# THE DISINTEGRATION OF COMPRESSED TABLETS

## The Effect of Age and Certain Associated Factors

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It is the purpose of this paper to examine some of the factors which influence the disintegration of a tablet, and then assess the possible effect of ageing upon the disintegration time of tablets after storage. In the past, reference has been made to the fact that tablets may show variation in their time of disintegration when stored over prolonged periods[1,2,3]. This has been summarised by Berry and Nutter Smith[2] who stated that ". . . Some tablets tend to harden on keeping, though this is by no means universal . . . . It is necessary, of course, to know the disintegration times when the tablets were first made before definite conclusions can be drawn as to the progressive effect of age."

The breakdown in water of a tablet consisting entirely of soluble substances is one of solution rather than disintegration. An examination was therefore made of tablets consisting of drugs which are either insoluble or slowly soluble in water. Disintegration is usually brought about by the use of one of a variety of starches, and all experimental tablets contained starch as a disintegrant.

Preliminary experiments showed that a study must be made of other factors which may have an adverse effect upon the initial disintegration of a tablet, and therefore obscure the effect due to age. The following factors are those primarily concerned in the initial rate at which a tablet disintegrates:—

(1) The variety of starch used.
(2) The amount of starch contained in the tablet.
(3) The method of granulation.
(4) The nature of the moistening agents.
(5) The pressure used during tableting.

As a result of this work, a formula was devised for use in preparing a series of tablets which, when freshly made, would disintegrate rapidly. Tablets thus produced were kept over a period of four years, and determinations made of the rate of disintegration after certain intervals of time.

Before discussing the experiments it is important to define the nature of the tests used in the physical examination of the various batches of tablets.

## Experimental

*Disintegration Test.* The British Pharmacopœial apparatus was used and the time taken when complete disintegration was observed in all 5 tubes. These times were recorded to the nearest half minute.

*Friability Value.* Hardness in tablets is a term which is difficult to define. A number of tests have been suggested from time to time, but the true test is that the tablet should reach the consumer in as good a condition as when it was made. It must, therefore, be hard enough to be handled in bulk quantities without "rubbing" and to withstand the hazards of packaging and transit tests. It is desirable to have some mechanical means of measuring this resistance to wear, other than the time-honoured method of the snap produced when a tablet is broken between fingers and thumb.

If a weighed number of tablets are vigorously agitated by controlled mechanical means for a fixed period of time, the percentage of powder produced by this treatment indicates the resistance to wear of the tablet and may be called the Friability Value.

In practice, 20 tablets were weighed into a two ounce, screw-capped, wide mouthed, round bottle, and placed in a laboratory shaking machine, similar to the one which has been fully described and illustrated in a recent paper by Nutter Smith[4]. After shaking for 5 minutes, the powder produced was separated from the tablets by means of a sieve (16 mesh. 26 S.W.G.). The rubbed tablets were weighed and the difference, expressed as a percentage of the original weight, was called the Friability Value. Findings are given to the nearest whole number.

It is important that there should be no tendency towards "capping" in the batch, otherwise an unduly high value will be obtained.

*Moisture Content.* The moisture contents of the tablets were determined by drying to constant weight at 100°C., except in the cases of aspirin, cinchophen, sulphonal, guaiacol carbonate, guaiacum and sulphur and mercury with chalk, which were dried in a vacuum desiccator over concentrated sulphuric acid. Determinations were made upon freshly produced tablets, and after storage for four years.

*Granulation Processes.* In preparing batches of tablets, use was made of the three recognised methods of granulation. These may be described briefly as follows:—

*Moist Granulation Process.* This may be divided into two methods, A and B, depending upon whether all the starch is included when the mixed powders are moistened, or added as a powder to the dried granules.

*Dry Granulation Process.* If the drug is insoluble, it is reduced to a suitable particle size and with it is mixed an amount of dried starch. The mixture is then suitable for compression.

*Granulation by Preliminary Compression.* The starch and other ingredients, in fine powder, are well mixed and roughly compressed into large tablets. These are broken down into granules of suitable size before final tableting.

Granules obtained by the above methods may require the addition of a lubricant before compression.

*An Examination of Common Varieties of Starch.* The use of starch as a disintegrating agent lies in its property of rapidly absorbing water, thereby swelling and creating a pressure inside the tablet, which

causes it to disintegrate. The following starches may be used:—maranta, potato, sago, tapioca, maize and rice. In order to determine their comparative values, 6 batches of tablets of phenobarbitone were made, differing only in the fact that each contained 15 per cent. of a different variety of starch. The moist granulation process A was used and care taken to ensure that there was no alteration in pressure whilst making the tablets. Similarly, 6 batches of aspirin tablets were made by the dry granulation process using 9 per cent. of starch. The disintegration times for the tablets and the moisture contents of the starches are shown in Table I.

TABLE I

DISINTEGRATION TIMES OF TABLETS MADE WITH DIFFERENT STARCHES

| | Moisture content | Phenobarbitone gr. 1 | Aspirin gr. 5 |
|---|---|---|---|
| | per cent. | | |
| Potato starch ... ... ... ... | 13·1 | < ½′ | < ½′ |
| Sago ,, ... ... ... ... | 14·9 | < ½′ | < ½′ |
| Maranta ,, ... ... ... ... | 15·4 | < ½′ | < ½′ |
| Tapioca ,, ... ... ... ... | 12·5 | < ½′ | < ½′ |
| Maize ,, ... ... ... ... | 8·5 | < ½′ | < ¼′ |
| Rice ,, ... ... ... ... | 12·1 | < 1′ | < ½′ |

Reference to this table indicates that, using the amounts of starch shown above for the purpose of disintegration, there is no significant difference in any of the six varieties, despite considerable variation in the size of the starch grains. It was decided to use maize starch as the disintegrating agent in all future experiments.

*The Amount of Starch Contained in the Tablet.* Whilst 15 per cent. and 9 per cent. of maize starch were used in the above experiment, and proved satisfactory, it is desirable to investigate the effect of starch when used as in disintegrant in larger or smaller proportions.

Batches of tablets of phenobarbitone, phenobarbitone and theobromine, and sulphathiazole were made by the moist granulation process A and tablets of aspirin by the dry granulation process. Varying amounts of maize starch from 0 per cent. to 20 per cent. were used in each case and lactose was used to replace starch in the varying proportions.

It is seen that 10 per cent. of maize starch is adequate to ensure disintegration within the pharmacopœial limits for the four different tablets examined. To give a margin of safety, 15 per cent. of starch is to be used for all future experimental batches made by moist granulation process A.

*The Method of Granulation.* In this experiment, tablets were made by three of the processes previously described:—Moist granulation process A; moist granulation process B; granulation by preliminary compression.

A constant amount of disintegrant was added for three different methods of granulation in order to ascertain whether this results in a noticeable variation in the disintegration times of the tablets.

TABLE II

EFFECT OF PERCENTAGE OF STARCH ON DISINTEGRATION TIMES

| Maize starch per cent. | Phenobarbitone gr. 1 | Phenobarbitone and theobromine B.P.C. | Sulphathiazole 0·5 g. | Aspirin gr. 5 |
|---|---|---|---|---|
| 0 | >60′ | >60′ | >60′ | >60′ |
| 1 | >60′ | 45′ | 5′ | >60′ |
| 2 | >60′ | 40′ | 2′ | >60′ |
| 5 | 40′ | 1′ | ½′ | 1′ |
| 10 | 5′ | < ½′ | < ½′ | < ½′ |
| 20 | < ½′ | < ½′ | < ½′ | < ½′ |

TABLE IIIA

DISINTEGRATION TIMES OF TABLETS MADE BY DIFFERENT PROCESSES

| | Moist granulation process A. | Moist granulation process B. | Preliminary compression |
|---|---|---|---|
| Carbromal, gr. 5 | 1′ | 1′ | < ½′ |
| Phenobarbitone, gr. 1 | ½′ | 1′ | < ½′ |
| Sulphathiazole, 0·5 g. | 1′ | < ½′ | 1′ |
| Calcium lactate, gr. 5 | 6′ | 9′ | 1′ |

The result of this experiment shows there is little difference in the relative disintegration times of tablets made by the three methods of granulation, and all are well within the Pharmacopœial limits. It is interesting to note that the act of moistening the starch in granulation process A has not adversely affected its function as a disintegrant. It was further observed that tablets made by this method were less friable than when starch was added as a dry powder. Friability values were therefore determined, using the same batches of tablets as for Table IIIA, with the following results:—

TABLE IIIB

FRIABILITY VALUES OF TABLETS MADE BY DIFFERENT PROCESSES

| | Moist granulation process A. | Moist granulation process B. | Preliminary compression |
|---|---|---|---|
| Carbromal, gr. 5 | 2 | 39 | 49 |
| Phenobarbitone, gr. 1 | 3 | 14 | 12 |
| Sulphathiazole, 0·5 g. | 2 | 4 | 28 |
| Calcium lactate, gr. 5 | 4 | 9 | 13 |

This shows that tablets made by moist granulation process A have considerably lower friability values than those made by the other two methods, although all appeared to be equally hard at the time of manufacture when tested between the fingers and thumb. This is of particular

importance when resistance to wear has to be considered in relation to the handling and packing of tablets.

It is suggested that a satisfactory tablet should have a friability value not exceeding 8.

*The Nature of the Moistening Agent.* A number of suitable moistening agents are mentioned in the British Pharmacopœia. Of these, starch mucilage (10 per cent. w/v) and acacia mucilages (50 per cent. w/v and 25 per cent. w/v) are commonly used, and were employed in the granulation of similar batches of a number of different drugs.

As before, the moist granulation process A was used and the formula included 15 per cent. of maize starch. The disintegration times of the tablets produced from these batches of granules are shown in Table IV.

TABLE IV

EFFECT OF MOISTENING AGENT USED ON DISINTEGRATION TIMES

| | Starch mucilage 10 per cent. w/v | Mucilage of Acacia | |
|---|---|---|---|
| | | 50 per cent. w/v | 25 per cent. w/v |
| Guaiacum and sulphur ... ... ... | 1′ | > 60′ | > 60′ |
| Phenobarbitone, gr. 1 ... ... ... | 1′ | 9′ | 6′ |
| Calcium lactate, gr. 5 ... ... ... | 6′ | 28′ | 15′ |
| Carbromal, gr. 5 ... ... ... ... | 1′ | 36′ | 11′ |
| Sulphathiazole, 0·5 g. ... ... ... | 1′′ | > 60′ | 27′ |
| Phenacetin compound, B.P.C. ... ... | 1′ | 35′ | 15′ |

The most striking result of this experiment was the retarded disintegration of tablets when mucilages of acacia of the strengths indicated had been employed, despite the inclusion in the formulae of an adequate amount of disintegrant. They contrast unfavourably with similar tablets of approximately equal hardness made with starch mucilage as the moistening agent.

*The Pressure Used During Tableting.* Provided that disintegration is not seriously affected, the harder the tablet the better. Two batches of tablets were made from portions of the same batch of granule. In the first case, moderate pressure was used to produce a tablet of normal hardness; in the second case, excessive pressure was used to produce a tablet which was extremely hard, and could only be broken in the fingers with difficulty. The results of the disintegration times and friability values for 4 different tablets are given in Table V.

It was interesting to observe in the series of tablets examined that a tablet could be produced which still had a satisfactory disintegration time despite the use of pressure much in excess of that which would normally be used in tablet practice.

*The Effect of Age Upon the Tablet.* The following conclusions were made from the results obtained with these preliminary tests.

TABLE V

EFFECT OF EXCESSIVE PRESSURE ON DISINTEGRATION TIMES AND FRIABILITY VALUES

| | Moderate pressure | | Excessive pressure | |
|---|---|---|---|---|
| | Disintegration Time | Friability Value | Disintegration Time | Friability Value |
| Phenobarbitone, gr. 1 ... ... | ½′ | 3 | 4′ | 2 |
| Carbromal, g. 5 ... ... ... | 1′ | 2 | 3′ | 1 |
| Sulphanilamide, 0·5 g. ... | ½′ | 2 | ½′ | 2 |
| Phenobarbitone and theobromine B.P.C. ... ... ... ... | ½′ | 4 | 1′ | 3 |

The inclusion of 15 per cent. of maize starch was sufficient to give satisfactory disintegration when tablets were made by any of the methods described. Mucilage of acacia should be used with caution, since it can result in the production of a tablet with retarded disintegration.

The use of the moist granulation process A has been shown to give satisfactory tablets with a low friability value and able to withstand the application of excessive pressure without causing serious increase in the rate of disintegration.

As a result of this information, 13 different batches of tablets were made by the moist granulation process A, each containing 15 per cent. of maize starch as the disintegrant, and using starch mucilage (10 per cent. w/v) as moistening agent. A small proportion of magnesium stearate was used for the purpose of lubricating the dry granules. A batch of aspirin tablets was also made by the dry granulation process employing aspirin crystals mixed with 9 per cent. of dried maize starch.

The tablets were kept in partially filled glass jars and stored on a shelf at room temperature. They were examined over a period of 4 years for disintegration rates, and determinations were also made of the friability values and moisture contents of the tablets at the beginning and end of this period. It was thought that if any significant increase in the time of disintegration was observed as a result of ageing, this might be related to a corresponding change in the moisture content of the tablet.

Table VI shows the results of these experiments.

The following observations can be made from an examination of Table VI.

Batches of different tablets show variations in their initial rates of disintegration, although all comply with the requirements of the British Pharmacopœia. It is interesting to note that calcium lactate, which is the most soluble of the drugs examined, takes the longest time to disintegrate when in tablet form. The remainder of the series of tablets show only slight differences in the rates of disintegration at the beginning and conclusion of the period under review, and where increases do occur they have no practical significance.

## TABLE VI

THE EFFECT OF STORAGE ON DISINTEGRATION TIMES, FRIABILITY VALUES AND MOISTURE CONTENT

| Tablet | Disintegration Times | | | | | | | | | Friability Values | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Months | | | Years | | | | | |
| | Initial | 1 Week | 1 | 3 | 6 | 1 | 2 | 3 | 4 | Initial | 4 Years |
| ·. 5 ... ... ... | 2 | 2 | 1 | 1 | 1½ | 1½ | 1½ | 2 | 2⅓ | 1 | 1 |
| ate, gr. 5 ... ... | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 4 | 4 |
| gr. 5 ... ... ... | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 1 |
| gr. 5 ... ... ... | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 5 | 6 |
| onate, gr. 5 ... ... | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 6 | 3 |
| nd sulphur ... ... | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1½ | 3 | 2 |
| n chalk, gr. 1 ... ... | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 12 | 8 |
| ompound ... ... | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 4 | 2 |
| ne, gr. 1 ... ... | ½ | ½ | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 2 |
| ne and theobromine ... | ½ | ½ | ½ | ½ | ½ | ½ | ½ | ½ | ½ | 4 | 4 |
| de, 0·5 g ... ... | ½ | ½ | ½ | ½ | ½ | ½ | ½ | ½ | ½ | 2 | 3 |
| le, 0·5 g ... ... | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 1 |
| ·. 5 ... ... ... | ½ | ½ | ½ | ½ | ½ | ½ | ½ | ½ | 1 | 4 | 5 |
| 5 ... ... ... ... | ½ | ½ | ½ | ½ | ½ | ½ | ½ | ½ | ½ | 5 | 5 |

In general, the friability values have decreased and the tablets may be said to have " hardened " a little after storage.

The moisture contents of the tablets show both increases and decreases, but they do not bear any relation to the friability values or disintegration times.

SUMMARY

1. Factors affecting the initial time of disintegration of tablets made from insoluble drugs have been discussed.

2. Experiments have been made to examine the influence which each of these factors may have upon disintegration.

3. An experimental formula has been devised in which factors adversely affecting initial disintegration have been eliminated.

4. Thirteen batches of different tablets have been made using this formula and the effect of age upon the time of disintegration examined over a period of 4 years.

5. Results of these experiments show that there is no significant increase in the time of disintegration after prolonged periods of storage.

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## DISCUSSION

An abstract of the paper was read by Mr. Burlinson.

MR. A. NUTTER SMITH (Nottingham) referred to the friability test used by the authors. With this test, it was necessary to standardise all the conditions to obtain reliable results. The true hardness of certain tablets, such as aspirin and mercury with chalk, was not apparent at first. All those who had worked on the subject were convinced that there was no direct relationship between hardness and disintegration. Starch was a very good lubricant, but it must be dry. It might contain as much as 20 per cent. of moisture but he had found from 8·5 to 9 per cent. to give the best results, if the starch were added last. The method of storage for ageing tests was important, as moisture could be readily absorbed by the tablets. The authors' method of partially-filled glass jars gave the worst possible conditions. In the keeping tests, many of the friability values were low. This may have been due to the absorption of water. However, he had found it difficult to link up friability values and moisture content.

DR. G. E. FOSTER (Dartford) asked how the hardness had been measured.

DR. NORMAN EVERS (Ware) asked whether the authors had investigated the effect of elevated temperatures, which no doubt caused an increase in disintegration time. He wondered whether the question of disintegration had been over-emphasised; there might well be cases where it would be a great advantage to have a tablet which would disintegrate slowly.

MR. S. G. STEVENSON (Birkdale) pointed out that disintegration was a function of the permeability of a tablet to water, and it was necessary for the moisture to penetrate right through the tablet. If alginic acid were used would not the gel hold the water and prevent it from reaching the centre of the tablet?

PROF. H. BERRY (London) stated that with alginic acid as disintegrant the granules themselves split and in the disintegration test a powder was obtained and not granules.

MR. H. BURLINSON, replying to the discussion, said that he agreed with Mr. Nutter Smith's remarks about the effect of physical form, especially with phenobarbitone which was difficult to work with in some forms and easier in others. It was suggested that mercury with chalk tablets should be crushed before use. The figures given in the paper showed them to be considerably softer than the other tablets when first made. They had used maize starch not because it had a low moisture content, but because it was widely used and was reliable. The drying of the starch was particularly important when it was added to the dry granules but not in the wet granulation process. For the storage conditions they had tried to reproduce the conditions in an average pharmacy. They did not use any elevated temperatures in the test. The degree of hardness of the tablets was not measured but they did not alter the pressure and took care to produce a uniform granule in the sieving process. The machine was a single punch machine working at 60 r.p.m. Disintegration was related to permeability and the latter to the way in which the disintegrant was used. He thought that the type of disintegration obtained by the use of alginic acid could be obtained by incorporating the starch prior to granulation.