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II. SEGREGATION OF ACTIVE CONSTITUENTS FROM TABLET FORMULATIONS DURING GRINDING: SIGNIFICANCE TO PHARMACEUTICAL ANALYSIS.

by

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ABSTRACT

The preparatory step in the analysis of active drugs in tablet dosage forms has generally consisted of the grinding or milling of a given number of the tablets into a fine powder. Certain drugs formulated as tablets have been shown to undergo physical separation from other tablet components as a result of grinding. This phenomenon accounts, at least in part, for the poor reproducibility found in duplicate assays for these drugs in tablet composites. This same phenomenon also explains discrepancies between the average of the individual tablet assay values of samples prepared by direct dissolution, and the assay value of the corresponding composites.

This paper illustrates this phenomenon using a problem dosage form and suggests methods of sample preparation that avoid segregation of ingredients. These methods include the direct dissolution of a representative number of individual tablets in a suitable solvent, the sieving and regrinding of the ground tablets, the grinding of a composite

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with a suitable organic solvent and the evaporation of the solvent, and the dissolution of the total composite tablet sample in a solvent.

INTRODUCTION

A previous report (1) examined some of the theoretical considerations which explain the segregation of active constituents from other components when tablets are ground. A number of tablets have been shown to undergo physical separation of their constituents during grinding as a result of differences in the size, shape, density, roughness, and resiliance of the particles produced by the grinding (1). At particle sizes of less than approximately 400 μm, Van der Waals forces, electrostatic forces, adsorption, and valency forces which are normally insignificant, become influential and bring about this separation and produce non-uniformity in a mixed powder (1,2).

This paper shows that methocarbamol tablets obtained from certain manufacturers exhibit segregational problems, and that a number of alternate analytical procedures will improve the reproducibility of duplicate assays while maintaining the accuracy of the analytical procedure.

EXPERIMENTAL

Methocarbamol tablets containing 500 mg of drug substance were obtained from nine manufacturers. Twenty tablets from each sample was ground to a fine powdered composite by means of a glass mortar and pestle, and assayed by a spectrophotometric procedure (3). From the duplicate assay values (Table 1), it was evident that segregation was occurring in both lots of methocarbamol tablets obtained from manufacturer F. To determine how the active ingredient was distributed within the powder bed immediately after grinding, samples were collected from several places. Surface powder was sampled from the side and from the bottom of the bed (locations A and B, Figure 1). The bulk of the powder

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Table 1

Results of the Assay of Methocarbamol Tablets from Several Manufacturers as Ground Composite Samples.

	Found, % of declared				
Manufacturer	Run 1	Run 2	Avg.	Range	Major Excipients
A	99.9	99.9	99.9	0.0	Primojel
B	99.8	99.7	99.8	0.1	PVP + Avicel
C	100.2	100.4	100.3	0.2	Cab-o-Sil + Starch
D	97.3	97.1	97.2	0.2	Explotab + Cab-o-Sil + PVP
E	100.9	103.1	102.0	2.2	Explotab
F (Lot 1)	91.1 101.3	97.7 101.8	94.4 101.6	6.6 0.5	Explotab
F (Lot 2)	100.4 103.5 90.6	101.2 97.2 89.8	100.8 100.4 90.2	0.8 6.3 0.8	Explotab
G	100.7	102.1	101.4	1.4	Explotab
H	98.2	99.8	99.0	1.6	Explotab
I	98.4	99.7	99.1	1.3	Polyethylene Glycol 6000

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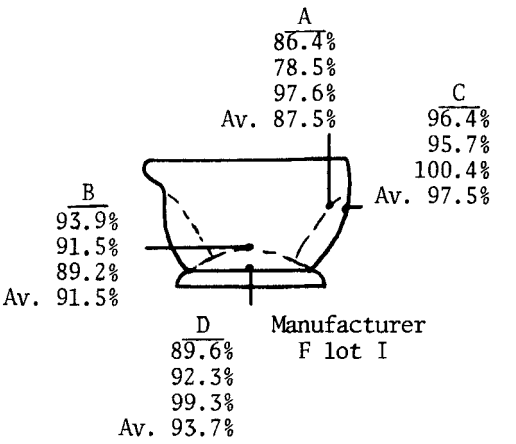

Figure #1: Segregating tablets.

was then removed with suction and discarded, and powder samples were taken from the side and bottom of the mortar (locations C and D, Figure 1).

To improve the reproducibility of the composite assays, tablets from manufacturer F, lot 1, (referred to from now on as the F tablets) were subjected to the following procedures: (a) Twenty tablets were directly dissolved in water and an appropriate dilution was assayed. (b) Twenty tablets were ground for 20 minutes in a glass mortar to a powder that would pass through a 60 mesh sieve. Grinding was repeated on the retained particles until all of the sample had been passed through the sieve. The combined powders were then mixed and assayed. (c) A suitable number of tablets was ground in a glass mortar to a fine powder. A sufficient volume of benzene was added so to produce a layer of solvent over the powder. The mixture was mixed uniformly with grinding, the solvent evaporated, and the residue assayed. (d) A suitable number of tablets was ground in a glass mortar to a fine powder. The powder was mixed with a small volume of water and ground further to obtain a fluid paste. This paste was transferred to a volumetric flask, diluted to volume with water, mixed, and a suitable aliquot of the solution assayed.

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RESULTS

Composited samples of methocarbamol tablets from nine different manufacturers were assayed spectrophotometrically in duplicate and the results obtained are given in Table 1. Both lots of tablets from manufacturer F gave assay values which ranged from 91.1 to 101.8% of declared (lot 1) and from 89.9 to 101.2% of declared (lot 2). Tablets from the other manufacturers did not exhibit this problem, the worst being duplicate results that differed by 2.2% from each other.

The F tablets were ground in a mortar to a fine powder and samples from various parts of the powder bed removed and assayed for drug content. The mean values of triplicate assays ranged from 87.5 to 97.5% of declared (Figure 1), depending on the location of the powder in the mortar. Powder obtained from the walls of the mortar (locations C and D) had the highest methocarbamol content, and that from the side of the powder bed surface (location A) gave the lowest. To determine whether the observed variability in methocarbamol concentration was the result of variability in particle sizes, particles were removed from these areas and found to differ microscopically as shown in Figure 2 (surface of the powder bed) and Figure 3 (walls of the mortar). For comparison, tablets from manufacturer D, which did not show any assay reproducibility problems, were similarly examined. Methocarbamol content of powder samples taken from various surfaces of the mortar and powder bed did not differ by more than 4% (Figure 4). Particles from the surface of the powder bed (Figure 5) and from the walls of the mortar (Figure 6) did not differ in size as markedly as did the powders for the F tablets.

Tablets from these two manufacturers were directly dissolved in water and the solutions assayed for methocarbamol. When the average of duplicate assays by this procedure was compared with average results obtained by assaying the composites, they differed by 3.6% for manufacturer D. By contrast, the same treatment of the F tablets produced averages that differed by 24.3%. Furthermore, the spread in the results

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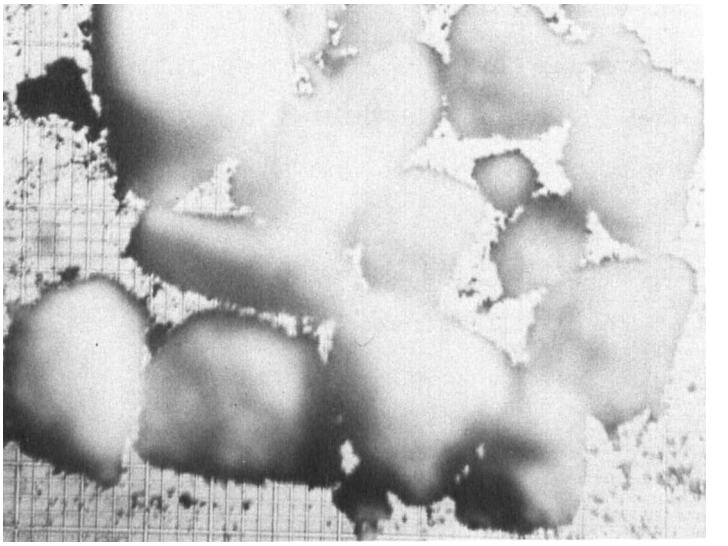

Figure #2. Segregating tablets from manufacturer F, lot 1. Sample taken from surface of the powder bed, location A, Figure #1 (32.5x).

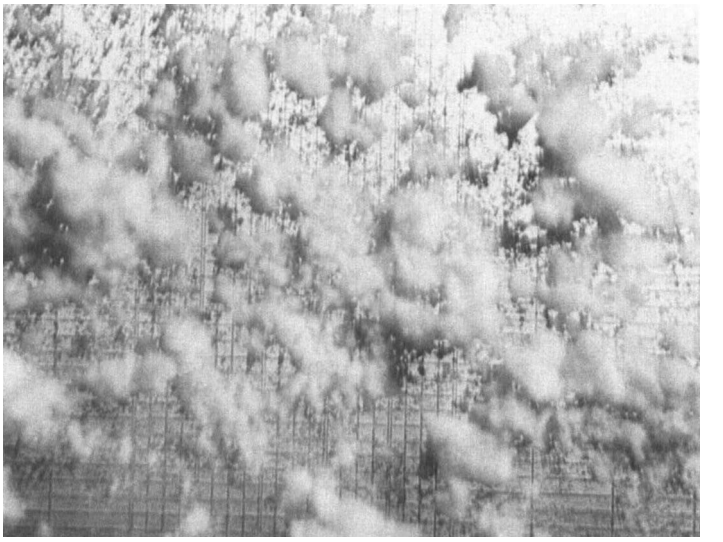

Figure #3. Segregating tablets from manufacturer F, lot 1. Sample taken from surface of the glass mortar, location C, Figure #1 (32.5x).

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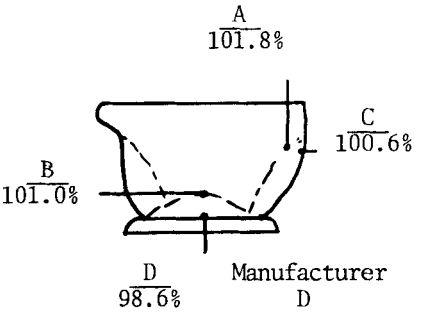

Figure #4: Nonsegregating tablets.

obtained by assaying ground composites was 10.7% for the F tablets, much greater than that noticed for the D. All of this is clearly displayed in Table 2.

Twenty F tablets were thoroughly ground to a powder, and reground as necessary, to completely pass through a number 60 sieve. Difference between the mean values of two sets of duplicate assays done on this powder was less than 0.5% from each other (Table 2 and Figure 7). To verify whether there were any significant differences in assay values between the material passing through a sieve upon a single grinding and that retained by the sieve, each portion of powder was assayed separately in duplicate. The retained material was reground and sieved prior to analysis. Assay values for the fine powders were 104.4 and 105.0% of declared, respectively; those for the retained material were 80.6 and 89.9% of declared, respectively.

A separate powdered composite produced from twenty F tablets was treated with a small volume of benzene, the fluid paste was mixed uniformly with grinding and the solvent was allowed to evaporate. The residue was then assayed for drug content. The difference between the values of duplicate assays was less than 0.5% of declared (Table 2). Material obtained from both the surface of the powder bed and from the

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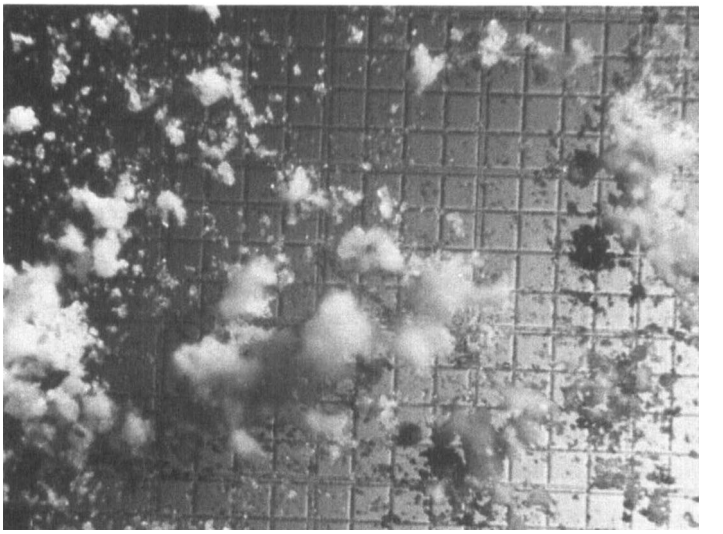

Figure #5. Nonsegregating tablets from manufacturer D. Sample taken from surface of the powder bed, location A, Figure #4 (81.9x).

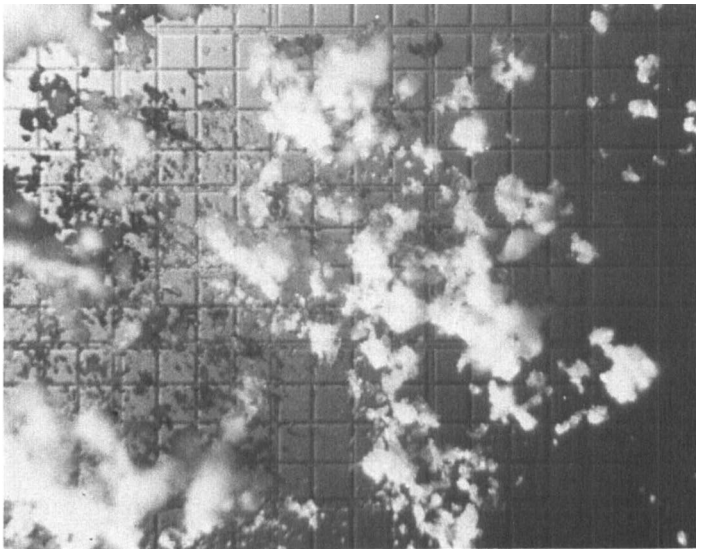

Figure #6. Nonsegregating tablets from manufacturer D. Sample taken from surface of the glass mortar, location C, Figure #4 (81.9x).

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Table 2

Determination of Methocarbamol in Tablet Samples Prepared by Five Different Methods

Manufacturer	Found, % of declared[a,b]: Ground composite, 20 tablets	Direct dissolution, 20 tablets	Grinding with solvt, 4 tablets	Grinding with solvt, 10 tablets	Grinding with sievg, 20 tablets	Grinding + dissoln + solvt evaporn, 20 tablets
D	97.3, 97.1 (97.2)	98.8, 102.8 (100.8)	N.D.[c]	N.D.	N.D.	N.D.
F (Lot 1)	91.1, 97.7 (94.4)	74.1, 74.1 (74.1)	99.5, 95.7 (97.6)	83.5, 87.1 (85.3)	97.3, 97.7 (97.5)	94.3, 95.3 (94.8)
	101.3, 101.8 (101.6)	75.2, 71.2 (73.2)	94.7, 97.5 (96.1)	83.3, 85.8 (84.6)	96.8, 97.4 (97.1)	94.3, 94.4 (94.4)
Avg. ± SD	98.0 ± 4.9	73.7 ± 1.7	96.9 ± 2.1	84.9 ± 1.8	97.3 ± 0.37	94.6 ± 0.49

[a]Methocarbamol content per tablet, 500 mg

[b]Numbers in parentheses represent average values of duplicate assays

[c]N.D. = not done

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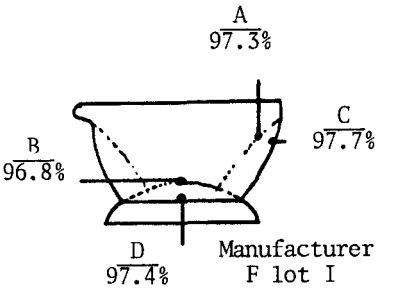

Figure #7: Sieved ground tablets.

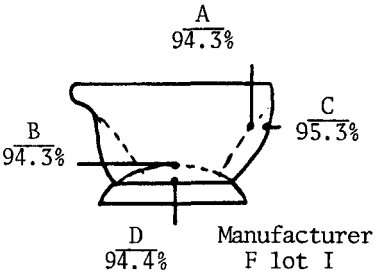

Figure #8: Dissoln. + Solvt. Evaporn., of ground tablets.

immediate walls of the mortar did not differ significantly in either drug content (Figure 8) or in particle size (Figures 9 and 10).

Two groups of F tablets, one containing four tablets and the other ten, were separately ground in a mortar with a small volume of water to a fine paste, which was then diluted to a known volume, mixed, and assayed in duplicate. The sample prepared from four tablets was assayed twice, giving a mean assay value of 98.0% of declared, and the mean assay values for each set of duplicates differed by less than 3.5% of declared from each other. Using ten tablets, the mean assay values of two sets of duplicate values differed by less than 3% of declared from each other but the overall mean assay value was only 73.7% of declared (Table 2).

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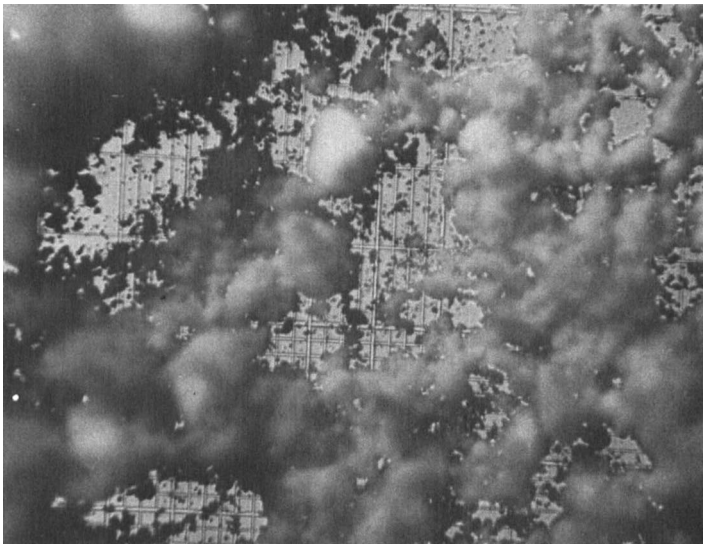

Figure #9. Segregating tablets from manufacturer F, lot 1. Sample prepared by dissolution plus solvent evaporation of the ground tablets. Sample taken from surface of the powder bed, location A, Figure #8 (32.5x).

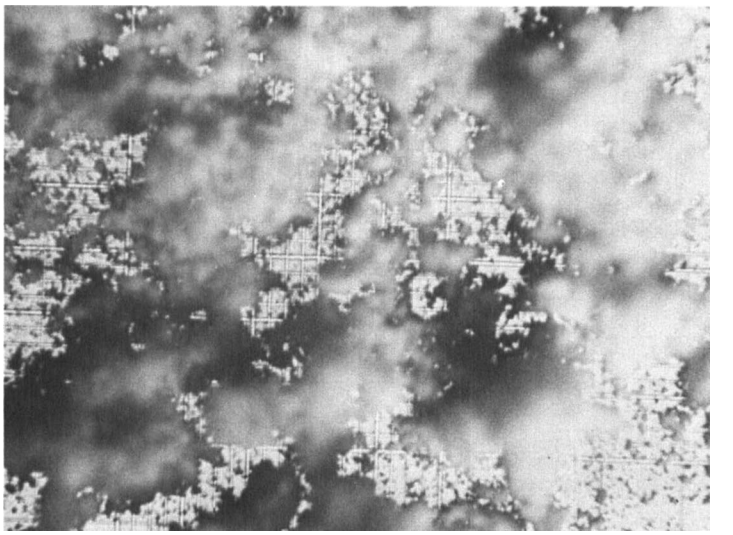

Figure #10. Segregating tablets from manufacturer F, lot 1. Sample prepared by dissolution plus solvent evaporation of the ground tablets. Sample taken from surface of the glass mortar, location C, Figure #8 (32.5x).

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DISCUSSION

Methocarbamol tablets constitute a good subject for demonstrating the existence of a segregation problem and of the effects of this problem on the reproducibility of multiple assays. This dosage form is commercially available from several manufacturers and its active ingredient can be readily analyzed.

Following the preparation of powdered composite samples by grinding in a mortar, two of the nine samples tested and identified as manufacturer F, lots 1 and 2, gave evidence of segregation problems, as inferred from the results presented in Table 1. Microscopic examination of powdered samples removed from the surface of the powder bed and immediately from the walls of the mortar revealed differing particle sizes (Figures 2 and 3). In general, particles from the surface were larger than particles from the walls. This difference appeared to correlate well with the noted differences in assay values recorded for samples from locations A and B of the powder bed and locations C and D from the center and lateral walls of the mortar (See Figure 1).

Direct dissolution of methocarbamol tablets in water significantly improved reproducibility but at the expense of the accuracy (Table 2). No such problems, however, were encountered with tablets from manufacturer D (Table 2). This raised the possibility that the conflicting results obtained with tablets from manufacturer F may be the result of the type of excipients used in the dosage form or in the technique used for their manufacture.

Table 1 summarizes some of the major excipients found in the various samples of methocarbamol tablets studied. In the production of directly compressible tablets, three major types of disintegrants are commonly used. The first group comprises the chemically modified starches, referred to as carboxymethyl starches or as sodium starch glycolates (Explotab^{R} and Primojel^{R}). The second group is represented by the cross-linked polyvinylpyrrolidones (Polyclasdone XL^{R}). The

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third group includes the chemically modified celluloses (Ac-Di-Sol^R, CLD Cellulose^R, Nymcel^R). When any of these tablet disintegrants contact water, they absorb it and can swell to many times their original particle size. The solubility of all these excipients in water decreases as their content in carboxymethyl groups or as the degree of polymerization or of cross-linking increases (4). Although the modified starches are water insoluble, they can still swell considerably when exposed to an aqueous environment, to the point of causing tablet disintegration. These swollen granules, however, can retain an otherwise water soluble active drug within its pores making the drug inaccessible to water and hence preventing its dissolution in it. This phenomenon explains the low results obtained by direct disintegration of some tablets in water (Table 2).

Grinding tablets completely to a uniformly fine powder was found to be critically important to achieving reproducibility between replicate assays. This is undoubtedly related to the increased rate of solution of methocarbamol resulting from its increased exposure to the liquid medium. Grinding, reducing a drug tablet powder to small particle sizes, increases the surface area of the active ingredient that comes into contact with the liquid, and therefore the rate of drug dissolution. Grinding can also expose any active drug that may have become trapped within the pores of a tablet excipient to a surrounding solvent. Tablets containing modified starches may exhibit this effect, particularly if larger particles are present in the final composite sample. Partial grinding of methocarbamol tablets to a powder that does not entirely pass through a 60 mesh sieve resulted in fairly reproducible assay values which differed by as much as 9.3% from each other. Interestingly, sieving in itself can act as a segregating process because during the passage of drug particles through a sieve, electrostatic charges can be induced on these particles and segregation may occur if the charges accum-

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ulate (1,5). Consequently, in order to insure reproducible assays, sieving must be followed through by mixing of the resulting powder.

Reproducible assays can also be achieved by dissolving a powdered composite sample in a volatile organic solvent in which the active drug ingredient is soluble, and evaporating this solvent to obtain a residue that has the active drug in a more homogeneous environment. The use of an organic solvent can prevent the particles from behaving as independently free flowing entities, thus eliminating most of their tendencies for segregation. Since at any time either the drug particles are temporarily present as a suspension or in solution, the final sample will be more uniform in composition and more likely to give reproducible analyses. Figure 8 to 10 indicate the suitability of this approach to sample preparation.

A fourth method of sample preparation involves the grinding of a certain number of tablets to a fine powder which is reground further in the presence of a small volume of solvent. The assay is then performed on a dilution of this mixture. This method was tested on two groups of F tablets. When four tablets were used, the variation between the highest and lowest assay values for two sets of duplicate assays was less than 0.4% of declared, with an overall mean value of 96.4% of declared (Table 2). When this procedure was repeated using ten tablets, the corresponding variation was less than 0.8% of declared but the mean assay value was only 84.9% of declared, in spite of the fact that all of the powdered composite had passed through a 60-mesh sieve. By using this method, one expects to release the active drug into a solvent, independently of the dissolution characteristics of the tablet, and to have the total composite powdered sample in a liquid medium, thus minimizing the possibility of segregation. The divergent results obtained for both groups of tablets, however, indicates that compositing a large number of tablets and trying to dissolve this com-

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posite in a solvent may result in significant quantities of active drug being left undissolved probably because the solubility limit of the drug has been approached. Consequently, when this method of sample preparation is used, the sample composite must be of a size that will both ensure total solubility of the active drug in the solvent, and be representative of the lot of tablets studied.

CONCLUSIONS

Repeated assays of one brand of methocarbamol tablets as ground composite sample resulted in assay values which differed markedly from each other.

Four alternate methods of sample preparation were evaluated on the problem tablets as alternatives to conventional grinding in a mortar and pestle, and as possible solutions to the irreproducibility of assays. These methods are summarized in Table 3.

Direct dissolution of the tablets in water significantly improved the reproducibility of the assay but with a sacrifice in the accuracy.

Exhaustive grinding of the tablets to a powder that completely sifted through a given mesh sieve resulted in assay values which were both reproducible and accurate, provided that the powder sample was thoroughly mixed prior to its assay.

Further grinding of a powdered composite tablet sample in the presence of a volatile organic solvent, followed by evaporation of the solvent, gave a sample that afforded reproducible assay values but which were slightly lower than those obtained by simple sieving of the powdered composite sample.

Grinding of a certain number of tablets to a fine powder, mixing with a suitable solvent, and performing the assay on an aliquot of the total composite tablet sample lead to a sample giving reproducible assay results but whose accuracy was dependant on the number of tablets taken and the type of solvent used. The number of tablets taken may insure

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Table 3

Advantages and Disadvantages of Various Methods of Sample Preparation for Overcoming Segregational Problems Due to Grinding

Method	Summary of Method	Advantages	Disadvantages
A	1. Directly dissolve tablet in suitable solvent. 2. Assay aliquot of soln..	Eliminates segregation.	Drug must dissolve completely in solvent upon tablet disintegration.
B	1. Grind tablets to fine powdered composite. 2. Dissolve powder in suitable solvent. 3. Assay aliquot of soln..	Eliminates segregation. Drug is released independently of dissolution characteristics of tablets.	Some active ingredient may remain undissolved because solubility limit of drug may be reached. False low results.
C	1. Grind tablets to fine powdered composite. 2. Pass powder through #60 mesh sieve. 3. Assay sievings.	Eliminates segregation tendencies. Produces particles of uniform size.	Sieving may generate electrostatic charges among particles, another cause for segregation.
D	1. Grind tablets to fine powdered composite. 2. Dissolve powder in organic solvent. 3. Continue grinding. 4. Evaporate solvent. 5. Assay residue.	Eliminates free flowing particles and segregation tendencies. Facilitates dissolution of drug in solvent.	Drug and other tablet ingredients may be chemically altered by the organic solvent.

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optimum solubility of the drug in the solvent but may not correspond to a representative sample of the lot of tablets tested.

For the direct dissolution method to be successful, one must take into account the nature of the excipients present in the tablet and, possibly, the type of manufacturing procedure used in the preparation of the tablets. Likewise, direct grinding of the tablets with a suitable solvent must consider the solubility limits of the drug of interest in the solvent. When an organic solvent must be used, the possibility of a solvent-drug interaction that might result in molecular changes of the active drug, and hence in false results, or of a solvent-excipient interaction to yield products that may interfere with the assay method, should also be considered.

Each of the methods of sample preparation presented here should be individually tested on a problem dosage form, and the corresponding results compared with each other in order to determine the best course of action for insuring reproducible and accurate assays. Advantages and disadvantages of each method are summarized in Table 3.

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