DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 8(2), 145-168 (1982)

TABLET-TO-TABLET DISSOLUTION VARIABILITY AND ITS RELATIONSHIP TO THE HOMOGENEITY OF A WATER SOLUBLE DRUG

Z.T. Chowhan, A.A. Amaro and Y.P. Chow

Syntex Research
Division of Syntex (USA) Inc.
3401 Hillview Avenue
Palo Alto, CA 94304

ABSTRACT

The homogeneity of a water soluble drug in a tablet granulation was studied by mixing the granulated drug with excipients in a V-shaped tumbling mixer. Samples were withdrawn from five different locations of the mixer for homogeneity and dissolution studies at different mixing times. For dissolution studies, tablets were compressed at a constant compression load. Qualitatively, the coefficient of variation of mixing and dissolution looked similar, suggesting that the mixing homogeneity may have some relationship to the tablet-to-tablet dissolution variability. The addition of magnesium stearate resulted in an increase

in the coefficient of variation of mixing and a decrease in the dissolution rate. A large decrease in the dissolution rate occured during the first minute of mixing with the magnesium stearate. The tablet crushing strength continuously decreased during the first 10 minutes of mixing with the magnesium stearate. The results suggested that the formulation in which a major portion of the excipients was not wet granulated with the drug resulted in higher tablet-to-tablet dissolution variability. The addition of sodium starch glycolate or sodium carboxymethyl cellulose to starch for enhancing disintegration neither improved the tablet-to-tablet dissolution variability nor increased the rate of drug dissolution.

INTRODUCTION

During the development of a tablet formulation, the formulators are generally faced with the formidable problem of large tablet-to-tablet variability in dissolution of the drug. The USP XX(1) established a three-stage criteria requiring that the individual tablets meet certain minimum requirements in order to ensure compliance with the dissolution specifications,

when stated, in the individual monographs. The importance of some of the mechanical factors influencing the tablet-to-tablet variability in drug dissolution has been emphasized (2). In order to minimize the influence of the mechanical factors on dissolution variability, the USP XX has set forth guidelines such as smooth rotation without wobble of the rotating member and without significant contribution from any part of the apparatus to motion, agitation or vibration.

Large tablet-to-tablet variability in dissolution seen in disintegrating tablets, at least in part, could be attributed to the differences in the effective surface area exposed to the dissolution medium.
Tablets containing a large percentage of hygroscopic and highly soluble drugs generally do not disintegrate in the dissolution medium. The drugs dissolve mainly from the effective surface area of the exposed tablet. For non-disintegrating tablets, the variability in dissolution caused by the physical characteristics of the dosage form may be more pronounced compared to the tablets which disintegrate during the dissolution process.

Since the dissolution variability resulting from the physical characteristics of the dosage form have not been thoroughly investigated, it was the purpose of this study to evaluate the relationship between mixing homogeneity of dry granulation blends and tablet-to-tablet dissolution variability of non-disintegrating tablet formulations. The effect of improving the homogeneity of dry granulation blends on variability in dissolution data was also studied. Under constant compression load, mixing magnesium stearate with dry granulation blends decreased the tablet crushing strength and increased the dissolution coefficient of variation. Combinations of starch with sodium starch glycolate or sodium carboxymethyl cellulose as disintegrants were included in the formulations to study their effect on the dissolution rate and the tablet-to-tablet dissolution variability.

MATERIALS AND METHODS

Materials

The drug, naproxen sodium [sodium-(+)-2-(6'-methoxy-2'-naphthyl) propionate] was obtained (Syntex Research, Palo Alto, CA) with a purity of at least 99%. The excipients used in this study were

microcrystalline cellulose (Avicel pH 102, FMC Corporation, Philadelphia, PA), spray dried lactose USP (Foremost - McKesson, San Francisco, CA), starch USP (corn, Staley Manufacturing Co., Decatur, IL.), povidone USP (K 29-32, GAF Corp., New York, NY), magnesium stearate USP (Mallinckrodt Manufacturing Co., St. Louis, MO.), sodium starch glylolate (Explotab, Edward Mendell Co. Inc., Carmel, N.Y.) and sodium carboxymethyl cellulose (Ac-Di-Sol, FMC Corporation, Philadelphia, PA).

Granule Preparation:

Tablet formulations used in this study are given in Table I. Either the drug or the drug and the appropriate excipients were granulated with water or with an aqueous solution of povidone. The excipients and/or the drug were mixed in a planetary mixer (Kitchen Aid model K5-A, Hobart Manufacturing Co., Troy, OH.) for 10 minutes prior to the wet granulation. The wet granulations were passed through a # 14 screen and dried in a forced air oven at 65 - 70° C until the desired moisture level was obtained. The dried granulation was passed through a # 16 mesh screen.

Dry Granulation and Excipient Mixing:

The dry granulation and the excipients were mixed in a V-shaped tumbling mixer (Patterson - Kelley Co., East

TABLE I TABLET FORMULATION

	Ingredients as Percent of Total Tablet Weight						
Formulation	1)$_A$	2)$_B$	2,3)$_C$	4)$_D$	4)$_E$	5)$_F$	1)$_G$
Naproxen Sodium	65.85	66.10	65.73	65.64	65.61	65.61	65.77
Microcrystalline Cellulose	19.16	-	-	-	-	-	19.13
Starch	-	9.61	9.56	9.55	9.53	9.56	-
Sodium Starch Glycolate	-	-	-	2.39	3.81	-	-
Sodium Carboxymethyl-Cellulose	-	-	-	-	-	2.86	-
Lactose	9.33	17.06	16.97	14.56	13.10	14.08	9.33
Povidone	-	1.92	1.91	1.91	1.91	1.91	-
Magnesium Stearate	1.45	1.45	1.43	1.43	1.43	1.43	1.43
Water	4.21	3.86	4.39	4.52	4.72	4.57	4.34
Tablet Weight mg.	208.8	208.0	418.36	418.36	419.82	419.16	418.15
Tablet Crushing Strength s.c.u.	-	-	9.53 ±0.74	10.50 ±1.21	9.40 ±0.66	10.52 ±1.11	11.32 ±1.01

Footnotes

1) Only drug was wet granulated with water.
2) Drug and excipients except magnesium stearate were wet granulated.
3) Drug and excipients except magnesium stearate and starch were wet granulated.
4) Drug and excipients except sodium starch glycolate and magnesium stearate were wet granulated.
5) Drug and excipients except 1.43% sodium carboxymethyl cellulose and magnesium stearate were wet granulated.

Stroudsburg, PA). Each mixing study used a total load of 1 ± 0.1 kg. The granules were added first to the mixer and then the excipients were individually loaded through one side of the mixer. The mixing was carried out for appropriate time intervals.

Content Uniformity:

At each time point, 5 locations in the mixer were sampled. Twenty samples, each equivalent to the weight of one tablet, were obtained. The samples were dissolved in 50 ml of purified water and appropriately diluted. The absorbance (Unicam SP 1800 spectrophotometer, Pye Unicam LTD., Cambridge, England) of naproxen sodium samples was measured at 332 nm. For each time point, the mean naproxen sodium weight, the standard deviation and coefficient of variation were calculated.

As a baseline determination, the content uniformity of the naproxen sodium in the granules was determined prior to mixing.

Tablet Compression:

A total of 22 tablets were compressed at each sampling point on a Carver press (Fred S. Carver Inc. Summit,

N.J.) at constant load using 0.79 cm diameter flat-face punches and die. For formulation A, the compression load was 635kg and for formulation B, it was 454kg. The other formulations were compressed to the same crushing strength by selecting the compression load from compression load versus crushing strength profiles.

Crushing Strength:

The tablet crushing strength was determined by the Schleuniger hardness tester (model 2E). Ten tablets were tested for each sampling point and the mean and standard deviation were calculated.

In Vitro Dissolution:

The USP method II was used. For each sampling point, 12 tablets were tested. Only 6 tablets were tested for formulations C through G. The apparatus consisted of USP paddles driven by a multiple - spindle drive with a variable speed control (model 72R, Hanson Research Corp., Northridge, CA), 1-liter round-bottom plastic flasks (Elanco, Indianapolis, IN) and a water bath. The dissolution medium was 600 ml deaerated water equilibrated at 37° C and stirred at 50 rpm or 120 rpm. The dissolved drug was analyzed by recording

the absorbance at 332 nm. using an automated monitoring system consisting of a peristaltic pump (model 1210, Harvard Apparatus, Millis, MA), micro spectrophotometer flow cells and an automatic sample changer/spectrophotometer (model 25, Beckman Instruments, Fullerton, CA). The absorbances were plotted on a recorder every minute until complete dissolution was achieved. The mean percent dissolved and the standard deviation at several time points along the dissolution curve were calculated.

The dissolution apparatus was calibrated using USP dissolution calibrator tablets (prednisone 50 mg). The mean dissolution and the standard deviation were within the required specifications.

Results and Discussion

Two mixing studies were carried out to investigate the effect of the homogeneity of the final tablet granulation blend on tablet-to-tablet dissolution variability. In the first study, the dry drug granules (formulation A) were mixed with the excipients including magnesium stearate and samples withdrawn at different time points to determine the

granulation blend homogeneity. For the dissolution study, tablets were compressed at a constant compression load. Fig. 1 gives the plots of the coefficient of variation of mixing and dissolution versus the mixing time. Qualitatively, the coefficient of variation of mixing and dissolution look similar, suggesting that the mixing homogeneity of the final granulation blend may have some relationship to the tablet-to-tablet variability in dissolution.

The dry drug granules were mixed with the excipients except magnesium stearate (formulation A) for 15 minutes in the second study. After 15 minutes of mixing, magnesium stearate was added and mixing continued. Fig 2 gives the plots of the coefficient of variation of mixing and dissolution versus mixing time. Similar shapes of the plots of the coefficient of variation of mixing and dissolution suggest that the tablet-to-tablet variability in dissolution may be related to mixing homogeneity of the final tablet granulation blend.

For the two studies, the plots of the percent dissolution at 4 minute and 8 minute time points as a function of the mixing time are given in Fig 3-4. The

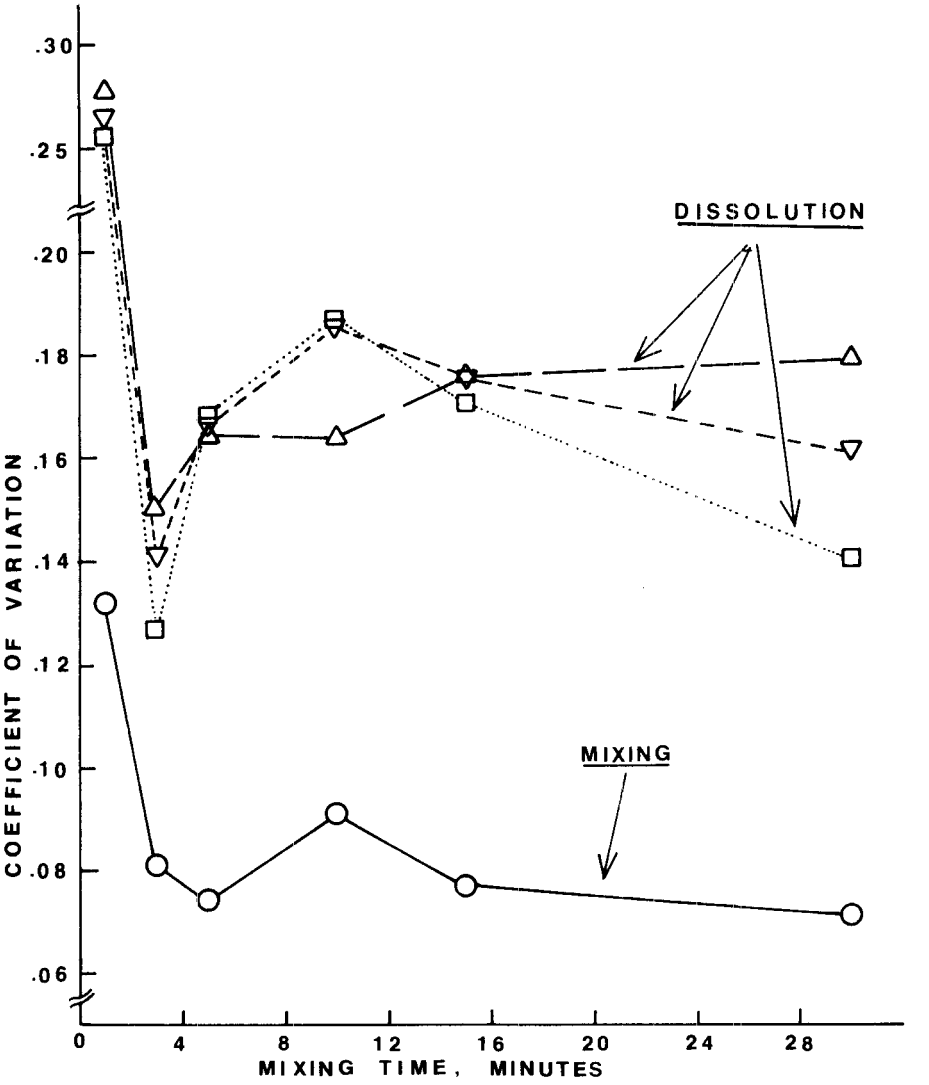

FIG 1:

Plots of the coefficient of variation of dry granulation mixing and tablet dissolution versus mixing time. All excipients were mixed with the drug granules. The stirring speed for the dissolution experiments was 120 rpm. Key: ○, mixing variation coefficient; △, 4 minute dissolution; ▽, 6 minute dissolution; □, 8 minute dissolution.

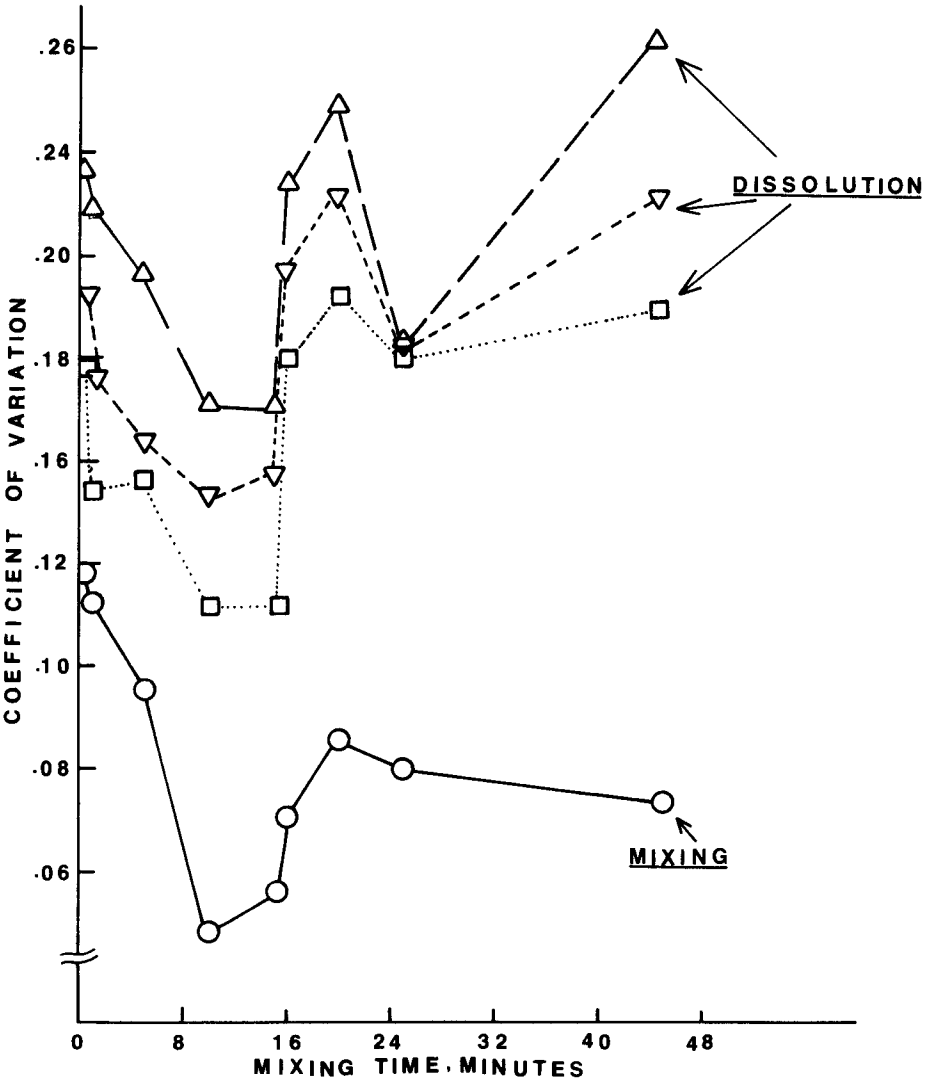

FIG 2:

Plots of the coefficient of variation of dry granulation mixing and tablet dissolution versus mixing time. Magnesium stearate was added after mixing the drug granules and other excipients for 15 minutes. The stirring speed for the dissolution experiments was 120 rpm. Key: ○, mixing variation coefficient; △, 4 minute dissolution; ▽, 6 minute dissolution; □, 8 minute dissolution.

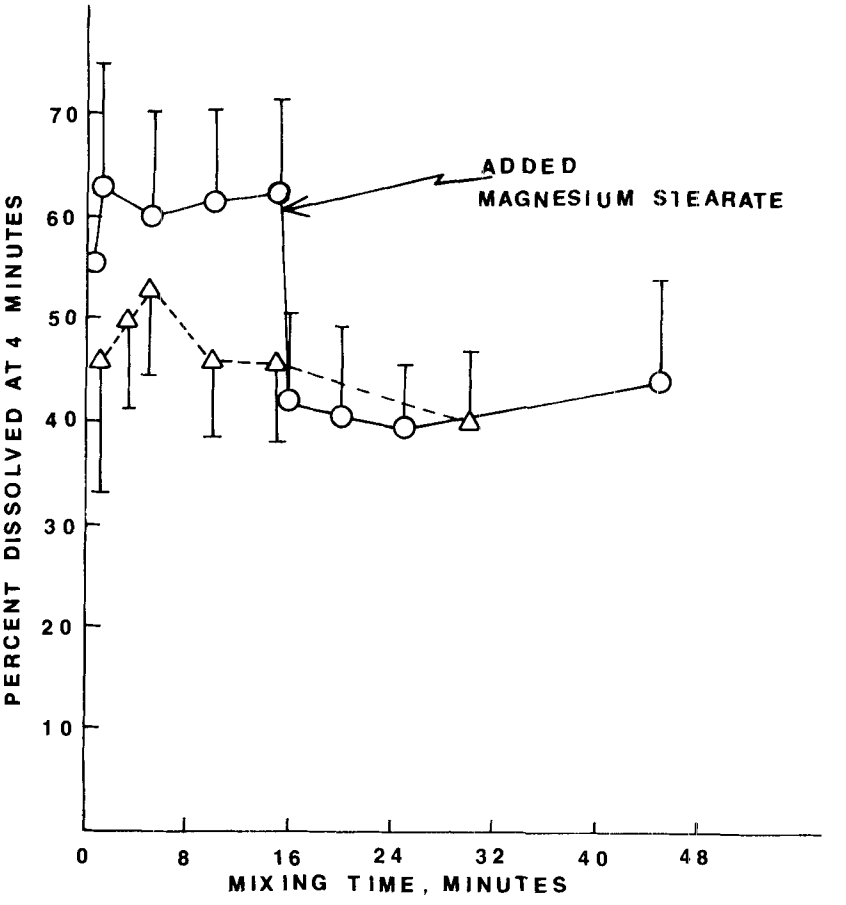

FIG 3:

Effect of the dry granulation mixing time on drug dissolution at 4 minute time point. The drug granules were mixed with the excipients (Table I, formulation A) and compressed into tablets at 635 kg load. Key: ○ , magnesium stearate added after 15 minute mixing; △ , all excipients mixed with the drug granules. Vertical lines show standard deviations.

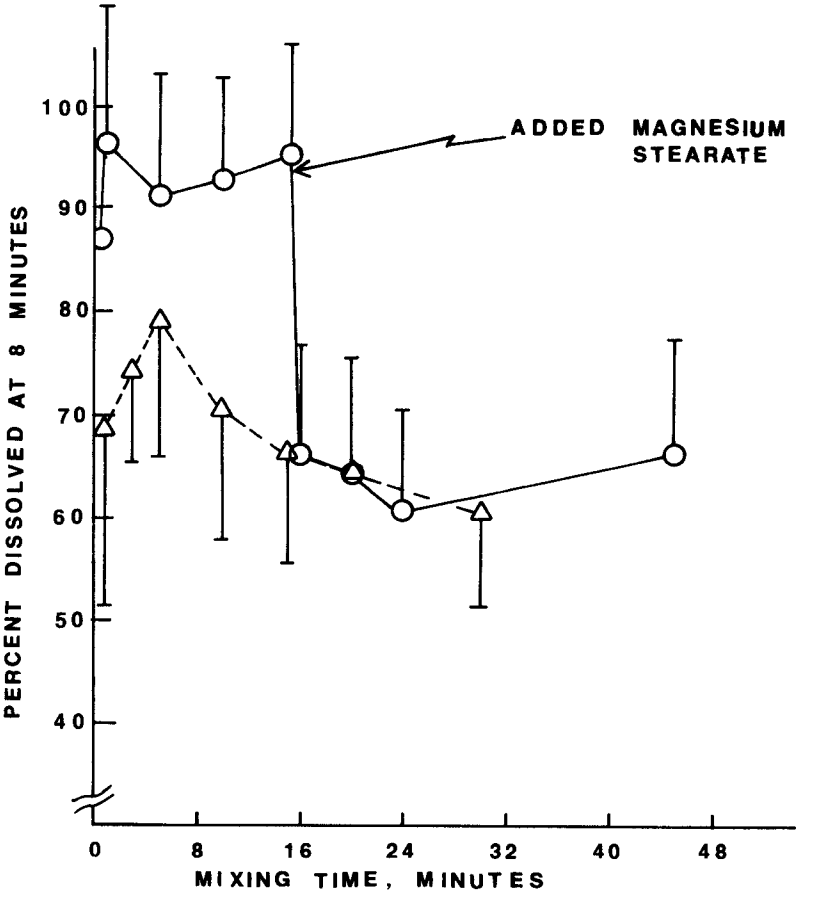

FIG 4:

Effect of the dry granulation mixing time on drug dissolution at 8 minute time point. The drug granules were mixed with the excipients (Table I, formulation A) and compressed into tablets at 635 kg load. Key: ◯, magnesium stearate added after 15 minute mixing; △, all excipients mixed with the drug granules. Vertical lines show standard deviations.

results indicate a significant reduction in the drug dissolution caused by the addition of magnesium stearate. This reduction in drug dissolution occurred during the first minute of mixing with magnesium stearate. Additional mixing up to about 30 minutes did not appear to either reduce the amount of drug dissolved or increase the tablet-to-tablet variability.

Because the tablets were compressed at a constant compression load in both studies, it was important to investigate the effect of magnesium stearate and mixing time on tablet crushing strength. Fig. 5 gives the tablet crushing strength versus mixing time plots for the two studies. The tablet crushing strength decreased due to mixing with the magnesium stearate and reached a plateau value after mixing for 10 minutes.

The drug homogeneity in the tablet may be improved by mixing and wet granulating the drug with other excipients except the lubricant, which is usually blended in the dry form. Formulation B (Table I) was used for this study and the drug and the excipients except magnesium stearate were mixed, wet granulated, dried, screened and mixed with the lubricant. The

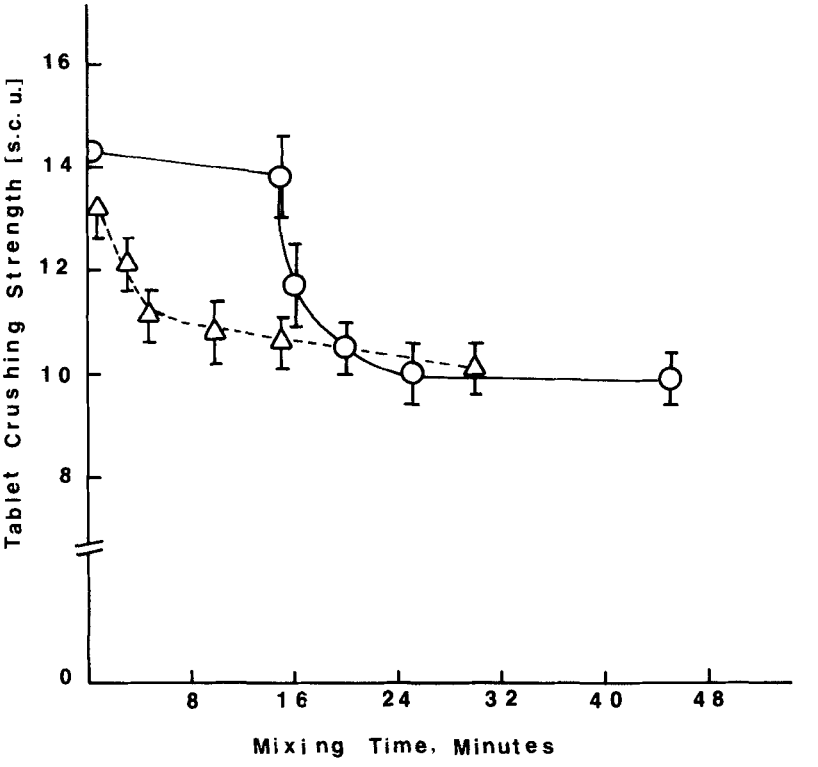

FIG 5:

Tablet crushing strength versus dry granulation mixing time of tablets compressed at 635 kg load. Key: ○, magnesium stearate added after 15 minute mixing; △, all excipients mixed with the drug granules.

homogeneity of the dry granulation blend and the coefficient of variation of dissolution determined at 50 and 120 rpm are given in Fig. 6. For this formulation, the coefficient of variation of mixing increased due to the segregation caused by the

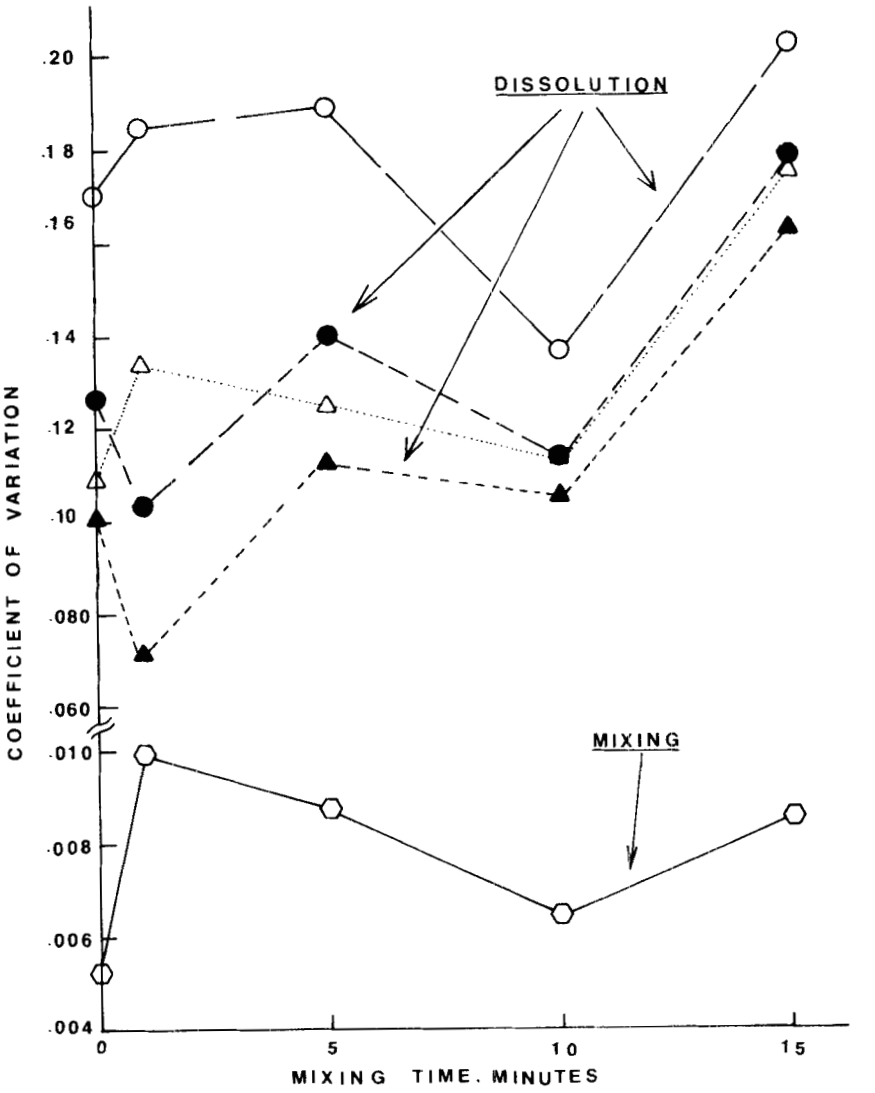

FIG 6:

Plots of the coefficient of variation of dry granulation mixing and tablet dissolution versus mixing time. Only magnesium stearate was mixed in the dry state with the drug-excipient granules (Table I, formulation B). Key: ○, 6 minute dissolution at 50 rpm; △, 10 minute dissolution at 50 rpm, ●, 4 minute dissolution at 120 rpm; ▲, 6 minute dissolution at 120 rpm; ⬡, mixing.

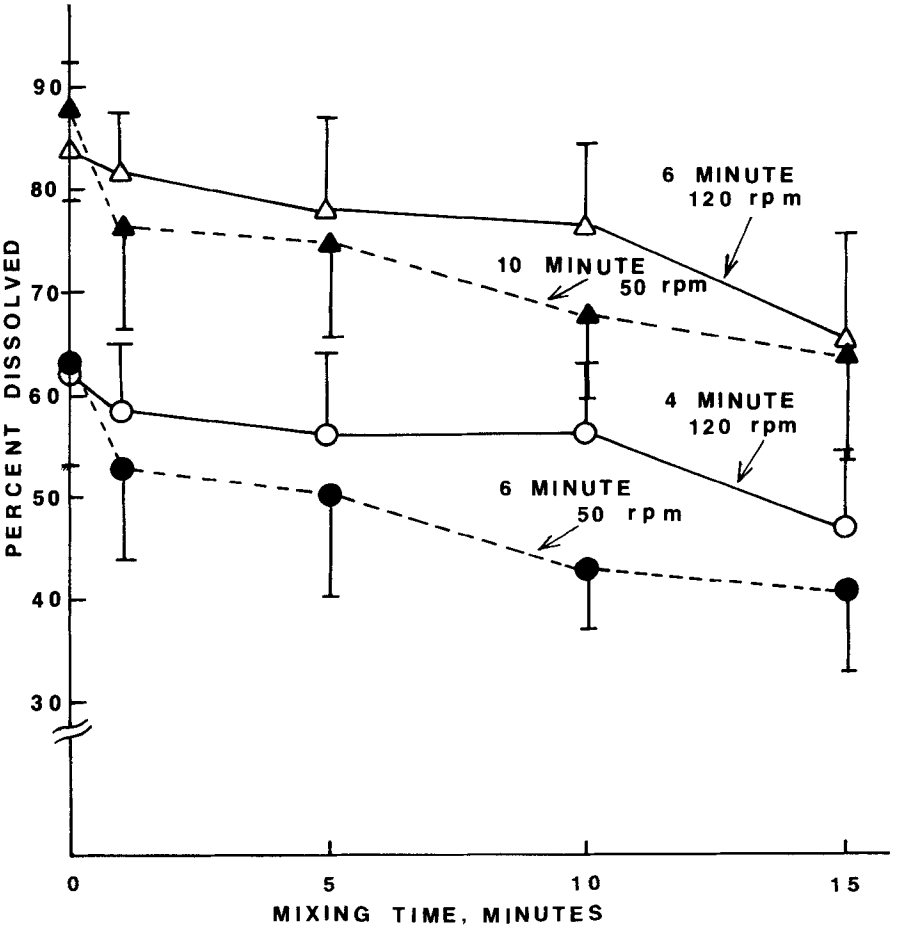

FIG 7:

Effect of dry granulation mixing time on drug dissolution. The drug and the excipients (Table I, formulation B) except magnesium stearate were wet granulated, dried, mixed with the magnesium stearate and compressed at 454 kg load. Key: Open data points represent stirring speed of 120 rpm while closed data points represent stirring speed of 50 rpm.

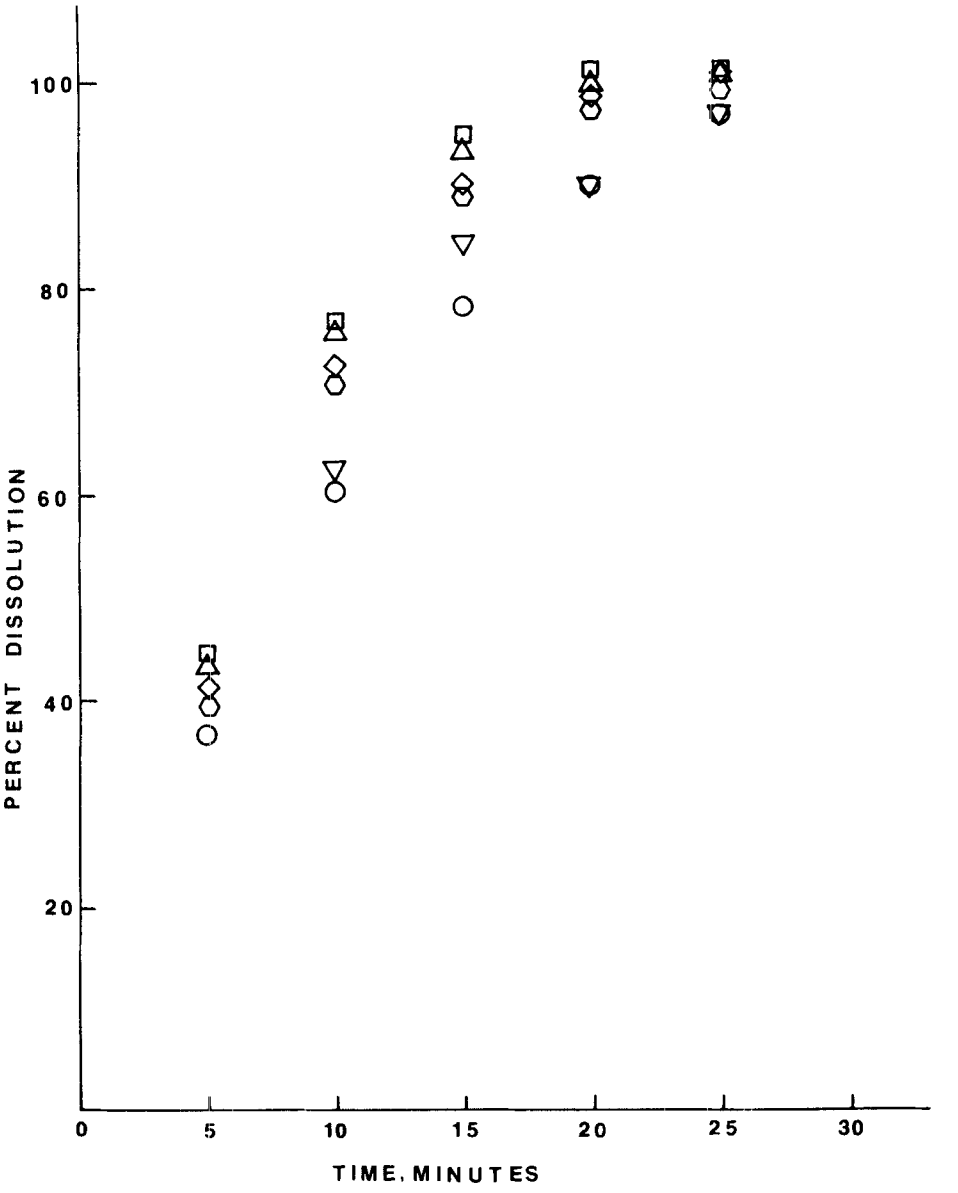

FIG 8:

Dissolution-time profiles. Key: ○, formulation G; △, formulation [3)]C; ▽, formulation [2)]C; □, formulation D; ◇, formulation E; ⬡, formulation F.

magnesium stearate. At early mixing time points, an increase in the mixing coefficient of variation resulted in an increase in the dissolution variation coefficient at 50 rpm stirring speed. This was not true at a stirring speed of 120 rpm. At later mixing times, the mixing and the dissolution coefficients of variation showed qualitative similarity, suggesting some relationship between mixing homogeneity and tablet-to-tablet dissolution variability. Comparisons of the results given in Fig. 6 and Fig. 2 (after magnesium stearate was added) suggest that the wet granulation of the drug and the excipients resulted in better mixing homogeneity compared to the mixing of the drug granules and the excipients (coefficient of variation 0.0065 vs. 0.08 after 10 minutes mixing). However, only a small decrease in the coefficient of variation of dissolution was seen, suggesting that the homogeneity of mixing of the final tablet blend is only one of the several factors affecting physical characteristics of the final dosage form.

Fig. 7 gives the plots of the drug dissolution at different time points and stirring speeds as a function of the mixing time of the final tablet granulation blend (formulation B). These results

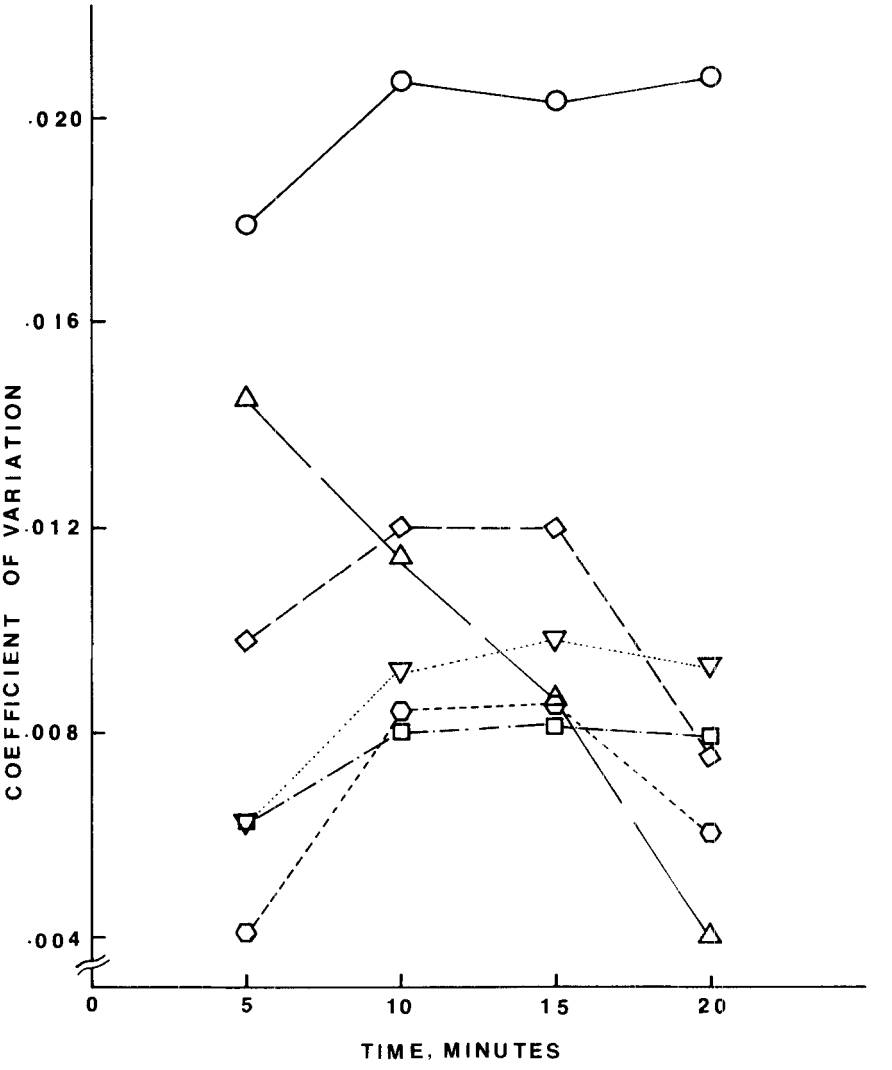

FIG 9:

Coefficient of variation of dissolution versus dissolution time plots. Key: ○, formulation G; △, formulation [3)]C; ▽, formulation [2)]C; □, formulation D; ◇, formulation E; ⬡, formulation F.

suggest no effect of the stirring speed on tablet-to-tablet variability in dissolution and also indicate a decrease in the amount of drug dissolved due to the continued mixing with the magnesium stearate.

In an attempt to improve the variability in dissolution results, several modifications in the formula (Table I, formulations C through G) were tried. Fig. 8 gives the dissolution profiles of the modified formulations as a function of time. Formulation G, which is essentially the same as formulation A, was slower in dissolution rate compared to the formulations containing starch and also a combination of starch with either sodium starch glycolate or sodium carboxymethyl cellulose. The plots of the coefficient of variation of dissolution versus time for formulations C through G are given in Fig. 9. These results indicate that the formulation in which the major portion of the excipients were not wet granulated with the drug resulted in higher tablet-to-tablet variability. The addition of sodium starch glycolate or sodium carboxymethyl cellulose to starch for enhancing disintegration neither improved the tablet-to-tablet variability nor increased the rate of drug dissolution.

Conclusion

Although the formulations used in this study contained a high percentage of a water soluble and hygroscopic drug (66%), the results suggested that the homogeneity of the final granulation blend is just one of several factors causing dissolution variability in compressed tablets. Since these tablets did not show obvious signs of disintegration in the dissolution medium, additional disintegrating agents were tried. Sodium starch glycolate and sodium carboxymethylcellulose in addition to 10% starch neither improved dissolution variability nor increased the rate of drug dissolution. A large increase in the dissolution variability and a decrease in the dissolution rate resulted during the first minute of mixing with the magnesium stearate. On further mixing with this lubricant the dissolution rate and the dissolution variability remained essentially the same, but the tablet hardness showed a continuous decrease during the first 10 minutes of mixing. This study suggests that an understanding of the physical characteristics of the dosage form is needed in designing tablet formulations.

REFERENCES

1. The United States Pharmacopeia, 20th Revision, Easton, PA, Mack Publishing Co., 1980.

2. W.I. Hanson, Pharmaceutical Technology, 1, 31 (1977).