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# The influence of compression and formulation on the hardness, disintegration, dissolution, absorption and excretion of sulphadimidine tablets

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Sulphadimidine tablets were prepared with different binding agents and compressed at different compression levels, ranging from 200–2000 $MNm^2$. The disintegration time and dissolution rate of the different tablets were determined. Tablets formulated with gelatin or starch mucilage and compressed at 600 $MNm^2$ were selected for *in vivo* experiments using a urinary excretion method. Although both tablets complied with the disintegration requirements of the British Pharmacopoeia, dissolution rate and urinary excretion showed a difference in availability of drug from the two tablets.

Recently it was shown that a dissolution rate method in combination with an urinary excretion method can be used to evaluate sulphonamide tablets from different sources. With both methods a large difference in availability was found between sulphadimidine tablets from different sources. This was not so with sulphafurazole tablets, where all of the tablets had a rapid dissolution rate (Goossens & Van Oudtshoorn, 1969; van Oudtshoorn & Potgieter, 1970).

The dissolution rate of sulphamidine tablets has been examined by Smits & Nienhuis (1969), and the effect of dissolution rate from tablets on the absorption and excretion of sulphadimidine, using blood level data by Taraszka & Delor (1969). Dissolution rate methods were also used to study the effect of granulating agents on the dissolution time of sulphadimidine from tablets (Krowzynski & Stozek, 1968).

We have examined the effect of different compressional forces and formulation factors on the parameters used to characterize a particular sulphadimidine tablet formulation.

## MATERIAL AND METHODS

*Sulphadimidine powder*, with an arithmatic mean particle size of 9·6 $\mu$m was used to prepare three different tablet formulations, I, II and III, each containing drug, 500 mg, starch 82 mg and magnesium stearate 6 mg. Formulation I was massed with methylcellulose (4 mg/tablet) (Tylose MH50), formulation II with 8% starch mucilage (12 mg/tablet) and formulation III with 8% gelatin mucilage (12 mg/tablet).

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*Method of preparation.* Formulation I was prepared according to the micro-granulation technique of de Jong (1969). The sulphadimidine and starch were mixed in a plough-type mixer (Lödige) during 30 min. Methylcellulose was added as a 5% aqueous solution in three portions. The wet mass was passed through an 8 mm screen in a hammer mill (Apex). The microgranules were dried over 6 h at 35° and passed through a 310 $\mu$m screen.

Formulation II and III were prepared by mixing the sulphadimidine and starch in a planet type mixer while the mucilages of starch and gelatin respectively were added in small portions. Granulation was in a Manesty oscillating granulator with a 710 $\mu$m screen. The mass was dried at 35° over 16 h and passed through a 1200 $\mu$m screen. Before compression the three formulations were mixed with 5% starch and 1% magnesium stearate.

*Compression.* Tablets of 13·5 mm were compressed with flat punches on a single punch tablet machine, instrumented and calibrated as described by de Blaey and Polderman (1970). Six different compression levels varying from 200–2000 $MNm^2$ were chosen to obtain information over a wide compression range. The tablets were compressed once without ejection and a second time in order to calculate the work required to compress a particular formulation. The measurement was done by using force-displacement curves (de Blaey & Polderman, 1970). The hardness of the tablets was determined with a Heberlein hardness tester.

*Assay method.* The method of the British Pharmacopoeia (1968) was used for both the tablets and the powder.

*Tablet disintegration.* The tablet disintegration time was determined according to the British Pharmacopoeia (1968) using a Manesty tablet disintegration test unit with and without a disc.

*Dissolution rate.* Dissolution rate determinations were made using a beaker apparatus similar to that of Ganderton, Hadgraft & others (1967); 0·1N hydrochloric acid at 37° in a constant temperature bath was used as dissolution medium. The stirring rate was 100 rev/min. Samples were assayed continuously using an automated Bratton & Marshall (1939) method. The volume was kept constant by continuous addition of dissolution medium at 37°.

*In vivo experiments.* Tests were made on three healthy males between the ages of 22 and 28 who were slow acetylators of sulphadimidine (White & Evans, 1968). Two sulphadimidine tablets (1 g) were taken after an overnight fast and no food was taken for at least 1 h after. Quantitative urine collections were obtained at the times in Fig. 1. Aliquots of urine specimens were assayed according to Bratton & Marshall (1939) for free and total sulphadimidine. All hydrolysable conjugates were regarded as acetylated drug. The experiments took place under normal urine conditions. A digital computer program was used to calculate the rate and other constants according to the pharmacokinetic model and differential equations described by Nelson & O'Reilly (1960).

## RESULTS AND DISCUSSION

Only two of the tablets from the tablet series (II and III compressed with an upper punch pressure of 200 $MNm^2$) would not have been acceptable according to the disintegration time requirements of the British Pharmacopoeia (1968) (Table 1). Their disintegration time with the disc was more than 15 min. When the time required for 50% of drug to go into solution (T50%) is also considered for II the

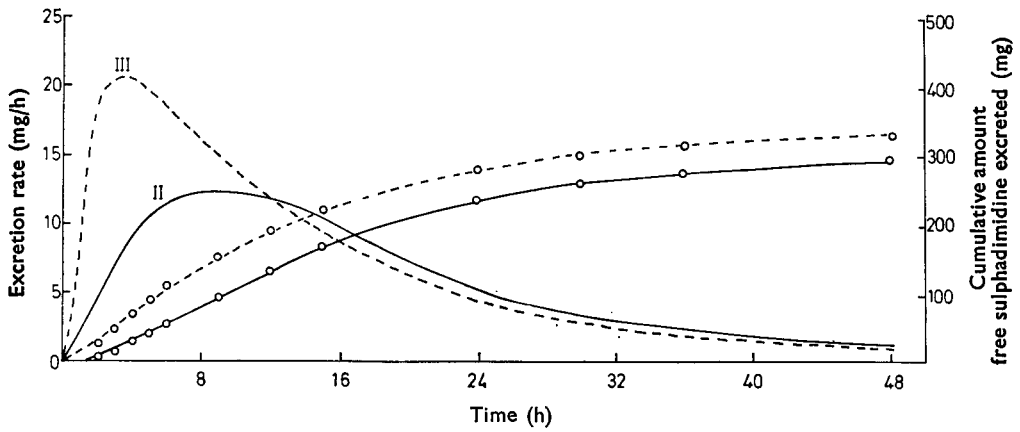


FIG. 1. Computed curves and experimental data points (○) for urinary excretion of free sulphadimidine from tablets II and III for test subject A under normal urine conditions.

dissolution time is much longer than the disintegration time and there is no correlation between dissolution rate and disintegration time as was shown by van Oudtshoorn & Potgieter (1970) for a series of sulphadimidine tablets.

Tablets of the three formulations compressed with an upper punch pressure of 600 $MNm^2$ were selected for further *in vitro* and *in vivo* tests because of the relatively short disintegration time, hardness and low friability. During the dissolution rate determinations it became obvious that tablet II had a much slower dissolution rate than might have been anticipated. Tablet I with the fastest disintegration time (0·91 min) also gave the best *in vitro* performance. This can be attributed to the microgranulation technique used and also to the hardness (8·5 kg) which is much lower than that of tablets II and III although compressional forces during manufacture were identical.

Because tablets II and III had approximately the same disintegration time, but different dissolution behaviour, they were selected for further *in vivo* experiments using a urinary excretion method. The results for one test subject are in Fig. 1. Both the cumulative amount of free sulphadimidine excreted as well as the excretion rate calculated from the slope of the cumulative amount excreted are given. The total amounts of sulphonamide excreted by the three test subjects over 48 h are shown in Table 2. From the figure for tablet II the dissolution rate can be seen to be a rate

Table 1. *Hardness, disintegration and dissolution of sulphadimidine tablets I, II and III.*

| Upper punch pressure ($MNm^2 \pm 20$) | Hardness* (kg) (Heberlein) | | | Disintegration time* (min) Without disc | | | With disc | | | Dissolution* ($T_{50\%}$, min) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | I | II | III | I | II | III | I | II | III |
| 200 | 3·0 | 5·2 | 5·5 | 0·68 | >40·0 | >40·0 | — | >40·0 | >40·0 | 0·5 | 54·0 | 10·0 |
| 400 | 5·5 | 8·0 | 11·5 | 0·68 | >40·0 | 26·8 | — | 3·6 | 11·7 | 0·8 | 42·0 | 4·5 |
| 600 | 8·0 | 12·5 | 15·5 | 0·92 | 7·1 | 6·0 | — | 1·7 | 7·1 | 1·1 | 35·0 | 3·0 |
| 800 | 10·0 | 15·0 | >16·0 | 1·07 | 4·1 | 8·0 | — | 1·3 | 6·6 | 1·2 | 10·0 | 4·6 |
| 1000 | 12·0 | >16·0 | >16·0 | 1·7 | 2·5 | 10·8 | — | 1·0 | 10·7 | 1·4 | 7·0 | 4·9 |
| 2000 | 15·0 | >16·0 | >16·0 | 4·00 | 2·3 | 12·4 | — | 2·1 | 10·8 | 1·8 | 3·3 | 6·5 |

* All figures are the average of three determinations.

Table 2. *Urinary excretion values (mg total sulphonamide) for three test subjects after ingestion of two sulphadimidine tablets (1·0g) II and III.*

| Time (h) | Tablet II Test subject A | B | C | Tablet III Test subject A | B | C |
|---|---|---|---|---|---|---|
| 1 | 1·75 | 2·15 | 2·41 | 10·25 | 15·60 | 14·31 |
| 2 | 8·76 | 10·10 | 10·43 | 40·62 | 49·10 | 47·57 |
| 3 | 21·10 | 23·85 | 25·05 | 82·67 | 92·94 | 86·50 |
| 4 | 38·42 | 43·05 | 43·31 | 126·30 | 137·97 | 125·73 |
| 5 | 61·26 | 66·81 | 68·15 | 171·04 | 184·31 | 163·55 |
| 6 | 87·61 | 94·39 | 96·47 | 207·84 | 224·35 | 197·94 |
| 9 | 183·25 | 193·73 | 198·09 | 334·50 | 355·98 | 318·47 |
| 12 | 285·17 | 301·58 | 304·82 | 448·65 | 473·28 | 422·09 |
| 15 | 372·30 | 391·90 | 393·34 | 539·01 | 562·70 | 510·9 |
| 24 | 545·56 | 560·86 | 563·77 | 715·62 | 718·95 | 670·22 |
| 36 | 635·95 | 645·69 | 654·35 | 803·95 | 804·27 | 760·65 |
| 48 | 668·70 | 676·48 | 682·33 | 832·09 | 834·78 | 787·63 |

limiting factor in the absorption process. The results are in agreement with those published earlier on sulphadimidine tablets of unknown composition (van Oudtshoorn & Potgieter, 1970).

During the dissolution experiments on tablet II it was noticed that a part of the tablet core was still intact on completion of the dissolution experiment. This might explain the low recovery of sulphadimidine in this particular *in vitro* and *in vivo* experiment. It is doubtful whether the difference observed between the two tablets would influence the therapeutic efficacy of the particular product to any extent. It does, however, show that an *in vitro* test procedure may be used to study the effects of formulation and process changes and to verify the physical quality of a product.

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