There is apparently no general relationship that exists between tinctures and solutions of germicides and their efficiency following diffusion, as shown by the conflicting results obtained with such preparations of iodine and mercurochrome. Topley and Wilson, generalizing, state: "Germicides dissolved in alcohol . . . are deprived of the greater part of their power." In this study this seems to hold true only in the case of iodine. Solutions of germicides containing soaps, such as Amphyl, apparently do not diffuse readily through collodial material. This is shown by their low coefficient of diffusion. Two factors probably are important in any consideration of such solutions; first, soaps alter the germicidal powers (Tilley and Schaffer, 1925, and Tilley, 1939) of germicides and, second, as noted in these experiments, the soap brought about changes in the colloidal gel itself thus preventing diffusion through it. Such solutions cannot be accurately judged by the agar cup-plate method, but the fact remains that Amphyl and its solutions have found little value in obstetrics where diffusion through mucous-like materials is desired.

A detailed study involving the various germicides mentioned in this treatise, as well as many others, is now being carried out in respect to diffusibility and clinical usefulness.

CONCLUSIONS

1. The coefficient of diffusion has been explained and its significance discussed.

2. Germicides having a high coefficient of diffusion have been found to be of value in obstetrics; those having a low coefficient were found to be of little value.

3. The agar cup-plate method is recommended especially for the evaluation of germicides where their use will involve diffusion through colloidal material.

REFERENCES

Bronfenbrenner, J., Hersey, A. D., and Doubly, J., "Evaluation of Germicides by a Manometric Method," *J. Bact.*, 37 (1939), 583–597.

Miller, R. E., and Rose, S. B., "Studies with the Agar Cup-Plate Method. III. The Influence of Agar on Mercury Antiseptics," *Ibid.*, 38 (1939), 539–547.

Rose, S. B., and Miller, R. E., "Studies with the Agar Cup-Plate Method. I. A Standardized Agar Cup-Plate Technique," *Ibid.*, 38 (1939), 525–537.

Ruehle, G. L. A., and Brewer, C. M., United States Food and Drug Administration Methods of Testing Antiseptics and Disinfectants," *U. S. Depart. Agric., Circ.* 198 (1931).

Topley, W. W. C., and Wilson, G. L., "The Principles of Bacteriology and Immunity," Wm. Wood & Co., Baltimore, Md., 1936.

Tilley, F. W., and Schaffer, J. M., "Germicidal Efficiency of Cocoanut-Oil and Linseed-Oil Soaps and Their Mixtures with Cresol," *J. Infect. Dis.*, 37 (1925), 359-367.

Tilley, F. W., "An Experimental Study of the Relation between Concentration of Disinfectants and the Time Required for Disinfection," *J. Bact.*, 38 (1939), 499–510.

Problems Encountered in the Manufacture of Compressed Tablets*

By L. W. Busse and A. H. Uhl

The chief problems encountered in the manufacture of compressed tablets are binding, picking, capping, sticking and splitting. These problems are particularly annoying because they do not occur until the last step in the process of manufacture; namely, that of compression.

Capping and splitting are alike in the respect that they usually occur together and in many cases may be attributed to the same cause.

Capping is the term applied when the upper surface of the tablet splits off.

Splitting is the term applied when the tablet does not hold together after compression.

In discussing the remedies for capping and splitting, one must of course first know the reason for their occurrence. The reason given by many authors is that of excess powder in the granulation. This excessive amount of fine powder requires a great deal of pressure to form the tablet. It has been said, that this extreme pressure makes the tablet very hard in the center causing the upper surface of the tablet to split off. This fine powder also causes air to be trapped in the powder upon compression and after release of the pressure causes the upper surface of the tablet to split off.

Capping and splitting may also result from a worn upper punch, too much pressure or too damp or too soft a granulation.

It has been our experience, that in most cases capping and splitting were caused by

* From the School of Pharmacy, University of Wisconsin.

having too soft a granulation. When this occurred all attempts to remedy these troubles, aside from regranulation, were unsuccessful. Reduction of pressure would yield too soft a tablet. Sifting out the fine powder using a number 30 screen was also unsuccessful. A worn condition of the upper punch was ruled out because in the majority of cases the set happened to be new. Regranulation, however, which resulted in a hardening of the granules most always succeeded in eliminating these troubles.

One of the most essential qualities of a granulation as far as compression is concerned is hardness. If you have a hard granulation, satisfactory tablets will most always result upon compression. This seems to be in accord with a statement made by Bentley, that the formation of the tablet on compression is assisted owing to the interlocking of the granules. The amount of fine powder allowed in the granulation also will depend upon the hardness of the granules. A hard granulation permits a higher percentage of fine powder than a soft granulation.

Tests were run on granulations containing various percentages of fine powder in order to determine at what amounts capping would be most likely to occur. These tests could not be carried out with any degree of accuracy, but in most cases thirty per cent of fine powder seemed to be the most satisfactory amount. However, granulations containing fifty and sixty per cent of fine powder were also satisfactory in some cases indicating the amount of fine powder is not always the cause of this trouble.

It was found that capping would also occur if not enough fine powder was present in the granulation. This would occur especially in the compression of crystalline substances such as methenamine, sodium bromide etc. Crystals or granules of a No. 16 mesh were purchased but it was found that these had to be forced through a No. 20 mesh screen to provide some fine powder with the crystals before they would compress satisfactorily.

In attempts to remedy these troubles once they occurred, the steps followed were (1) to reduce the pressure; (2) sift out the fine powder and regranulate. It was found also that the addition of $^1/_2$ to 1 per cent of stearic acid sometimes remedied these troubles, especially when they occurred with granulations prepared with powdered sugar.

Another method recommended by Moseley is to spray a 1 per cent solution of glycerin in 60 per cent alcohol on the granulation and allow to dry, then compress.

Binding, picking and sticking may also be grouped together for purposes of discussion because they most always occur at the same time and in many cases may be attributed to the same cause.

Binding is the term applied when the granulation sticks to the dye and causes a friction between the lower punch and the dye.

Picking is the term applied when the granules adhere to the face of the upper punch forming a concavity in the upper surface of the tablet.

Sticking is the term applied when the granules adhere to the face of the upper punch causing the surface of the tablet to be dull and pitted.

Binding, picking and sticking are usually the result of improper lubrication or using a granulation which is not quite dry.

Binding was found to occur quite frequently with substances such as sodium salicylate and calcium lactate. These substances were found to be very difficult to lubricate properly. The common lubricants such as talc, mineral oil, stearic acid, etc., were not satisfactory in amounts usually recommended. Soaps, however, were found to be very good as lubricants to prevent binding with sodium salicylate. Of the soap powders used, magnesium stearate in the impalpable powder form was found to be the most satisfactory. Three to four per cent of the total weight of the formula was required.

Calcium lactate was found to be lubricated equally well with talc or magnesium stearate. These were necessary in amounts of four per cent.

If the binding was the result of a granulation not thoroughly dry, it was found practically impossible to eliminate. Further drying was found to be the only satisfactory remedy. Mineral oil would remedy it for a

few minutes, but picking and sticking would also occur after operation of the machine for a few minutes so that the granulation would have to be dried.

Picking and sticking were found to occur most always with a granulation which was not quite dry. The first precaution, however, is to be sure that the upper punch is clean and highly polished. The use of chromium plated punches is now recommended as a precaution against the occurrence of these conditions.

It was observed that if these troubles occurred to any degree, they were almost impossible to eliminate. Talc served as a remedy in some cases, but a high percentage was usually required which was objectionable. Lubricants such as stearic acid, mineral oil, magnesium and sodium stearate are also objectionable when added in amounts necessary to overcome these difficulties. Stearic acid in amounts above four per cent retards disintegration. Mineral oil was found to decrease the binding properties when used in amounts above three per cent and as a result produces a soft tablet. The stearates if used in too large a quantity tend to produce sticking and picking in themselves.

In making this study it was observed that these troubles most always occurred with compounds such as aspirin, sodium salicylate or compounds which behaved similarly to those upon the addition of water. When water was used as the granulating liquid, the substances became pasty and sticky, making them difficult to granulate and also difficult to dry. When powdered sugar was used as the binder, which permits the use of high concentrations of alcohol in water as the moistening agent, these substances were very easy to granulate as well as to dry. As a result picking, sticking and binding with these substances was entirely eliminated.

One of the important observations made, during the last year, was the fact that these problems can be prevented much easier than they can be remedied. A thorough study of the proper moistening, binding and lubricating agents used to granulate the substance will in the majority of cases eliminate these difficulties encountered in the manufacture of compressed tablets.

Each substance must be studied as an individual compound and treated as such. Compounds when granulated with various binders and moistening agents exhibit different physical properties. This was observed particularly with sodium salicylate. All attempts to granulate this substance using aqueous granulating liquids were unsuccessful. However, the use of powdered sucrose and seventy per cent alcohol proved very satisfactory. When magnesium stearate was found to be a good lubricant all the problems encountered with this compound were eliminated.

With the compound aspirin formula, consisting of aspirin, phenacetin and citrated caffeine, all of the difficulties were encountered until it was found that the use of water as a moistening agent with aspirin was undesirable for the following reasons. One because of the hydrolysis which might occur and two, because of the difficulty in drying it thoroughly at a low temperature. These problems were greatly eliminated by using a crystalline aspirin and mixing these with the granules formed from the mixture of phenacetin, citrated caffeine and powdered sugar. In this manner the aspirin does not come into contact with water, and is added to the granulation along with the starch and the lubricant. This method is used for all formulas of two or more ingredients, which contain aspirin as one of the active ingredients.

Our experiences are presented with the hope that they will stimulate others engaged in the manufacture of tablets to present their problems and solutions so that we can all benefit from each other's experiences in this field. This will eliminate, to some extent at least, that problem which all teachers of tablet manufacturing are confronted with, namely, "practical experience" which is so necessary in the successful manufacture of compressed tablets.

"The more extensive a man's knowledge of what has been done, the greater will be his power of knowing what to do"—DISRAELI