

# RESEARCH PAPERS

## AN EXAMINATION OF SUGAR-COATINGS OF MEDICINAL TABLETS

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THE work which is described in this paper was undertaken with four chief objects in view. These were to determine the disintegration times of commercial sugar-coatings and sugar-coated tablets, to devise methods for the removal of the coatings from sugar-coated tablets, to investigate the composition of commercial sugar-coatings and to suggest, wherever possible, suitable pharmacopœial standards for sugar-coated tablets.

### (I). THE DISINTEGRATION TIMES OF SUGAR-COATINGS

The time required for a sugar-coating to dissolve or disintegrate in an aqueous medium depends upon the composition of the coating and upon its thickness. A commercial coating, consisting of about 88 per cent. of sugar with 11 to 12 per cent. of starch, disintegrated in water at 37° C. in less than 5 minutes; one containing sugar, calcium carbonate and starch required 30 minutes for complete disintegration, whilst another containing a large proportion of calcium carbonate with gelatin did not completely disintegrate but fell away from the tablet in small flakes.

A batch of tablets was divided into two equal portions. Both halves were coated by the same method using exactly similar materials but in one the coating was approximately two and a half times the thickness of the other. The thin coating disintegrated in water at 37° C. in 2 minutes but the thicker one, under similar conditions, required 15 minutes for complete disintegration.

The apparatus used to determine the disintegration times of sugar-coatings and sugar-coated tablets was that described by Prance, Stephenson and Taylor<sup>1</sup>. 5 tablets were taken for each test and, since it was sometimes difficult to determine when individual tablets had been freed from coating, the end-point of the test was considered to have been reached when the surface of 3 of the 5 tablets was seen to be free of adhering coating fragments. This arbitrary end-point gave reproducible results and no difficulty was experienced in its observation whether the tablets were white as, for example, tablets of quinine bisulphate, or coloured, as in the case of tablets of cascara sagrada. The times required for the complete disintegration of the tablets were also noted. Tests were carried out in water maintained at 37° C. and in many cases also in acid pepsin solution at 37° C. The results are set out in Table I.



The majority of the tablets tested had required longer—in many cases very much longer—times for complete disintegration than the standard time of 15 minutes for uncoated tablets in the British Pharmacopœia. As, however, the majority of such tablets were aperients or alteratives, a total time of from 1 to 2 hours is perhaps not unreasonable.

It is of interest to note that in the case of tablets of cascara sagrada 6 out of 9 samples had a longer disintegration rate in acid pepsin solution than in water at the same temperature, but in general tablets disintegrated more rapidly in the former.

## (II). METHODS FOR THE REMOVAL OF SUGAR-COATINGS

It is desirable that tests for uniformity of weight should be applicable to coated tablets as well as to uncoated ones. To apply such tests the weights of the tablets without the coatings must be determined. Sugar-coated tablets which could be easily separated from their coatings would not be readily handled or transported and manufacturers take care to ensure that sugar coatings are firmly bound to the surface of the tablets. Consequently, it is improbable that a simple and universally applicable method of separating tablet from coating could be devised.

The only published method known to us<sup>2</sup> was applied to sugar-coated tablets of cascara sagrada extract; it directs that the tablets should be placed in a 250-ml. glass measuring cylinder lined with sandpaper and rotated on a wheel until the sugar coating was worn away at the circumference of the tablets. The remainder of the coating was then removed with a small knife. In our hands this method gave no better results than chipping and scraping with a scalpel and had the disadvantage for our purpose that the whole of the coating could not be collected.

No method has been found which can be recommended for all tablets. Unsatisfactory methods have been recorded in the hope of stimulating other workers to more successful efforts. Good results were obtained for a wide range of tablets by heating and dropping the tablets into alcohol.

*Method No. 1.* Heat the tablets in an oven at 105° C. for 5 to 15 minutes; cool by dropping into alcohol. Immediately remove the coating by pressing the tablets between the thumb nail and first finger. The time of heating which will loosen the coating without softening the tablet must be found by varying the heating times for each sample of tablets.

This method of removal has given satisfactory results with tablets of ferrous carbonate, tablets of ferrous phosphate with quinine and strychnine, tablets of ferrous sulphate, compound tablets of ferrous sulphate and tablets of quinine sulphate, quinine bisulphate, quinine hydrochloride and quinine dihydrochloride. Tablets from which the coatings had been removed by this method were quite suitable for examining for uniformity of weight. The method has proved unsuccessful when applied to tablets containing vegetable extracts which soften when heated.

In the case of tablets which had been given an undercoating of water-

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proof material such as a resin or shellac, heat alone was sufficient to soften this layer and loosen the coating. In other cases it seemed probable that one of two factors or a combination of both was required for the success of the above method; (i) The moisture in the tablet may soften the binding material at the surface of the tablet; (ii) Sudden changes in temperature may cause unequal expansion of coating and tablet, resulting in a splitting of the bond.

To investigate the first possibility samples of tablets from batches of tablets of ferrous carbonate and from batches of compound tablets of ferrous sulphate differing only in moisture content were subjected to the treatment, with the results shown in Table II.

TABLE II

Tablets	Batch	Moisture content	Length of time heated at 105°C.	Remarks
Tablets of ferrous carbonate ...	A	per cent. 2.90	minutes 10	Coating unsplit on dropping into alcohol but removed by firm pressure.
	B	3.10	10	As 'A.'
	C	5.62	10	Coating unsplit but easily removed with gentle pressure.
Compound tablets of ferrous sulphate	A	0.92	10	Products not split before dropping into alcohol. Coating removed by gentle pressure.
	B	1.73	10	As 'A' but more easily removed.
	C	5.62	5	Coating split open and easily removed without dropping into alcohol.

The coatings were most easily removed from those tablets which had the highest moisture content.

Some tablets of ferrous carbonate from Batch C and some compound tablets of ferrous sulphate from Batch C had each a small hole drilled the coating before being heated in the oven. On cooling, the coatings could not be removed by pressure between the thumb nail and first finger. It would appear that the moisture in the tablets had escaped through the hole in the coating and had not been available to soften the bond.

To investigate the second factor, tablets were submitted to wide variations of temperature by transference from heated Wood's metal at 150° C. into a solid carbon dioxide and ether mixture at approximately -100° C. and back again into the Wood's metal. The coatings were not loosened but after a number of such transfereces tablets and coatings began to crumble. The crumbling was most marked in the case of tablets containing vegetable extracts but occurred also with tablets such as compound tablets of ferrous sulphate and tablets of ferrous carbonate. It is concluded that Method No. 1 for the removal of sugar coatings is

effective for tablets in which the moisture content can be given up without causing softening of the tablet itself.

*Method No. 2.* Expose the tablets to an atmosphere saturated with moisture until the coating can be scraped away from the tablet.

The use of a piece of wire gauze, having 8 or 10 meshes to the inch and made from fine gauge wire, suspended above a dish of water in a "desiccator" was found to give the best results. The softening process was hastened by agitating the air by means of a propeller type stirrer passed through the neck of the "desiccator" cover, and still further accelerated by maintaining the apparatus at a raised temperature. At room temperature (20° C.) the time required for completely softening the coating varied between 12 and 24 hours and at 37° C. between 4 and 8 hours, depending upon the nature and the thickness of the coating. Tablets so treated were dried in a desiccator over calcium chloride or sulphuric acid. Using this method some success was obtained with certain makes of compound tablets of colocynth and jalap and cascara sagrada tablets which had not been successfully treated by Method No. 1. The method was most effective when the tablets had an undercoating of shellac or other varnish.

A number of other lines of investigation which have been followed with results at present less satisfactory than those described above may be briefly reported. It was found that a tablet which contained in its coating calcium carbonate in contact with an acid, when heated to about 40°C. for some time became loose in its coating and could be shelled out very easily. This fact suggested that if sodium bicarbonate, which is stable at 37°C., but slowly dissociates at 50°C., were included in the undercoating, coated tablets might be prepared from which the coatings could be readily removed by heating above 50°C. Such proved to be the case and tablets were made whose coatings were distended and loosened by heating at 100°C. for 10 minutes so that the coatings could be easily separated from the tablets by gentle pressure. In other respects the tablets appeared to be quite normal. The minimum amount of sodium bicarbonate which was effective was 4 mg. per tablet. Storage tests showed that the disruptive property of the undercoating decreased with age and the decrease was more rapid the higher the storage temperature, being most marked in those tablets whose coatings contained the smallest amounts of sodium bicarbonate.

The effects of various organic solvents upon sugar coatings were investigated. Solvents were chosen in which sucrose was insoluble or very sparingly soluble, and varying proportions of water were added with the object of penetrating the coating with the possibility of softening the bond. All these experiments were quite unsuccessful in loosening the coatings. A very marked degree of penetration of the coating was obtained with aqueous acetone, and it is of interest to note that the addition of certain surface-active agents, notably sodium sulphosuccinic acid di-octyl ester, increased the rate of penetration.

Attempts to invert the sucrose of coatings under controlled conditions

were quite unsuccessful, as were experiments designed to change the sugar into a more brittle form.

### (III). THE COMPOSITION OF SUGAR COATINGS

Sugar coatings usually comprise four layers:—i. *An Undercoating* which frequently consists of a gum, dextrin or gelatin layer which forms a bond between the tablet and the outer layers of the coating. In some cases—particularly when the tablets contain very hygroscopic substances—a thin layer of a water-insoluble varnish such as shellac is first applied to prevent absorption of moisture. ii. *An Opaque Zone* consisting usually of sugar with white insoluble powders. The qualitative examination of a number of commercial coatings has shown that the substances most frequently used in forming this white opaque layer include the following: starch, talc, calcium carbonate, magnesium oxide and magnesium carbonate. iii. *A Translucent Zone* consisting almost entirely of sugar usually encloses the opaque layer giving a smooth appearance to the tablet. iv. *A Glaze* usually a very thin layer of white beeswax or carnauba wax or a mixture of these waxes which gives the coating an attractive polish.

*Quantitative Examination.* The proportion of water-soluble and insoluble ingredients was determined in a number of commercial sugar coatings. Where possible the coatings were removed by Method No. 1 described under (II). In cases in which this method was unsatisfactory the coatings were removed by chipping and scraping with a scalpel until the coating was completely removed, and the fragments collected. Although tedious, this method proved practicable even when applied to white tablets enclosed in white sugar coating.

The coatings from 5 tablets were finely powdered and 0.2 to 0.3 g. was accurately weighed into a Gooch crucible with an asbestos mat; crucible and mat had been previously suspended in an asbestos ring within a nickel crucible, and the whole heated in a Bunsen flame until the Gooch crucible and contents were of constant weight; the asbestos mat was then moistened with distilled water and the crucible and mat re-dried to constant weight at 105°C. All water-soluble matter was removed by washing with distilled water at a suction pump until a few drops of wash water gave no residue on evaporation. The crucible and contents were dried at 105°C. to constant weight and the loss in weight recorded as water-soluble matter. The Gooch crucible was ignited as before until crucible and contents were again of constant weight. The weight of the residue was recorded as mineral matter. Under the conditions of the experiment insoluble organic matter such as starch was readily burnt off and calcium carbonate and magnesium carbonate were not decomposed.

The reproducibility of the results obtained is affected by:—(i) The extent to which the separation of the coatings from the tablets has been affected. (ji) Variations in the composition of the coatings of individual tablets in a sample. Variations from both sources are reduced by taking

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the coatings from 5 tablets. The assays were repeated, in some cases twice.

From the results in Table III it will be seen that water-soluble matter in the 17 samples examined ranged from 51 to 91.6 per cent. In only one sample was the figure less than 61 per cent.

TABLE III

Product	Maker	Water-insoluble matter	Water-soluble matter (by difference)	Mineral matter	Insoluble organic matter (by difference)
		per cent.	per cent.	per cent.	per cent.
Cascara compound...	F	31.7	68.3	30.4	1.3
		32.5	67.5	31.6	0.9
Cascara sagrada gr. 2	B	9.6	90.4	4.6	5.0
		8.4	91.6	4.6	3.8
		10.8	89.2	6.9	3.9
" " "	G	37.0	63.0	34.0	3.0
		35.2	64.8	31.6	3.6
" " "	H	49.0	51.0	44.0	5.0
		46.1	53.9	43.5	2.6
" " "	Unknown	27.5	72.5	20.1	7.4
		25.8	74.2	19.5	6.3
Colocynth and jalap, compound...	D	9.4	90.6	2.64	6.76
		8.9	91.1	3.42	5.48
" " "	I	32.0	68.0	9.0	23.0
" " "	K	32.6	67.4	11.6	21.0
		35.5	64.5	8.8	26.7
Ferrous carbonate ...	A	11.84	88.16	0.25	11.59
		11.24	88.76	0.29	10.95
Ferrous sulphate, compound	A	14.0	86.0	0.7	13.3
		12.9	87.1	1.21	11.69
" " "	B	17.2	82.8	16.7	0.5
		16.7	83.3	16.0	0.7
" " "	J	29.9	70.1	27.4	2.5
		29.8	70.2	26.6	3.2
A proprietary tablet	P	18.4	81.6	15.1	3.3
		16.1	83.9	13.2	2.9
Quinine bisulphate ...	A	10.4	89.6	0.57	9.83
		14.6	85.4	0.29	14.31
		14.6	85.4	0.27	14.33
Quinine dihydrochloride ...	A	10.4	89.6	0.28	10.12
		11.3	88.7	0.26	11.04
Quinine sulphate ...	E	21.0	79.0	20.4	0.6
" " "	K	25.6	74.4	6.9	18.7
		23.2	76.8	4.7	18.5

It seemed a reasonable assumption that the water-soluble matter represented the proportion of sugar in the coating, the amounts of gum and gelatin, etc., being negligible. To investigate this matter the amount of sugar in the wash water from different samples of coatings was determined by the method of Lane and Eynon<sup>3</sup>. The samples of coatings chosen had widely different compositions.

*Method.* The wash water from the determination of water-soluble matter was quantitatively collected and the sucrose inverted by boiling

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with 25 ml. of 0.5N hydrochloric acid for 5 minutes. The solution was cooled, made up accurately to a suitable volume, and used to titrate 10 ml. of standardised Fehling's solution adding methylene blue as indicator. The amount of reducing sugar present in the solution was calculated as sucrose and compared with the amount of water-soluble matter (see Table IV).

TABLE IV

Sample No.	Product	Maker	Water-soluble matter (by difference)	Sucrose found (volumetrically)
1	Colocynth and jalap, compound ...	Unknown	per cent. 62.95	per cent. 62.91
2	Ferrous carbonate ... ..	A	86.58	85.92
3	Ferrous phosphate with quinine and strychnine ... ..	Q	74.28	73.45
4	Ferrous sulphate, compound ...	A	87.04	86.98
5	Ferrous sulphate, compound ...	B	83.03	82.87
6	Ferrous sulphate, compound ...	J	71.19	70.99
7	Quinine dihydrochloride ... ..	L	96.98	95.63

The results indicate that the water-soluble matter found by difference in the quantitative examination of sugar coatings agrees closely with the proportion of sugar present in the coating, calculated as sucrose.

The water-insoluble matter includes white minerals used as pigments and insoluble organic matter such as starch which may have been used for the same purpose. The figures for ash reported as mineral matter may be taken as representing the inorganic fillers substantially unchanged and the difference between these figures and the corresponding figures for water-insoluble matter will represent the proportions of insoluble organic matter, such as starch, present in the coating. In cases where the percentage of mineral matter is low, organic matter, such as starch has been used as the pigment-filler. From the point of view of quality this is probably the ideal type of sugar coating, since only foodstuffs are used.

## (IV). STANDARDS FOR SUGAR-COATED TABLETS

The work which has been described in the foregoing sections of this paper seems to provide sufficient data for suggesting standards for sugar-coated tablets which might be included in the British Pharmacopœia.

(i) *Disintegration Time.* An allowance of 30 minutes for the disintegration time of the sugar coating would appear to be adequate. This should be added to the disintegration time for the uncoated tablets. Many widely-used sugar-coated tablets such as those containing vegetable extracts, differ from the uncoated tablets for which pharmacopœial standards for disintegration already exist. No limits have yet been set to the disintegration times of cascara sagrada tablets and compound tablets of colocynth and jalap because such tablets have always been sugar-coated.



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Similarly tablets containing ferrous sulphate have almost always been sugar-coated. Possibly well-made tablets of such types would, before coating, have disintegration times in excess of the standard pharmacopœial limit of 15 minutes. It is suggested that all sugar-coated tablets should be considered individually and not as a group, but in no case should the disintegration time for sugar-coated tablets exceed two hours when tested by the official method.

(ii) *Uniformity of Weight.* Attempts to devise an effective method for the removal of sugar-coatings from all tablets leaving the tablets intact have not been successful. It would not appear to be advisable at this stage to recommend the inclusion of tests for uniformity of weight of sugar-coated tablets in any pharmacopœial standards for these products.

(iii) *Composition of Sugar-Coating.* In its monograph on Tablets the British Pharmacopœia might usefully list the ingredients which are commonly used in the application of sugar-coatings. A number of materials found in commercial sugar-coatings have been noted at the beginning of Part III of this paper.

Despite the difficulty of separating sugar-coatings from the tablets they enclose, the separation can be effected sufficiently to enable determinations of the proportions of sugar, mineral matter, etc., to be made with a fair degree of accuracy. Whilst the authors would not recommend that pharmacopœial limits should be set to the proportion of mineral matter permitted in sugar coatings in view of the widespread use of such materials in commercial coatings, they do feel justified in suggesting that "sugar coated" should mean "coated with material which is predominantly sugar," and that a minimum limit should be set to the proportion of sugar which may be present. Consideration of the results set out in Table III prompts the suggestion that a sucrose content of not less than 50 per cent. would not be burdensome to the manufacturer. Such proportions of sugar could be used that when determined by the method about to be described the result would never be less than 50 per cent. of sucrose. The standard which we would suggest for this purpose is as follows:—

*Proportion of Sugar in the Coating.* Separate the coating from 5 tablets; collect the fragments of the coating and powder finely. Weigh out 0.4 to 0.5 g. of the finely powdered coating into a prepared Gooch crucible, Hirsch funnel, or other suitable apparatus. Wash the powder slowly with distilled water until all soluble matter has been removed as indicated by the absence of residue when a few drops of the wash water are evaporated on a water-bath. Add 25 ml. of 0.5 N hydrochloric acid and boil gently for 5 minutes, avoiding loss; cool and make up the volume to 250 ml. with water.

Carry out a trial titration by adding approximately 15 ml. of the sugar solution to 10 ml. of standard Fehling's solution accurately measured into a 250-ml. Erlenmeyer flask. Heat over a wire gauze and boil for about 15 seconds; add further quantities of the sugar solution until a faint blue colour remains. Add 2 to 5 drops of a 1 per cent. aqueous

solution of methylene blue and continue the titration at the boiling-point until the indicator is decolourised. Repeat the titration adding to 10 ml. of standard Fehling's solution 0.5 to 1 ml. less than the total volume of sugar solution required. Boil for 2 minutes. Add 2 to 5 drops of methylene blue solution and continue the titration at boiling-point until the indicator is decolourised and so that the entire titration is completed with a boiling time of 3 minutes. By means of tables (Lane and Eynon<sup>2</sup>) calculate the proportion of sucrose present in the powdered coating.

The proportion of sucrose in the sugar coating as determined by the method of assay described is not less than 50 per cent.

#### SUMMARY

(i) A large number of commercial sugar coatings have been examined for time of disintegration. In only one case was this more than 30 minutes and it was generally less than 15 minutes.

(ii) No simple and generally applicable method for the removal of sugar coatings from tablets has been found, but methods have been suggested which can be applied to a wide range of tablets.

(iii) The composition of a selection of different makes of sugar coating has been investigated and the proportions of water-soluble and insoluble matter, mineral matter and insoluble organic matter have been determined. The water-soluble matter has been shown (in all the cases examined) to consist almost entirely of sugar.

(iv) It is suggested that pharmacopœial standards for disintegration times of sugar-coated tablets should exceed by at least 30 minutes the normal disintegration time for uncoated tablets, but should never be longer than two hours.

It is further suggested that a pharmacopœial standard for sugar content of sugar coatings should be not less than 50 per cent. of sucrose and a simple method for the determination of the sugar has been described.

Much of the work described in this paper was carried out at the suggestion of the British Pharmacopœia Commission, Sub-Committee 6 C—Tablets. It is hoped that the publication of the results will stimulate further work in this field.

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