THE STERILISATION OF SULPHANILAMIDE POWDERS

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Introduction

Although sulphanilamide has been largely superseded by other substances and preparations, we feel that the work described below should be placed on record as illustrative of pharmaceutical problems wherein seemingly trivial impurities can exert a marked effect upon the quality of a final preparation, and that the results obtained may be useful in dealing with such problems.

The use of sterilised sulphanilamide powder for topical application to wounds during the last war led us to examine the problems involved in the sterilisation of this substance in unit containers. Some of the difficulties have been indicated in the many methods of preparation described[1-6, 8-10] for the production of a powder which is free from discolouration and is free-flowing to facilitate sprinkling the powder evenly over a wound.

The free-flowing property may be improved by controlling the particle size of the powder[2] or by admixture with certain substances[1,3], although caking and discolouration are not necessarily prevented by these methods. The admixture with insoluble substances, such as zinc oxide, kaolin, etc., is undesirable when the powder is to be used in the peritoneal cavity or in deep wounds, since foreign body reactions may arise.

In order to avoid discolouration Buckland[5] sterilised the powder in plugged tubes by heating in a dressings autoclave. McCartney and Cruikshank[6] used tightly closed screw-capped bottles and, providing the powder contained not less than 0·2 per cent. of moisture, sterilisation could be effected by heating in an autoclave. Caking and discolouration of the sulphanilamide was later reported by these authors[7].

Long[4] described a process for sterilising paper envelopes containing 5 g. of sulphanilamide. Discolouration of both the sulphanilamide and the paper in contact with it occurred when samples of sulphanilamide available in this country were used.

A package containing 5 g. of sulphanilamide in a paper envelope and enclosed in a second envelope was most suitable for use in the field since it was compact, light in weight, and easily and cleanly opened for use.

In our experimental work sterilisation was controlled by deliberately adding hay dust to a number of the packages in each batch so that the sample was grossly infected with spores of *Bacillus subtilis*, and tests

for sterility were carried out using aerobic and anaerobic media containing 0·1 per cent. of *p*-aminobenzoic acid. This was necessary, as the method referred to below as " heating at 150°C. for 1 hour " was carried out in a thermostatically controlled electric oven, the shelf temperature of which was found to vary between 145° and 155°C. and the time of heating at this temperature range was about 1½ hours to effect sterility.

Experimental

Certain factors, found to be important in the preparation of a suitable powder, were examined separately.

1. *The Effect of Electrification of the Powder During Grinding.* The particles appeared to become " electrified " when sulphanilamide was ground to a fine powder. It was then not free-flowing and could not be sprinkled evenly from a container. Sulphanilamide crystals were carefully broken and the resulting powder graded by means of silk sieves. Particles which passed through an 80-mesh, or more coarse, sieve, but were retained by a 100-mesh sieve formed free-flowing powders, but particles which were electrified were those that passed through a 100-mesh sieve.

McDougall and Shotton[1] had found that if certain substances were mixed with finely ground sulphanilamide a mobile powder was immediately formed, the mobility being retained after the powder was heated at 150°C. for 1 hour. Zinc oxide and kaolin were outstanding in this respect, calcium phosphate and the carbonates of calcium, magnesium and zinc were slightly less effective, whilst anhydrous sodium sulphate, anhydrous sodium citrate and potassium hydrogen tartrate gave a very weak effect in producing a free-flowing powder. Davis[3] suggested the added substance probably acted as an absorbent for the moisture present in the sulphanilamide. We found that a sulphanilamide in fine powder containing less than 0·1 per cent. of moisture was not free-flowing unless mixed with zinc oxide or kaolin. Anhydrous sodium sulphate, which could be expected to absorb moisture, was much less effective than zinc oxide, and it would seem, therefore, that the main effect of the added substance is concerned in some way with the removal of the charge on the particles.

In the above experiments the sulphanilamide was heated at 150°C. for 1 hour in screw-capped tubes of approximately ½-inch diameter and some discolouration of the powders occurred even in the presence of 5 per cent. of zinc oxide.

2. *The Effect of the Solvent used for the Crystallisation of Sulphanilamide.* The sulphanilamide used in the preliminary experiments had been crystallised from alcohol, thus the loss of weight on drying would represent this solvent. Alcohol was detectable by smell when the powder was warmed. The effect of the presence of a small amount of alcohol was examined. A quantity of sulphanilamide in 40/100 powder was divided into three portions, " A," " B " and " C." " A " was kept as a control " B " was crystallised from boiling alcohol

(95 per cent.) after charcoal treatment and filtration of the hot solution. "C" was crystallised similarly, but using distilled water as the solvent.

The crystals obtained from "B" and "C" above were dried at a low temperature and reduced to a 40/100 powder. The loss of weight on drying was determined. 15 g. of each of the three powders was heated at 150°C. for 1 hour in square, screw-capped bottles of 1 fl. oz. capacity. The results obtained are summarised in Table I.

TABLE I

EFFECT OF THE RESIDUAL SOLVENT ON THE COLOUR OF SULPHANILAMIDE POWDER HEATED AT 150°C. FOR 1 HOUR

Sulphanilamide Powder (40/100)	'A'	'B'	'C'
Loss of weight on drying	0·2 per cent.	0·32 per cent.	0·06 per cent.
Heated immediately after re-crystallisation ...	Brownish discolouration	Discolouration slight ; less than 'A'	White
Heated after 3 months storage at laboratory temperature ...	As above	Discolouration greater than 'A'	White

From these results it appears that the presence of a small quantity of alcohol is a cause of the discolouration which occurs when sulphanilamide is heated.

A little acetaldehyde was added to a portion of the above powder "C" both alone and also with 5 per cent. of zinc oxide present. Both powders developed a brownish colour and were caked after heating at 150°C. This suggests that on storage a change takes place in the powder crystallised from alcohol with the formation of a compound which is decomposed by heat. It seems probable that the alcohol undergoes atmospheric oxidation to acetaldehyde and this subsequently reacts with the sulphanilamide.

3. *The Effect of the Moisture Content of Sulphanilamide Powder.* Sulphanilamide was recrystallised from distilled water as above and divided into portions. These were dried slowly at about 40°C. in order to obtain powders with differing moisture content.

The moisture content of each portion was determined and the powders heated at 150°C. alone and with 5 per cent. of zinc oxide both in screw-capped bottles and in paper envelopes. When heated in screw-capped bottles, from which the moisture could not readily escape, caking occurred when the moisture content was above approximately 0·25 per cent., a small hard central core being formed when the moisture content approached 0·25 per cent. This result was obtained also when 5 per cent. zinc oxide was mixed with the sulphanilamide. Water vapour was lost quite readily from the paper envelopes containing sulphanilamide and a sample of powder containing 0·94 per cent. of moisture gave a satisfactory powder after heating in such a package. It was noticed, too, that

powders containing more than 0·5 per cent. of moisture were less readily electrified during grinding.

Paper Envelopes. Envelopes were made from many types and qualities of paper, but after heating some became too brittle and others were discoloured by, or caused discolouration of, the sulphanilamide in contact with them. Somerville[11] has described a colour reaction between sulphanilamide and an aldehyde accompanying lignin and this may afford an explanation of the mutual discolouration of the envelope and the sulphanilamide which occurred. A good quality vegetable parchment was found to be suitable, but as some variation occurred each delivery was tested for suitability.

Sulphathiazole. We found that if sulphathiazole was recrystallised from distilled water, as previously described for sulphanilamide, this too could be heated at 150°C. for 1 hour without becoming noticeably discoloured, whereas if recrystallised from alcohol it was discoloured.

The charcoal used in these experiments was a commercial sample purified by boiling with strong hydrochloric acid and washing with distilled water until free from acid. It was then substantially free from arsenic and lead.

Summary

1. A sterile free-flowing sulphanilamide powder may be prepared providing the powder is not finer than an 80/100 mesh.

2. Powders finer than 100 mesh appear to become electrified during grinding and are then not free-flowing. Powders containing more than 0.5 per cent. of moisture are less readily electrified by grinding.

3. The addition of certain substances, e.g., zinc oxide or kaolin, to fine powders resulted in free-flowing powders. This appears to be mainly connected with the loss of the electric charge.

4. Sulphanilamide recrystallised from alcohol became discoloured when sterilised by heating at 150°C. The discolouration was increased after the sample was stored for some time at laboratory temperature before sterilisation.

5. Sulphanilamide recrystallised from water, as described, was not discoloured when heated at 150°C. and remained satisfactory after storage at laboratory temperature.

6. Sulphanilamide powder heated in screw-capped bottles at 150°C. became caked, to some degree, if more than about 0·25 per cent. of water was present.

7. Sulphanilamide powder packed in thin layers in paper envelopes did not cake after heating at 150°C. even when the moisture content was nearly 1·0 per cent. since water vapour was readily lost through the paper.

8. A good quality vegetable parchment was found to be a suitable paper for the envelope in contact with the sulphanilamide.

9. Sulphathiazole recrystallised from distilled water was not discoloured when heated at 150°C. but if recrystallised from alcohol it was discoloured by heat in a similar manner to sulphanilamide.

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