased. This phenomenon was illustrated by Berry and Ridout[1] who studied phenacetin tablets with 15 per cent potato starch and phenacetin tablets with various proportions of alginic acid as disintegrant, and also by Higuchi and others[2] in their studies on aspirin, lactose, lactose-aspirin and sulphadiazine tablets.

The graphs may be used to indicate whether tablets produced from a particular mass will show a significant increase in disintegration time on storage.

Comparing the graphs of the "compression ratio" to disintegration time for the two sets of glutethimide tablets, the main differences are (1) the variation in the size of the angle formed by the two approximately straight lines making up each graph and (2) the pronounced difference in the disintegration time of the tablets made under the maximum compressional force applied. The disintegration time of normal tablets from the first mass increased from under three minutes when freshly prepared to approximately thirty minutes after six months storage, whereas the disintegration time of the tablets made from the second mass remained unchanged after two years storage. Therefore, the greater the value of this angle and the lower the initial disintegration time at maximum compression, the less the risk of obtaining tablets with increased disintegration time on storage.

The graphs of the "compression ratio" to disintegration time for the other products tested show that the calcium thiocyanate, nikethamide and theophylline, tablet graph and the phenyl (α-piperidyl) acetic acid methyl ester tablet graph exhibit relatively acute angles in comparison to the angle exhibited by either the tolazoline hydrochloride, reserpine or sulphathiazole tablets graphs. The suggestion that the smaller the angle formed by the lines making up each graph, the greater the risk of obtaining increased disintegration times of the tablets on storage applies to the products investigated.

It will be necessary to study a much wider range of products and formulations to prove that these observations are applicable in all cases.

REFERENCES

1. Berry and Ridout, *J. Pharm. Pharmacol.*, 1950, **2**, 619.
2. Higuchi, Elowe and Busse, *J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 688.

DISCUSSION

The Short Communication was presented by the AUTHOR.

THE CHAIRMAN. Had the Author any views about the mechanism responsible for the increasing disintegration time on storage? Did the angle between the two portions of the graph take into account all the factors?

MR. D. STEPHENSON (Dartford). The Author had recorded results with and without a wetting agent. Had the addition of the wetting agent

in a volatile solvent in which the glutethimide ingredients were insoluble been tried, and had the results been compared with a granulation in which the wetting agent had been included from the beginning?

DR. D. TRAIN (London). Was there any evidence that the 0·25 per cent of wetting agent affected the strength of the tablet or resistance to abrasion?

MR. H. S. BRAGG (Folkstone). Could details of the weight and thickness of the tablets be given? Hand manipulation might give a very hard tablet which would not be obtained in practice.

MR. G. R. WILKINSON (London). Had an attempt been made to measure the pressure in the tabletting machine used?

PROFESSOR E. SHOTTON (London). The compression ratio did not necessarily give a true measurement of the compression. Were the tablets of constant weight? The compression ratio was valid only with one set of punches and dies, and its effect would depend on whether the punches were flat or concave. Which were used?

MR. A. BRAGG (Liverpool). Were the granule size, fines content and moisture controlled? All these factors would affect the disintegration time and might have a significant effect on storage.

MR. ANDERSON (Liverpool). What were the storage conditions? What was the wetting agent used and why was it chosen?

MR. N. S. VAN ABBÉ (Loughborough). He had observed that fluctuating temperature in a sealed container could give a hardening effect, possibly due to redistribution of moisture and this, together with compression, might be the mechanism responsible for the effects.

THE AUTHOR replied. Increase in disintegration time was often experienced in tablets with a high proportion of active ingredient and with ingredients of low melting point and high solubility in water. The wetting agent had been added to the original mass and not to the granules. A wetting agent allowed water to penetrate the mass and the disintegration at maximum pressure was affected but there was no difference in hardness. The abnormal pressures were used only to see whether the formulation was suitable, normal pressure would give tablets on the horizontal part of the graph. They had no means of measuring the pressure and, therefore, used relative compression. The graphs could only be used for a particular set of dies and punches, and those used were flat. The tablets were 200 mg. $\pm$ 10 per cent. They had tried to keep the method of production of the granules the same; no analysis of granule size had been made. The moisture content was probably a significant factor in the increased disintegration time on storage. Normal laboratory conditions were used in storage. The wetting agent was a sodium laurylsulphate.