DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(9&10), 1889-1899 (1985)

III. SEGREGATION OF ACTIVE CONSTITUENTS FROM TABLET FORMULATIONS DURING GRINDING: EFFECTS ON COATED TABLET FORMULATIONS.(1)

by

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ABSTRACT

Grinding or milling coated tablets in preparation for their assay can cause the physical separation of an active ingredient from the coating and other tablet components. This phenomenon has been shown to partially account for the poor reproducibility between duplicate assays, and for discrepancies among assays for the same group of tablets but which were composited by different methods.

The effect of compositing methods on the assay results is shown with commercial enteric coated aspirin tablets from various manufac-

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(1) This report was presented at the Twenty-Third Eastern Analytical Symposium, New York Penta Hotel, November 13th 1984.

0363-9045/85/1109-1889$3.50/0

turers. Samples for assay were prepared by manual grinding with a glass mortar and pestle, mechanical grinding with an electric tablet grinder, direct dissolution of the tablets in a suitable solvent, and uncoating of the tablets with an organic solvent prior to their manual grinding.

Suggestions are offered to minimize the effects of segregation of an active tablet ingredient during grinding or milling on the assay results.

INTRODUCTION

The reliability of the assay results for a given dosage form are directly dependent on the characteristics inherent in the analytical method used, the proper execution of the method, and the optimal performance of the equipment needed. To these requirements one can add the role played by the sample preparation as a determinant of the reproducibility and accuracy of the assay results. When dealing with dosage forms such as tablets, grinding or milling usually represents the preparatory step of the analysis. During this step, active ingredients can undergo physical separation from other tablet components because of certain characteristics of the resulting particles. In a previous report (1) we described some of the factors that are responsible for the lack of reproducibility among multiple assays of the same sample, as well as some of the causative events that may develop during tablet milling or grinding. In a later report (2) various alternative methods of sample preparation were suggested in order to improve assay reproducibility while maintaining a good accuracy.

This paper is concerned with the segregation of a drug during the grinding of coated tablets. Using commercial enteric coated aspirin tablets, the effects of six methods of sample preparation on the assay results were examined, and the advantages and disadvantages of each method were contrasted.

EXPERIMENTAL

Materials.--Enteric coated 5 grains aspirin tablets from five manufacturers were obtained from commercial sources. Hydrochloric acid, methanol, chloroform, and acetone were of reagent grade.

Equipment.--All spectrophotometric readings were obtained with a Cary 219 spectrophotometer (Varian Associates, Inc., Palo Alto, CA). Tablets were ground with an electric tablet grinder fitted with stainless steel blades and housing (Chemical Rubber Co., Cleveland, OH) or an electric blender with stainless steel blades and glass housing (Waring Products Division, Hartford, CT). All sievings were done through a 60 mesh U.S. standard sieve (Dual Manufacturing Co., Chicago, IL).

Sample Preparation.--Unless otherwise indicated, the following procedures were used on groups of 20 enteric coated aspirin tablets: (A) Manual grinding: Using a glass mortar and pestle, to yield a powder that completely passed through a 60 mesh sieve. The final powder was thoroughly mixed prior to its assay; (B) Mechanical grinding on glass: Using an electric blender fitted with a glass housing. The final powder was thoroughly mixed prior to its assay; (C) Mechanical grinding on metal: Using an electric tablet grinder fitted with a stainless steel housing. The final powder was

thoroughly mixed prior to its assay; (D) Direct dissolution: In 20 ml of 1:50 methanolic hydrochloric acid and contained in a 1 L volumetric flask. After complete dissolution, the volume was made up with chloroform, and the solution mixed prior to its assay; (E) Manual grinding after enteric coating removal with methanol: Groups of 5 tablets were placed in a beaker containing methanol, and allowed to stand until the coatings started to separate from the tablets. The coatings were wiped off with a piece of lint-free paper (Kimwipes(R), Kimberly-Clark Corporation, Rosewell, GA), and the uncoated tablets were ground with a glass mortar and pestle to a powder that completely passed through a 60 mesh sieve. This procedure was repeated with an additional 4 groups of tablets. The powders were combined and mixed thoroughly prior to the assay; and (F) Manual grinding after enteric coating removal with acetone: As described for procedure (E) except that acetone was used instead of methanol.

RESULTS

Enteric coated aspirin tablets proved to be a good subject for demonstrating variability among replicate assays due to differences in sample preparation.

Table 1 gives the mean assay values for 5 brands of enteric coated aspirin tablets which were subjected to 6 methods (A-F) of sample preparation. All samples were assayed in duplicate using an official spectrophotometric method (3). To more clearly show the dependency of the assay results on the method of sample preparation, the mean assay values were corrected for potency discrepancies from 100%, so that the pooled mean values for each brand of tablets will equal 100%, as pre-

Table 1

Effects of Six Methods of Sample Preparation on the Assay Results for 5 gr Enteric Coated Aspirin Tablets: Uncorrected Values

	Found, % of declared[a,b]						
Manufacturer	I	II	III	IV	V	VI	Mean, all methods
A	98.4	103.6	94.5	101.3	99.0	94.1	98.5
B	99.7	100.3	99.0	99.4	99.2	98.6	99.4
C	101.1	98.5	96.3	98.4	95.7	92.7	96.9
D	101.8	100.0	100.7	101.8	101.5	96.7	100.4
E	104.6	104.0	99.1	103.0	101.6	98.8	101.8
Mean, all samples	100.9	101.3	97.9	100.8	99.4	96.2	

[a] All values represent the mean of two assays, and are uncorrected for differences from a mean of 100.0% of declared.

[b] I = manual grinding; II = mechanical grinding on glass; III = mechanical grinding on metal; IV = direct dissolution; V = manual grinding after removal of enteric coating with methanol; VI = manual grinding after removal of enteric coating with acetone.

Table 2

Effects of Six Methods of Sample Preparation on the Assay Results for 5 gr Enteric Coated Aspirin: Corrected Values

Manufacturer	Correction factor for 100% of decl.	Found, % of declared[a,b] I	II	III	IV	V	VI	Mean, all methods
A	+1.5	99.9	105.1	96.0	102.8	100.5	95.6	100.0
B	+0.6	100.3	100.9	99.6	100.0	99.8	99.2	100.0
C	+3.1	103.2	101.6	99.4	101.5	98.8	95.8	100.0
D	-0.4	101.4	99.6	100.3	101.4	101.1	96.3	100.0
E	-1.8	102.8	102.2	97.3	101.2	99.8	97.0	100.0
Mean ±, SD all samples		101.5±1.63	101.9±2.01	98.5±2.22	101.4±1.04	100.0±1.05	96.8±1.62	

[a] All values represent the mean of two assays. They were corrected for differences from a mean of 100.0% of declared by adding the listed correction factors to the values shown in Table 1.

[b] I = manual grinding; II = mechanical grinding on glass; III = mechanical grinding on metal; IV = direct dissolution; V = manual grinding after removal of enteric coating with methanol; VI = manual grinding after removal of enteric coating with acetone.

sented in Table 2. By plotting these corrected (mean ± SD) values against each method, one can ascertain the trends of the assay results as a function of the method of sample preparation (Figure 1).

DISCUSSION

Irrespective of the commercial source of the aspirin tablets used, the method of sample preparation will have a distinct effect on the assay results (Tables 1 and 2, Figure 1). Moreover, within a given method, variability in the assay results was also observed from one brand of tablets to another, probably due to differences in formulation and manufacturing characteristics. In general, these results also demonstrate the excellent reproducibility of the assay method.

Manual grinding with a mortar and pestle led to erratic assay results, possibly because this method is unable to reduce the coating material to the same state of comminution as that for the core material. Consequently, the powdered composite will be made up of drug particles of varying size which are unevenly distributed throughout the powdered bed, with the result that different aliquots will contain different amounts of the drug particles. This problem may be overcome by repeated resieving and regrinding of the larger particles to a uniformly sized powder.

Grinding enteric coated aspirin tablets with an electric grinder fitted with a glass housing resulted in higher assay values than with a metal housing. This discrepancy may be explained by assuming that the latter method will produce very fine, electrically charged particles, with most of the charges being distributed within the core material rather than within the coating material. Because of the dis-

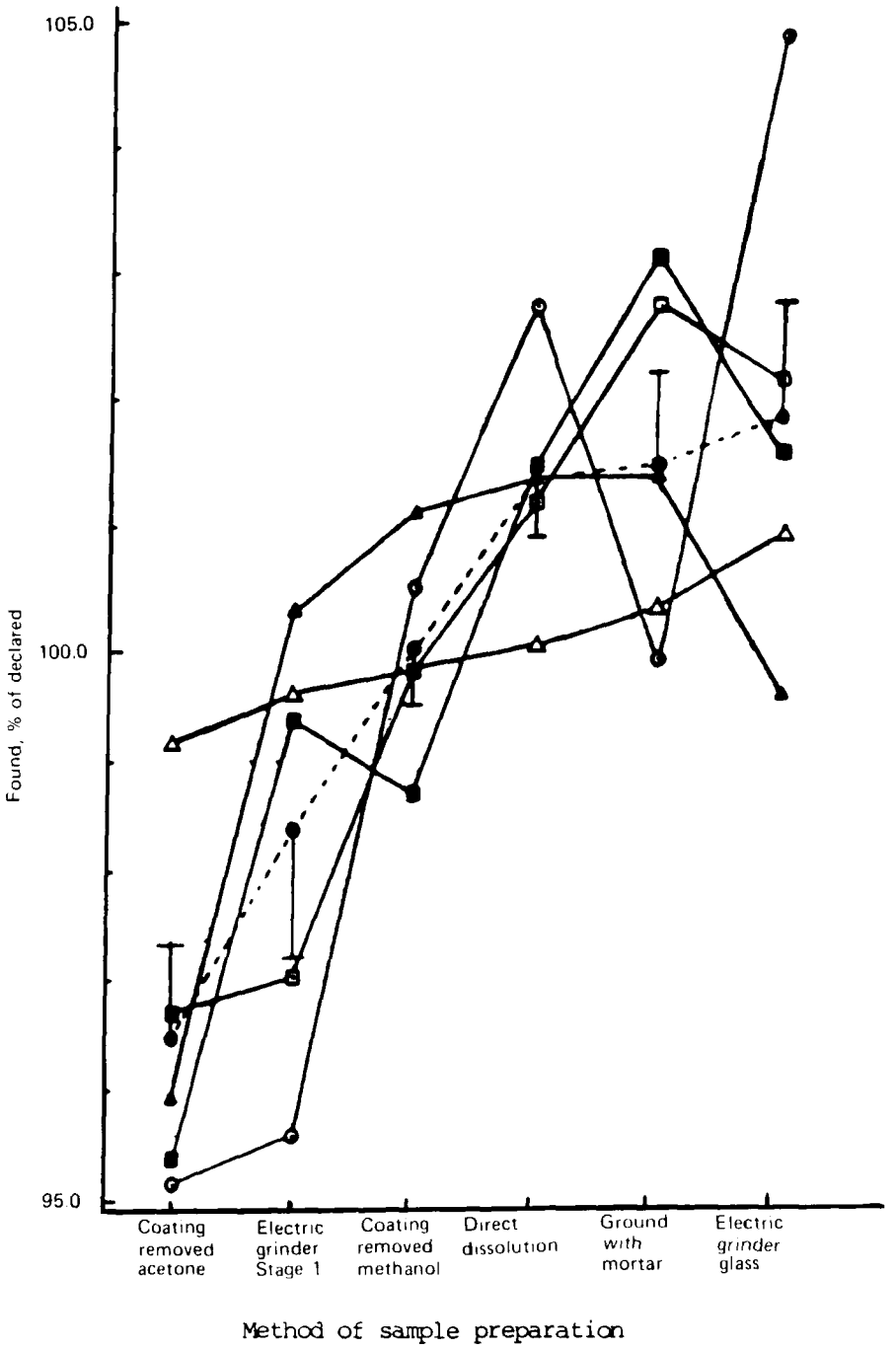

Figure 1. The effect of the method of sample preparation on the assay values of enteric coated aspirin tablets: O—O ; sample A, Δ—Δ ; sample B, ■—■ ; sample C, ▲—▲ ; sample D, □—□ ; sample E, and ●- -● the pooled mean for all samples assayed by the same method of sample preparation. Each point is the mean value of two assays. Vertical lines represent standard deviations. All values were corrected for differences from 100% of declared, as shown in Table 2.

proportionate charge distribution, particles of the active ingredient will tend to leave the core material during the grinding process, making it drug-poor. Therefore, assay values on this sample will be falsely low. Although the use of a glass housing can successfully eliminate this problem, this variation in the method can in itself produce the opposite effect, namely an apparently high assay value. This paradox may be the result of heat build up along the blade shaft and on the blades due to frictional forces generated when solid particles are rotated against metallic surfaces. Since a glass housing cannot serve as a good heat sink as a metal one does, the undissipated heat will tend to melt the coating material around the blade shaft, thus causing the powdered bed to become enriched with active ingredient.

Direct dissolution of an enteric coated tablet in a suitable solvent can effectively cause the release of the active drug into the liquid medium, and produce accurate and precise analytical results. However, this procedure will have to be individualized since not all drugs or tablet coatings will exhibit the same solubility characteristics in a given solvent.

Removing the tablet coating with an organic solvent prior to manual grinding will allow the tablets to be more uniformly ground to a fine powder, decrease segregational tendencies, and thereby increase the precision of the assay. However, the accuracy of the analytical method may still be affected if the solvent chosen removes the coating along with a significant quantity of active component, with the eventual result that the assay values will be falsely low. For illustrative purposes, two solvents such as acetone and methanol were separately tested and their effects compared.

Table 3

Summary of Methods of Sample Preparation with Individual Advantages and Disadvantages

Method	Description	Advantages	Disadvantages
I	Grind tablets with a mortar and pestle to a powder that will completely pass through a #60 mesh sieve.	Eliminates segregational tendencies by producing drug particles of uniform size.	Some tablet coatings will not become ground as fine as the core material. Due to the uneven particle size composition, it may yield erratic assay results.
II	Grind tablets with an electric tablet grinder fitted with a glass housing.	Produces very fine particles without the build up of electrostatic charges.	Tablet coating may melt due to the build up of heat along the blade shaft and leave the tablet composite matrix. Hence, assay results may be falsely high.
III	Grind tablets with an electric tablet grinder fitted with a metal housing.	Produces very fine particles.	Electrostatic charges may build up on the core material. Assay results may be falsely low due to the attraction of drug particles by metallic surfaces.
IV	Dissolve tablets in a suitable solvent and assay the solution.	Eliminates segregation of particles.	Requires a solvent that will be able to dissolve both tablet coating and active ingredient.
V, VI	Remove tablet coating with a solvent prior to manual grinding as in (I).	Eliminates segregational tendencies by allowing the tablet core to be ground to particles of uniform size.	May result in falsely low results due to the possible removal of some active ingredient along with the tablet coating.

CONCLUSIONS

Six methods of sample preparation were individually tested on various brands of enteric coated aspirin tablets. The analytical results varied according to the method of sample preparation used (Tables 1 and 2, Figure 1). Therefore, each approach should be individually tested on a problem dosage form and its effects on the precision and accuracy assessed. Each method of sample preparation was found to possess its own advantages and disadvantages (Table 3).

ACKNOWLEDGMENTS

The author wishes to thank Cesar A. Lau-Cam, Ph.D., Science Advisor, Food and Drug Administration, New York Regional Laboratory, and Professor of Pharmacognosy, St. John's University, College of Pharmacy and Allied Health Professions, Jamaica, New York, for his invaluable assistance in the preparation of this paper.

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