THE PREPARATION OF COMPRESSED TABLETS

PART III.—A STUDY OF THE VALUE OF POTATO STARCH AND ALGINIC ACID AS DISINTEGRATING AGENTS

BY H. BERRY AND C. W. RIDOUT

From the Pharmaceutics Research Laboratory, School of Pharmacy, University of London

Received June 30, 1950.

WHEN a drug intended for internal administration is, for convenience, presented as a compressed tablet, it should be axiomatic that the process of tableting should not alter either the therapeutic action of the drug or the time in which this action is produced. In other words the same effect should be produced in the same time when a tablet is swallowed as when the drug is taken in powder or solution form. Any deviation from these criteria is a measure of the pharmaceutical skill used in formulating and producing the tablets. The disintegration time of tablets intended to be swallowed whole is therefore of great importance, and the British Pharmacopœia 1948 has specified a test in which this time should not exceed 15 minutes except in the cases of tablets of barbitone and phenobarbitone, when the time is extended to 30 minutes.

The disintegration time is a function of (a) the formulation, (b) the degree of compression, (c) the speed of compression and (d) the type of coating used, if any.

The degree of compression is important, particularly to the manufacturer, for a tablet must be produced which will be hard enough to withstand abrasion during handling, transport and storage. Often, however, increase in the degree of compression causes an increase in the disintegration time, and a compromise has to be adopted. This compromise whereby the hardness is balanced against an optimum time of disintegration is referred to, in this paper, as the "*optimum compression.*"

This investigation is concerned with (a) ascertaining the effects of variation in degree of compression on disintegration time, the other factors being constant, i.e., formulation, speed of compression and absence of coating; (b) studying the relative values of potato starch and alginic acid as disintegrating agents when the other factors are constant, i.e., compression ratio, speed of compression and absence of coating.

It was hoped that, as a result of these investigations, it would be possible to recommend that the disintegration time for all uncoated tablets intended to be swallowed whole should be 15 minutes.

In previous papers[1,2] in this series it has been shown that 5-gr. phenacetin tablets were one of the types of compressed tablets that may

give extended and erratic disintegration times, and it was decided to use these tablets as a basis for study.

Experimental

The machine used for the compression of the granules was a single punch, hand operated, Manesty machine. This machine is fitted with an oscillating hopper which caused some segregation of granule size, and in order to avoid this the hopper was removed and the granules were hand-fed into the die. By using this method it was found that variations in weights of the tablets were decreased, as also were the variations in the disintegration times of any single batch of tablets.

Times of disintegration were measured by the method of the British Pharmacopœia, but in order to give more accurate values 12 tablets were used and a mean of these values taken. In order to standardise the experiments as much as possible a very large batch of granules was made by hand and stored in an air-tight container. From this batch, granules were taken as required, lubricant and disintegrating agent added and tablets compressed. Batches of approximately 40 to 50 tablets were prepared for each compression, and each batch was investigated by weighing and measuring 20 tablets selected at random from each batch.

Since the tablets were all prepared from the same batch of granules, it was decided that the degree of compression could conveniently be represented by a "compression ratio." $\frac{\text{Weight in g.}}{\text{"l" in cm.}}$ where "l" is the thickness along the axis of rotation (Fig. 1).

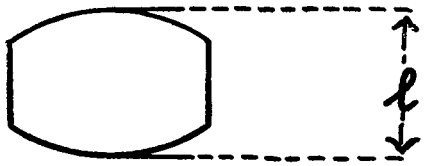

Fig. 1. "Compression ratio"—measurement of "l."

It is realised that the value of this expression "compression ratio" will vary with the curvature of the punches—using a die of constant size—and it is, consequently, a function of the particular punch used and it is not intended that this ratio should be used generally as a means of standardisation of compression. The moistening agent employed in preparing the granules was a 50 per cent. w/w solution of sucrose in water. The lubricant was 1 per cent. w/w of stearic acid.

The Investigation of the Effects of Variation in Degree of Compression on Disintegration Time

Table I shows the results of the average "compression ratio" measurements and disintegration times for 4 batches of tablets containing 15 per cent. of potato starch as a disintegrating agent, and it can be seen that there is a large increase in disintegration times on either side of the value 0·69. In order to determine whether this rise was accidental or

TABLE I

RESULTS OF DISINTEGRATION TESTS AND "COMPRESSION RATIOS" FOR THE FIRST BATCH OF TABLETS USING 15 PER CENT. OF POTATO STARCH

Average "compression ratio"	0·57	0·65	0·69	0·71
Average disintegration time	14′ 45″	6′ 5″	4′ 0″	7′ 10″

′=minutes. ″=seconds.

TABLE II

RESULTS OF DISINTEGRATION TESTS AND "COMPRESSION RATIOS" FOR THE SECOND BATCH OF TABLETS USING 15 PER CENT. OF POTATO STARCH

Average "compression ratio" ...	0·63	0·64	0·65	0·70	0·72	0·75
Average disintegration time ...	7′ 55″	8′ 20″	7′ 20″	2′ 10″	19′ 5″	25′ 10″

′=minutes. ″=seconds.

whether any significance could be attached to it, further batches of tablets were compressed, care being taken to produce compressions on either side of this value of 0·69. The results from this test are recorded in Table II. These results, combined with the previous results, give the graph shown in Figure 2.

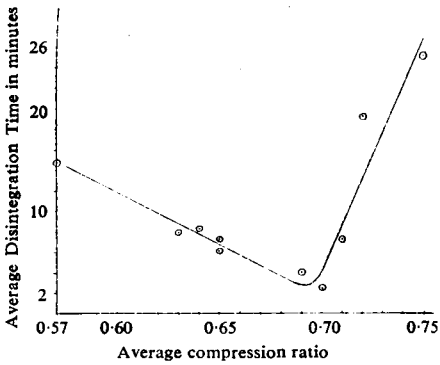

FIG. 2. Relation between Disintegration Time and "Compression Ratio" for Phenacetin Tablets using 15 per cent. of Potato Starch.

This graph shows that, using 15 per cent. of potato starch as a disintegrating agent, there is a critical compression which will give a minimum time of disintegration. A study of the manner in which the tablets disintegrate may lead to an understanding of the reasons for this critical compression. It was found that the tablets disintegrated from the outside but in a somewhat erratic manner. Fairly large pieces of the tablet would break off and these pieces, in turn, would then disintegrate. This would continue until all the tablet had broken up into small pieces. It is generally assumed that the disintegration of the tablets relies upon the swelling of the starch grains. Under a very light compression the grains can swell, but owing to large intergranular spaces they can do so to a considerable extent before they begin to exert pressure on the surrounding granules. Consequently disintegration time is long. At the critical compression, as soon as the grains swell they exert pressure on the surrounding granules and the tablets disintegrate rapidly. With a heavy compression, time is required for the water to seep through the outer layers of the tablets before the starch grains can start to swell and commence to disintegrate the tablet.

Actually, the critical pressure has very little importance in practice, since the tablet is far too friable and the "optimum compression" lies somewhere to the right of the dip in the curve.

Alginic Acid as a Disintegrating Agent

Alginic acid is a polymerised mannuronic acid extracted from certain types of seaweed. It is insoluble in water, but has the property of swelling with water. The acid used in the following experiments was a commercial sample supplied by Albright and Wilson, Ltd., of edible grade HS/LD and had the following characteristics:—

Viscosity. A 1 per cent. dry weight solution of the sodium salt had a viscosity of 6·3 c.s. at 20°C.

Mesh size. 100.

Moisture content. 14 to 16 per cent.

An attempt was made to incorporate the alginic acid into the bulk granules prepared previously, but this was not found to be successful since the acid was a fine free-flowing powder, had no "clinging" properties and, on placing in a hopper, separation of the powder and granules resulted. Fortunately, however, alginic acid can be treated with water or an aqueous solution, dried and still retain its full swelling properties. Consequently, it was decided to mix the phenacetin with the alginic acid and then proceed to granulate so that the alginic acid was incorporated within the granules. The same type of moistening agent was used as before, and batches of tablets were made incorporating 3, 6 and 10 per cent. of alginic acid. Tables III, IV and V give the disintegrating times for tablets of various "compression ratios" containing the above percentages of alginic acid.

TABLE III

Results of disintegration tests and "compression ratios" for tablets using 3 per cent. of alginic acid

Average "compression ratio"	0·56	0·61	0·68
Average disintegration time	2′ 20″	4′ 35″	25′ 25″

′=minutes. ″=seconds.

TABLE IV

Results of disintegration tests and "compression ratios" for tablets using 6 per cent. of alginic acid

Average "compression ratio"	0·56	0·58	0·62	0·65	0·75
Average disintegration time	1′ 20″	3′ 10″	1′ 0″	4′ 5″	45′ 15″

′=minutes. ″=seconds.

Figure 3 shows the graph of "compression ratio" plotted against disintegration times for these results.

A comparison of Figures 2 and 3 shows that the mechanism whereby alginic acid, added before granulation, acts as a disintegrating agent is

TABLE V

RESULTS OF DISINTEGRATION TESTS AND "COMPRESSION RATIOS" FOR TABLETS USING 10 PER CENT. OF ALGINIC ACID

Batch A.						
Average "compression ratio"	0·57	0·58	0·60	0·64	0·71
Average disintegration time	0′ 50″	1′ 15″	1′ 0″	2′ 15″	15′ 30″
Batch B.						
Average "compression ratio"	0·56	0·57	0·60	—	—
Average disintegration time	0′ 30″	0′ 35″	0′ 30″	—	—
Batch C.						
Average "compression ratio"	0·57	0·60	0·64	0·71	—
Average disintegration time	0′ 45″	1′ 0″	1′ 45″	14′ 15″	—

′=minutes. ″=seconds.

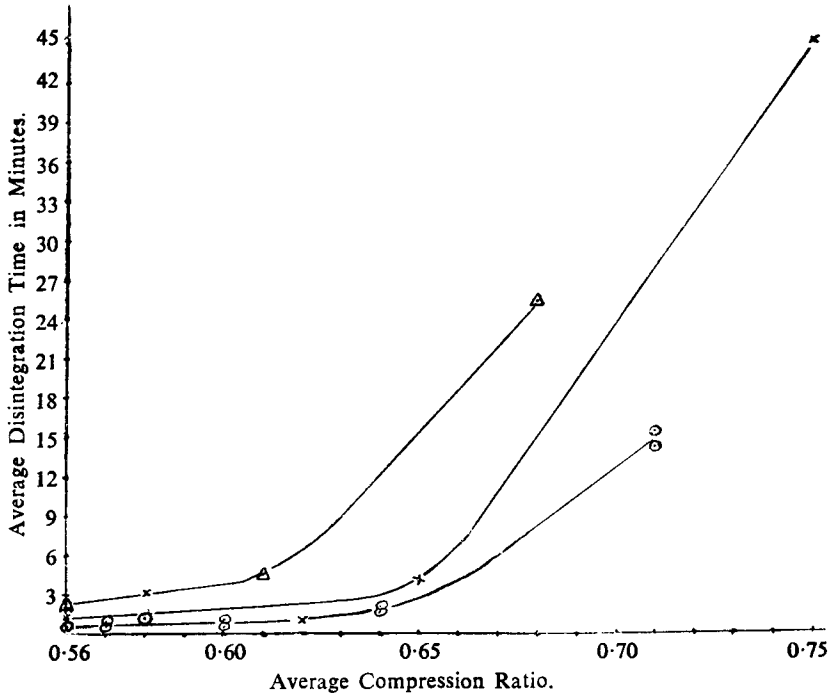

FIG. 3. Relation between Disintegration Time and "Compression Ratio" for Phenacetin Tablets using 3 per cent. (upper curve), 6 per cent. (middle curve), and 10 per cent. (lower curve) of Alginic Acid.

different from starch added after granulation. Once again, observation of the tablet during disintegration gives a clue as to the method involved. As before, disintegration begins from the outside of the tablet, but instead of large pieces breaking off, small fragments, smaller than the original granules, fall away and this continues until the whole tablet

has broken up. This appears to be due to the fact that the alginic acid is now an integral part of each granule, and as it swells, when immersed in water, it breaks up the original granules. Also, it is possible that the wet granules, when made by means of an aqueous solution contain enlarged alginic acid particles. On drying, these grains of alginic acid would decrease in size, leaving air spaces in the granules. Although it is likely that compression would decrease the size of these intragranular air spaces, yet their existence must present a narrow capillary through which water may be drawn into each granule and so aid the rupture of the granule and of the tablet itself.

Comparison of Potato Starch and Alginic Acid as Disintegrating Agents

Experiments were carried out on various B.P. tablets to compare the values of potato starch and alginic acid as disintegrating agents. As far as possible the same compression was used for each batch of tablets, irrespective of the disintegrating agent. The results of the disintegration tests are shown in Table VI.

TABLE VI

Results of disintegration tests on various Tablets using potato starch or alginic acid

		Disintegrating agent	Average "compression ratio"	Average disintegration time
Barbitone	gr. 5...	Potato starch 10 per cent.	0·78	greater than 60′ 0″
		Potato starch 15 ,, ...	0·78	5′ 0″
		Alginic acid 10 ,, ...	0·76	5′ 10″
Digitalis	gr. 1...	Potato starch 10 ,, ...	0·30	16′ 10″
		Alginic acid 10 ,, ...	0·28	9′ 20″
Phenobarbitone	gr. 1...	Potato starch 10 ,, ...	0·28	greater than 75′ 0″
		Potato starch 15 ,, ...	0·28	about 75′ 0″
		Alginic acid 10 ,, ...	0·27	8′ 0″
Thyroid	gr. 1...	Potato starch 10 ,, ...	0·27	6′ 45″
		Alginic acid 10 ,, ...	0·27	4′ 30″

′ = minutes. ″ = seconds.

Time did not permit hardness tests such as recommended by Smith[3,4] to be performed on these tablets, but it appears that more force is required to break, between the fingers, a tablet using alginic acid as a disintegrating agent than it does to break a similar tablet, having the same "compression ratio," but using starch as a disintegrating agent.

Ageing of Tablets

The batches of tablets shown in Table VI were subjected to disintegration tests after a period of 3 months. The results are shown in Table VII. No change was observed in the "compression ratio" for any of the tablets.

TABLE VII

RESULTS OF DISINTEGRATION TESTS ON VARIOUS TABLETS AFTER 3 MONTHS' STORAGE

	Disintegrating agent	Average disintegration time	
		At time of preparation	After 3 months
Barbitone gr. 5	Alginic acid	5′ 10″	7′ 25″
	Potato starch	5′ 0″	6′ 45″
Digitalis gr. 1	Alginic acid	9′ 20″	11′ 40″
	Potato starch	16′ 10″	16′ 25″
Phenobarbitone gr. 1...	Alginic acid	8′ 0″	10′ 20″
	Potato starch	about 75′ 0″	—
Thyroid gr. 1	Alginic acid	4′ 30″	4′ 30″
	Potato starch	6′ 45″	10′ 35″

′ = minutes. ″ = seconds.

The results of the few experiments so far carried out and the reports of other workers[5] indicate that the storage of tablets causes an increase in their disintegration times, and controlled experiments have been set up to determine the cause of this effect over long periods of time.

CONCLUSIONS

(1) In the experiments so far carried out 10 per cent. of alginic acid gave a more rapid disintegration than the corresponding percentage of potato starch.

(2) In the manufacture of phenobarbitone tablets, 10 per cent. of alginic acid gave a much better disintegration time than 15 per cent. of potato starch, and in the case of barbitone tablets the time of disintegration was approximately the same.

(3) From the results obtained it seems possible to recommend that the maximum disintegration time for all uncoated tablets which are to be swallowed whole, and which are in the British Pharmacopœia, be reduced to 15 minutes.

(4) The fact that alginic acid can be granulated with the medicaments in a tablet has the following advantages:—

(a) The addition of a very fine powder, such as starch to the granules before tableting, means that there is a considerable risk of separation of powder and granules during the transfer of the bulk material to the tablet machine and also, whilst the material is in the hopper, due to the vibration of the hopper or of the machine itself. This separation of fine powder will cause variation in weight of the tablets and also variation in the amount of active ingredient in each tablet. There is also the difficulty—by no means inconsiderable—of ensuring an even distribution of a large quantity of starch in a bulk of granules.

(b) Since the alginic acid in these experiments is an integral part of the granules, when the tablet breaks up it will do so to give material which is smaller than the original granule. The active constituents thus

being presented in a finer form will be more quickly absorbed and give a more rapid therapeutic action.

(c) The process of tableting will be simplified.

(5) In tablets prepared of barbitone, digitalis and phenobarbitone, using alginic acid as a disintegrating agent, some increase in disintegration time was noticed after 3 months' storage, but even so, all the tablets disintegrated within 15 minutes.

(6) Thyroid tablets showed no increase in disintegration time after storage for 3 months when alginic acid was used as a disintegrating agent, but showed a considerable increase in disintegration time when potato starch was used.

SUMMARY

(1) An investigation has been carried out to ascertain the effects of varying degrees of compression upon phenacetin tablets using either potato starch or alginic acid as disintegrating agents.

(2) The value of potato starch and alginic acid as disintegrating agents have been compared at the same compression, and alginic acid has been shown to have an advantage in that it can be incorporated within the granules, thus giving finer disintegration.

(3) There is a tendency for disintegration time to increase with storage and further investigations of this phenomenon are necessary.

(4) It is suggested that the maximum disintegration time for all uncoated tablets which are in the British Pharmacopœia and which are to be swallowed whole, be reduced to 15 minutes.

We wish to thank Albright and Wilson, Ltd., for supplying the alginic acid.

REFERENCES

1. Berry, *Quart J. Pharm. Pharmacol.*, 1939, **12**, 501.
2. Berry and Smith, *ibid.*, 1944, **17**, 248
3. Smith, *Pharm. J.*, 1949, **163**, 477.
4. Smith, *ibid.*, 1949, **164**, 73, 132.
5. Smith and Stephenson, *Pharm. J.*, 1950, **164**, 439.

DISCUSSION

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

THE CHAIRMAN (Mr. A. D. Powell) said that the subject of the paper had for some years assumed growing importance, with the control and standardisation of tablets in the British Pharmacopœia.

MR. N. ALLPORT (London) thought the idea of using alginic acid ought to appeal to everyone concerned with tablet manufacture. Did the mixture containing alginic acid run easily in the machines on a manufacturing scale, especially in rotary machines? Generally, hand machines gave results which could not be obtained on a manufacturing scale. Was it an economic proposition to use 10 per cent. of alginic acid instead of 15 per cent. of potato starch?

MR. A. NUTTER SMITH (Nottingham) said that one of the main difficulties with awkward drugs, such as phenobarbitone and phenacetin, was that these substances in a supposedly No. 60 powder contained a good deal which would not go through a No. 40 sieve. For these two substances it was necessary to have a minimum of an 80-powder or, preferably, a 100-powder to get a good product. There was a better chance of working moisture into these finer powders; coarse powders became sticky before sufficient moisture had been absorbed. For moistening he preferred a 10 per cent. solution of soluble starch to cane sugar (50 per cent.) or acacia (5 or 10 per cent.). He found it confusing that the authors had not stated the sieves used in the granulation. This was important as, with phenacetin, it was possible to get the results the authors had obtained by bad technique. He would use a No. 16 or 20 sieve. In the case of phenacetin tablets, he could not agree with the authors' conclusions. One reason was that there were many ways of incorporating starch as a disintegrant. The authors' experiments were inadequate. On the Continent, starch was often used in conjunction with pectin or agar, and he wished that the authors had tried alginic acid with starch. He asked what fillers were used to keep the compression ratio constant when 3 per cent. and 6 per cent. alginic acid were used. He imagined that the alginic acid was much lighter than starch. The disintegration time of 75 minutes for phenobarbitone tablets was surprising; a freshly-made tablet should not take that time to disintegrate if it were properly made. Three months was not a long enough period for the keeping tests; it was necessary to keep tablets over a period of years. He thought it would be wrong to alter the B.P. as a result of laboratory experiments, the results of which had not been proved on a manufacturing scale.

MR. A. W. BULL (Nottingham) referred to the authors' statement that the disintegration rate was affected by the speed of compression, and to their claim to have kept the latter constant. He suggested that this was very difficult to do with a hand-operated machine, and thought that a mechanically-operated one should have been used. Results were reported as average disintegration times; he would like to know what variation from the mean occurred within each batch of 40 to 50 tablets. How far was this factor responsible for the apparently large differences shown in Tables I and II in the disintegration rates for tablets of similar compression ratios? Table VII showed that the rate of disintegration of certain tablets made with alginic acid had increased more rapidly than when starch was used. Had the authors carried on their observations for more than three months, and was this increase significant? Was there any variation of disintegration rate due to humidity and storage?

MR. D. SMITH (Bexleyheath) asked whether the degree of whiteness was affected by the presence of alginic acid. He believed it caused a certain "off-whiteness" which might be a deterrent to its use if this were so in all cases.

DR. E. F. HERSANT (Dagenham) said that the physical form of the ingredients had a considerable influence on disintegration time. The authors had combined Tables I and II to produce one graph, but if two graphs were drawn they did not coincide. He thought it was always difficult to say exactly when a tablet had disintegrated. If the results were going to be quoted in seconds, it must be borne in mind that the B.P. did not prescribe any particular mesh size to take as a criterion of complete disintegration. The result might be very misleading if different authors took different mesh sizes as criteria of disintegration.

MR. R. W. GILLHAM (Leeds) asked whether they had standardised the moisture content of the starch before using it in the tablets as this would affect the disintegrating properties of the starch. Had the authors used maize starch, and did it cause any difference in the rates of disintegration? Could they give any information on the keeping properties of phenacetin tablets? One sample that he had recently handled had a disintegration time well beyond the B.P. limit after storage, although when originally purchased they disintegrated within 15 minutes. Some observations of the effect of alginic acid on the keeping properties of phenacetin tablets would be very interesting.

DR. F. HARTLEY (London) pointed out that, therapeutically, tablets might not necessarily be the most effective form of administering a substance orally. With fairly rapidly metabolised materials the therapeutic effect might depend on the intensity of pharmacological action. It was not certain that the same effect would be produced in the same time when a tablet was swallowed as when the drug was taken in solution form. The tablet might disintegrate in a reasonable time, say, 5 to 15 minutes, but other physicochemical factors, such as the rate of solution of the substance, were involved. For example, a substance soluble to the extent of 1 per cent. and metabolised on reaching the bloodstream in an hour or an hour and a half might well be best administered as a solution in a suitable solvent which would form a colloidal solution on mixing with the gastric juice. This might enable more rapid absorption into the blood stream. If the substance dissolved only slowly, and was metabolised quickly, no matter how quickly the tablet disintegrated, the concentration in the blood would never be sufficient to produce the maximum therapeutic effect. Conversely, it might not matter whether the tablet disintegrated in 15 or 30 minutes, so long as the substance was not metabolised in less than, say, one to one and a half hours.

MR. W. R. HOWARD (London) asked if the authors had considered the possible effects of their lubricants on the disintegration results. His experience had been that the lubricant, particularly if it were of a fatty nature, was apt to waterproof the tablet. Had that effect come into play to produce the increased disintegration times, which they had reported as compression was increased? Might it not have been better to try compressing in the absence of any lubricant, perhaps making use of some device such as a taper die to ease ejection and to prevent shatter-

ing of the specimen which, of course, would vitiate any disintegration determination carried out subsequently? Alginic acid was a most useful admixture in granulations already containing starch. Only small proportions were necessary.

MR. C. W. RIDOUT, in reply, admitted that they had not used a rotary punch machine, but he could see no reason why the process should not work just as well as on a single punch hand-operated machine. When the alginic acid was used internally there was less dust than when starch was used externally as a disintegrant, especially if 10 to 15 per cent. of the latter was used. Even if some starch was added before and some after granulation, there was a fair amount of fine powder which could separate. With alginic acid this did not occur, and the only fine powder to separate was the lubricant. A No. 22 sieve had been used and it was possible to feed the die from the hopper, but they had obtained more consistent results by hand-feeding. They had not used a mixture of alginic acid and starch as the paper set out to give a comparison of the two used separately. The disintegration time for phenobarbitone tablets was surprising, but the compressions used were not comparable with those used for a manufacturer's tablets. In all cases the tablets were much harder than normal as their main concern was to keep the compression ratio constant for all the tablets made.

He agreed that three months was insufficient for the keeping tests. The only reason for using three months was that the paper had to be ready by a certain date. Figures for 6 months' storage were now available, and in all cases showed some slight increase in disintegration time which was generally less than the increase after 3 months. It seemed to be falling off to a constant level. Hand-feeding the granules into the hopper avoided one difficulty about the speed of compression. Great care was taken to ensure that the handle was turned at a constant rate. The variation from the mean of the average disintegration times (Tables I and II) had been measured and the results submitted to the Student's "t" test, and the probability that the widely varying figures all came from the same group was very small.

Ten per cent. of alginic acid caused some discoloration, but it was doubtful if this could easily be noticed, unless the tablets were compared with others prepared with starch. Maize starch had been used, but not very successfully. Data gathered on the keeping properties of phenacetin tablets had unfortunately been lost. The effect of the lubricant had not been investigated, and throughout the work they had used 1 per cent. of stearic acid. The compression had never been hard enough to form a solid coating of lubricant, and prevent the water from seeping in; in these experiments he did not think that the lubricant had any effect on the disintegration times. If used in large proportions certain lubricants would have such an effect.