DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(10), 1327-1349 (1988)

THE EFFECT OF THE WET GRANULATION PROCESS ON DRUG DISSOLUTION

Hoshang M. Unvala, Joseph B. Schwartz and
Roger L. Schnaare
Department of Pharmacy
Philadelphia College of Pharmacy and Science
Philadelphia, PA 19104

ABSTRACT

Wet granulation can be an important processing step for pharmaceutical solid dosage forms. In this investigation emphasis was directed towards the influence of a "simple" wet granulation process on drug release from granules and their resulting tablets. Direct compression blends of the same materials were used as controls. Binary mixtures containing a 5% level of either theophylline, hydrochlorothiazide or chlorpheniramine maleate in microcrystalline cellulose or lactose were granulated

with water. Experimentally, the powders were dry blended in a planetary mixer, wet granulated, and subsequently wet milled and dried. No dry milling step was included. Granule characterization consisted of particle size, density, porosity, compression and dissolution testing. Dissolution results varied with the drug, as expected, and dissolution at 10 minutes ranged from 35 to 95 % release. In general, however, the results indicate that dissolution from granules and the corresponding direct compression blend are similar. Although differences in compressibility were observed in the systems studied, granulation was not found to be detrimental to drug release.

INTRODUCTION

Granulation is usually carried out on materials in order to facilitate flow and compressibility. Most of the information on granulation techniques available in the pharmaceutical and engineering literature[1-11] deals with complex formulations where more than three components have been included. Since they involve many variables, it is difficult to make conclusions about the granulation process itself[12-21].

In this study[22], the term wet granulation refers to the sequence of unit operations by which dry particulate material is moistened and caused to agglomerate into granules.

The granulating liquid is known to play a key role in the agglomeration process and it is believed that liquid bridges are formed between particles. The tensile strength of these bonds increases with increasing liquid levels, up to a certain point[23].

During the granulation process the action of machine parts and inter-particulate contact and abrasion may subject the agglomerates and particles to consolidating forces which may increase contact points between particles.

The work of Alleva[24], provides supporting data related to simple systems, and measurements of the physico-chemical properties have been correlated to the performance of excipients as single components and as simple binary mixtures.

The present investigation deals with binary systems which have been processed by carefully controlling the variables, and the information obtained serves to correlate key processing variables to properties of products and to isolate them from material properties and their effects on the properties of final products.

MATERIALS AND METHODS

Preparation of direct compression blends

The direct compression blends were prepared as binary mixtures containing 95% Microcrystalline

Cellulose, NF (Avicel PH-101, FMC Corporation, Philadelphia, PA) and 5% drug. The following three drugs, with solubilities ranging from very slightly soluble to freely soluble, were selected for this study: (1) Hydrochlorothiazide, USP (E. R. Squibb & Sons, Inc., Princeton, NJ); (2) Theophylline, USP (FMC Corporation, Philadelphia, PA); and (3) Chlorpheniramine Maleate, USP (Vita American Corporation, Little Falls, NJ).

The powders were blended in a planetary mixer for 5 minutes. Also, binary mixtures containing 5% hydrochlorothiazide and 95% Lactose, USP (Fast Flo, Foremost Foods Company, San Francisco, CA) were prepared in a similar manner.

Preparation of Granulation

The same powder mixtures that were used to prepare the direct compression blends (500 grams) were wet granulated with 500 ml purified water in a planetary mixer for 15 minutes. The granulated mass was wet milled through an 8 mesh screen and the resulting granules were dried overnight in an oven at 40 degrees Celsius.

In another part of the study, the formation of granules and their properties were investigated as a

function of mixing time. Three blends of 5% hydrochlorothiazide in microcrystalline cellulose (MCC) were granulated with 500 ml water for 5, 15, and 30 minutes mixing times respectively. The study was accomplished by measuring physical properties of the dry granules and constructing compression and dissolution profiles.

It is known that the amount of granulating liquid has considerable influence on the properties of a granulation[23]. The objective of another part of the study was to monitor the properties of granules as a function of liquid level in formulations containing 5% hydrochlorothiazide and MCC. Three granulations were prepared with 44.44, 50.00, and 54.54 percent (i.e., 400, 500, and 600 ml per 500 grams dry powder) purified water as granulating liquid respectively. In each case the wet mixing time was 15 minutes. The details of the granulation process have been described earlier. The percentage water added was calculated as follows:

$$\% \text{ water added} = \frac{W}{P + W} \times 100$$

where W is the weight of water added, and P is the weight of dry powder.

Compression of Granules and Direct Compression Blends

Compression of the granules and the direct compression blends was achieved by using a hydraulic Carver Laboratory Press by applying forces ranging from 2.2 kN to 22.0 kN (500 lb to 5000 lb) using flat-face, 1/2 inch round punches.

PHYSICAL TESTING AND DISSOLUTION

Particle size distribution was determined by conventional sieve analysis. Bulk and tapped densities were determined by packing the samples in a graduated cylinder to constant volume by tapping. Mercury intrusion porosimetry was used to obtain the porosity measurements and scanning electron micrographs of the samples were prepared (FMC Corporation, Princeton NJ). Tablet hardness was determined on an electric Heberlein hardness tester.

Dissolution testing was done on uncompressed direct compression blends (control), the 16/30 mesh fraction of granules and on the compressed tablets made from them.

The dissolution test was performed in 900 ml distilled water at 37 degrees Celsius using the USP Method I, at 50 rpm. All the samples were analyzed by UV spectrometry at appropriate wavelengths.

FIGURE 1

Scanning electron micrograph of direct compression mixture containing 5% theophylline and microcrystalline cellulose, magnification: 60X

RESULTS AND DISCUSSION

Theophylline/MCC

Scanning electron micrographs shown in Figures 1 and 2 indicate that the formulation containing 5% theophylline and 95% microcrystalline cellulose

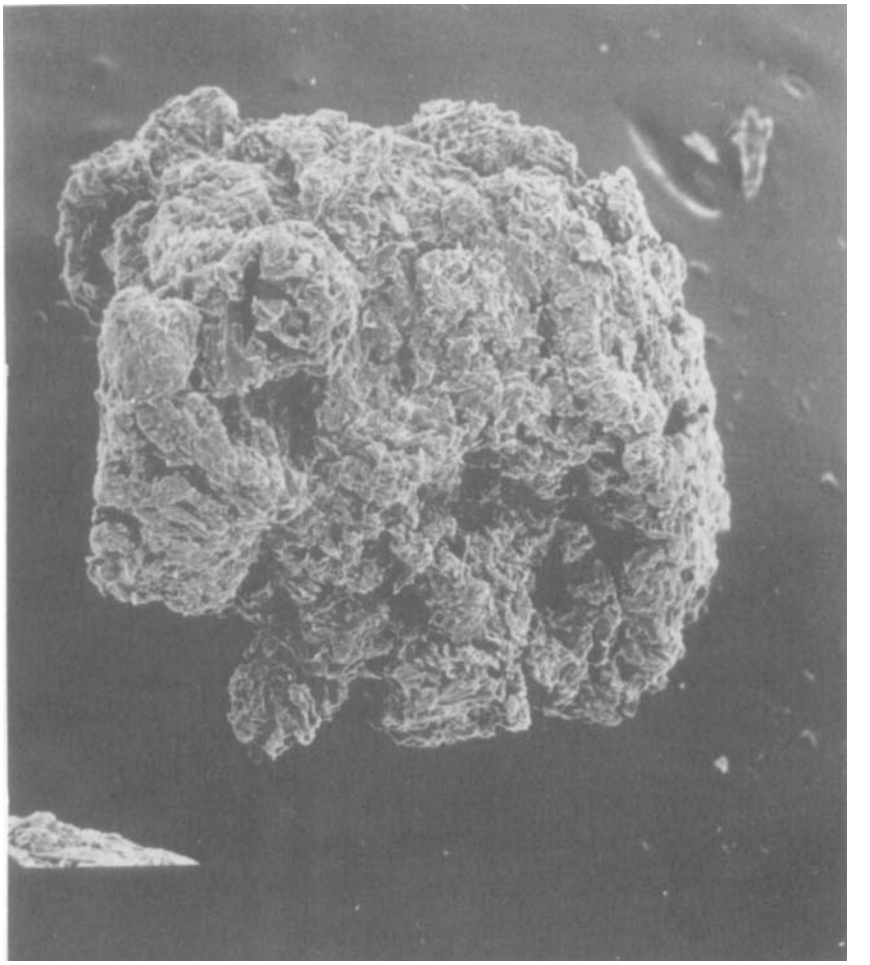

FIGURE 2

Scanning electron micrograph of granulated product prepared from 5% theophylline and microcrystalline cellulose with 50% water, magnification: 60X

underwent distinct physical changes during the wet granulation process, with an increase in the particle size. Similar observations were made for the MCC systems containing the other two drugs.

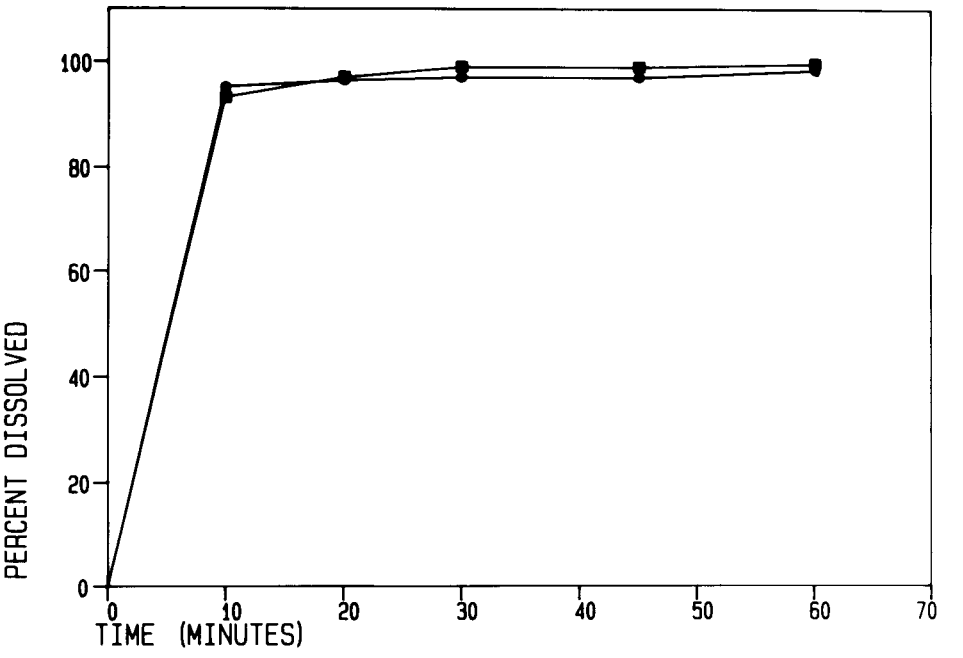

FIGURE 3

Percent drug released vs. time from uncompressed mixtures containing 5% theophylline and 95% microcrystalline cellulose.
Key: ■ 16/30 mesh granules
● direct compression blend

The dissolution profiles of products containing 5% theophylline in MCC are shown in Figures 3 and 4. The dissolution profiles of the uncompressed granules (16/30 mesh fraction), the direct compression blend and the tablets made from them are similar. It should be noted that the tablets made from the direct compression blend had a higher mean hardness value than those made from the 16/30 mesh fraction of

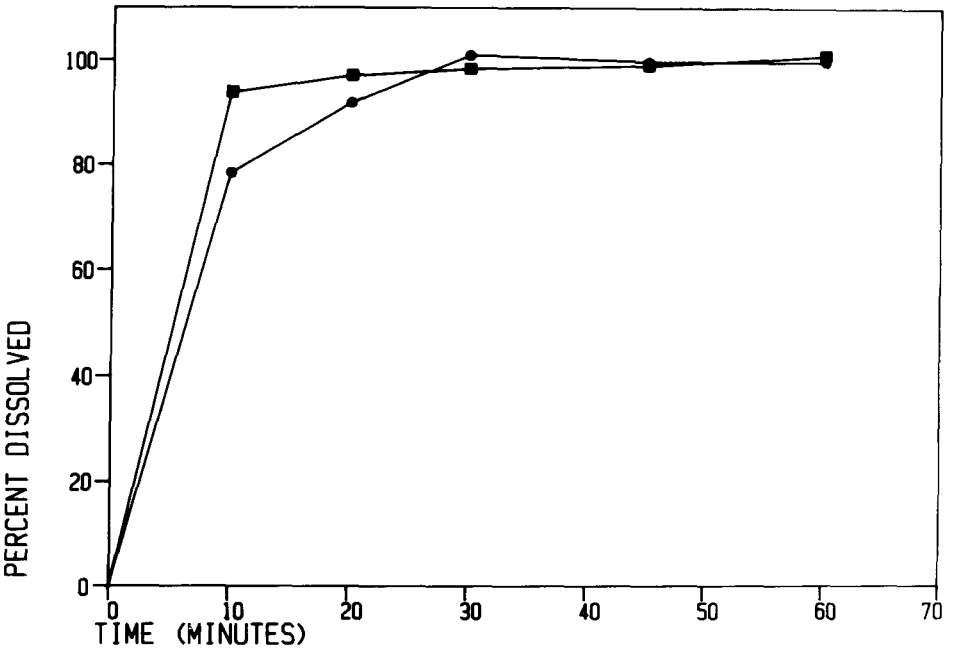

FIGURE 4

Percent drug released vs. time from tablets of 5% theophylline and 95% microcrystalline cellulose.
Key: ■ 16/30 mesh granules
● direct compression blend

granules (8.1 kg ± 0.59 and 12.8 kg ± 1.9) respectively.

Because the hardness of the tablets was not identical it is possible that the granulated product could be slightly faster in dissolution, but, the results as they stand support the conclusion that under the conditions of this test the granulation process did not negatively affect the dissolution behavior of the theophylline/MCC system.

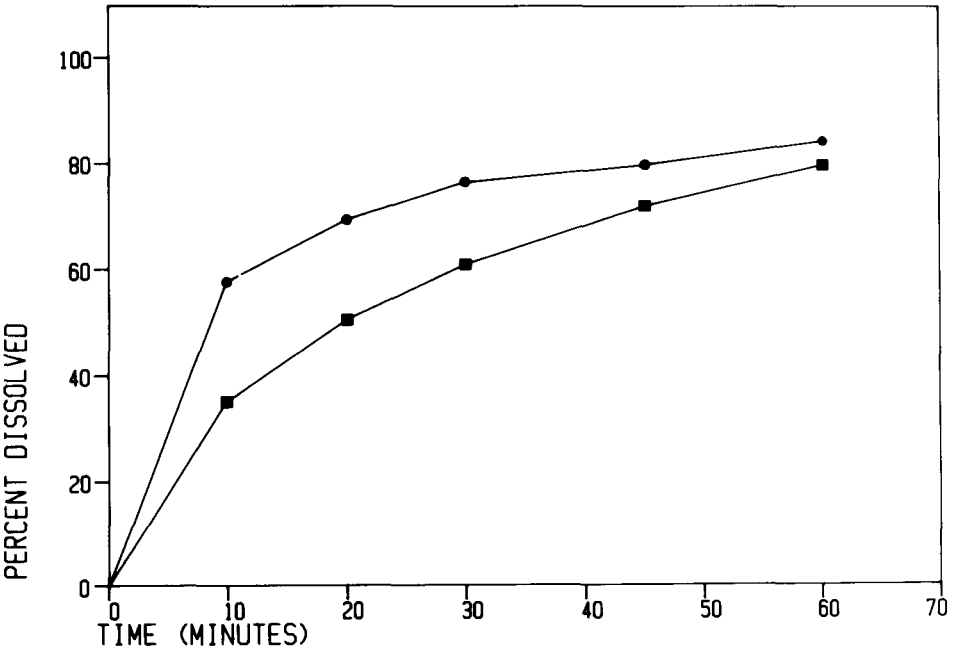

FIGURE 5

Percent drug released vs. time from uncompressed mixtures containing 5% hydrochlorothiazide and 95% microcrystalline cellulose.
Key: ■ 16/30 mesh granules
● direct compression blend

Hydrochlorothiazide/MCC

The release of drug from the direct compression blend of hydrochlorothiazide:MCC (5:95) is slightly faster than the 16/30 mesh fraction of granules (Figures 5 and 6). However, the difference seen in their tablets is much smaller. Mean tablet hardness for the tablets made from granules was 11.4 kg ± 0.9 and from the direct compression blend was 9.5 kg ± 1.77.

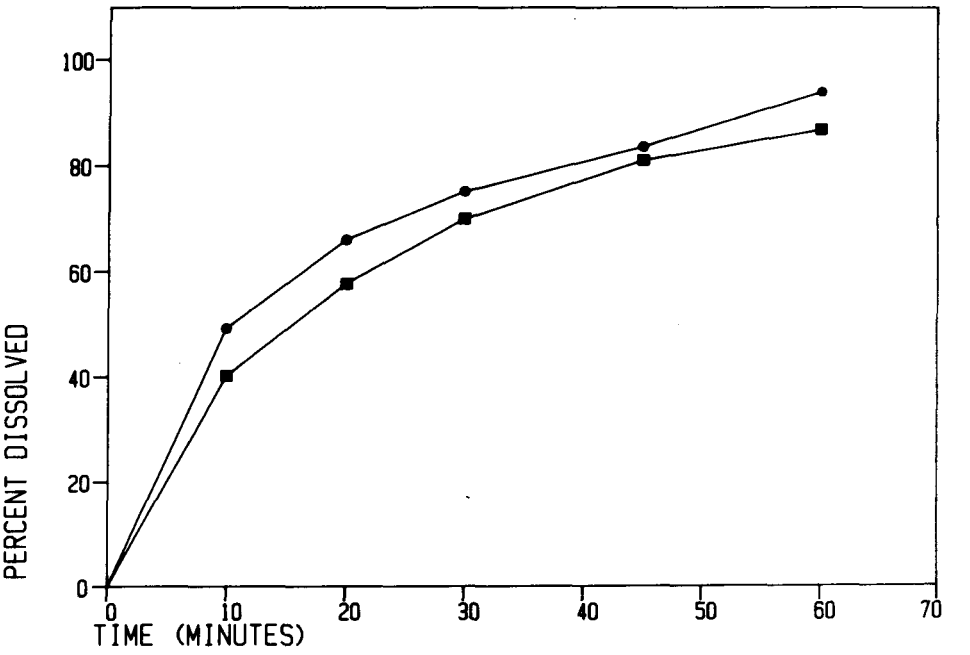

FIGURE 6

Percent drug released vs. time from tablets of 5% hydrochlorothiazide and 95% microcrystalline cellulose.
Key: ■ 16/30 mesh granules
● direct compression blend

From these data it can be concluded that the granulation process did not have much effect on the dissolution behavior of this formulation.

Chlorpheniramine Maleate/MCC

Unlike the case of theophylline and hydrochlorothiazide formulations, in the case of granules containing 5 percent chlorpheniramine maleate, it was observed that there was non-uniformity

TABLE 1

SIEVE FRACTION	PERCENTAGE OF THEORETICAL DRUG CONTENT	PERCENT GRANULATION RETAINED
Above #16 Mesh	70	15
#16 - #30 Mesh	82	30
#30 - #50 Mesh	85	39
#50 Mesh - Pan	126	17
Total Granulation	100	100

of drug content in different size fractions. The percentage of labeled drug content in each sieve cut and the sieve analysis data are shown in Table 1.

Based on the distribution and percentages shown in Table 1, one can account for the total amount of drug in the formulation. The dissolution data for the 16/30 mesh fraction of the chlorpheniramine maleate granules were therefore normalized, and the "Percent Drug Dissolved" was calculated to reflect the lower than theoretical assay.

From Figures 7 and 8 it can be seen that the release of drug from the 16/30 mesh fraction of granules is the same as from the direct compression blend. The dissolution of tablets made from the

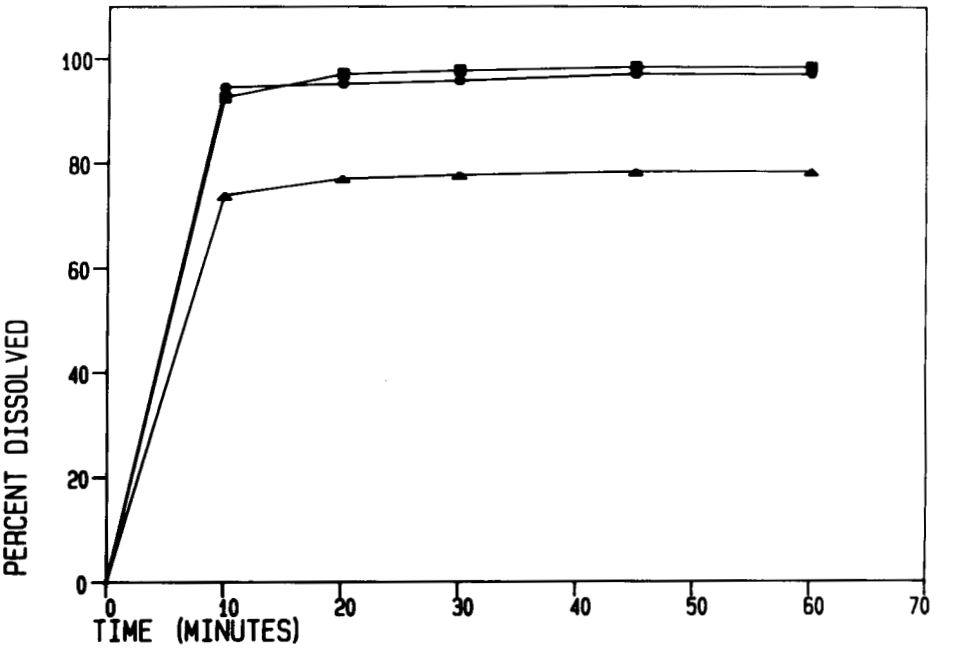

FIGURE 7

Percent drug released vs. time from uncompressed mixtures containing 5% chlorpheniramine maleate and 95% microcrystalline cellulose.
Key: ▲ 16/30 mesh granules
■ normalized 16/30 mesh granules
● direct compression blend

direct compression blend is slower than the tablets made from the 16/30 mesh fraction of granules.

Based on the data from Table 1 it appears that chlorpheniramine maleate, being a very soluble drug, migrates to the surface of the granules in the drying stage and the effective surface area of drug was thereby increased[25].

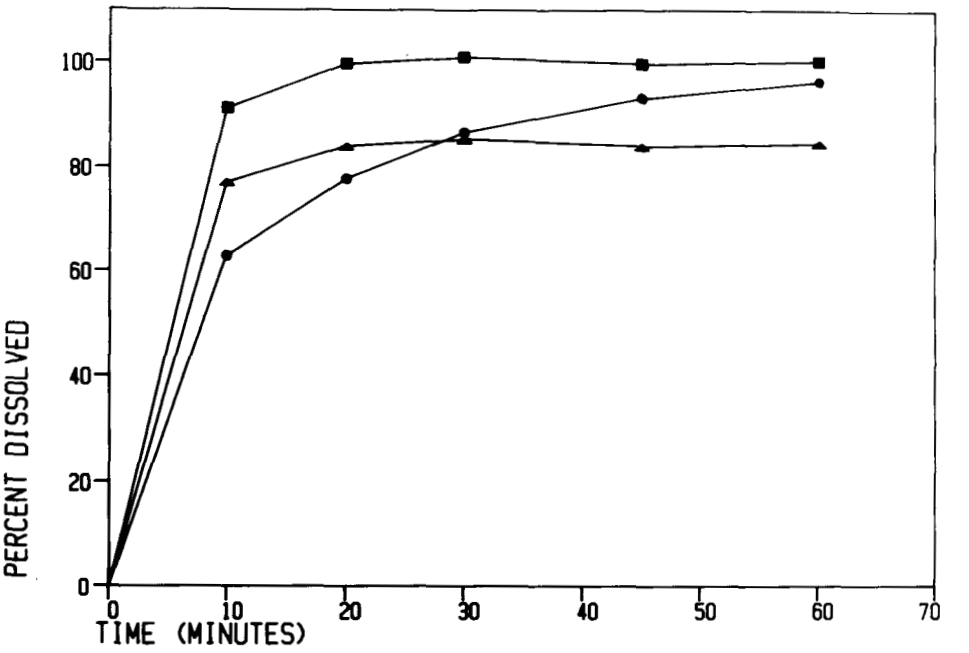

FIGURE 8

Percent drug released vs. time from tablets of 5% chlorpheniramine maleate and 95% microcrystalline cellulose.
Key: ▲ 16/30 mesh granules
■ normalized 16/30 mesh granules
● direct compression blend

Effect of Mixing Time

Blends of 5% hydrochlorothiazide and 95% MCC were wet granulated with 500 ml (50 percent) purified water. Dissolution of the 16/30 mesh fraction of granules was monitored as a function of three different mixing times i.e. 5, 15 and 30 minutes. The plots shown in Figure 9 represent data of percent drug dissolved versus time for these formulations. As

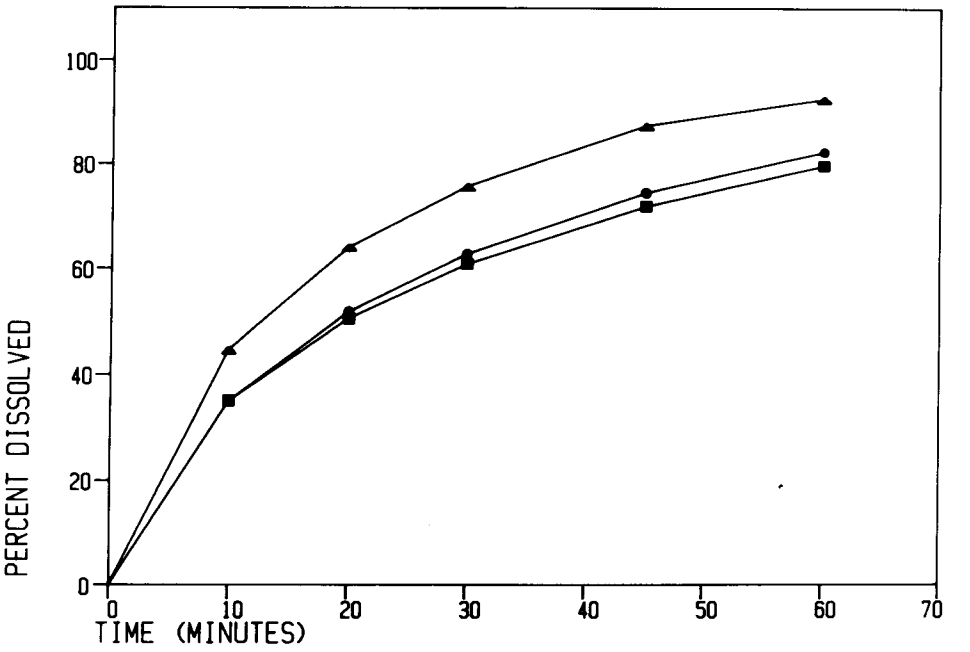

FIGURE 9

Percent drug released vs. time showing the effect of wet mixing time in 16/30 mesh granules of 5% hydrochlorothiazide and 95% microcrystalline cellulose.
Key: ▲ 5 minutes
■ 15 minutes
● 30 minutes

generally expected, an increase in wet mixing time results in an increase in the dissolution time.

Effect of Granulating Liquid Level

Three blends of 5% hydrochlorothiazide and 95% MCC were wet granulated with 400, 500 and 600 ml of purified water (per 500 grams dry powder). In each case the wet mixing time was 15 minutes. Dissolution

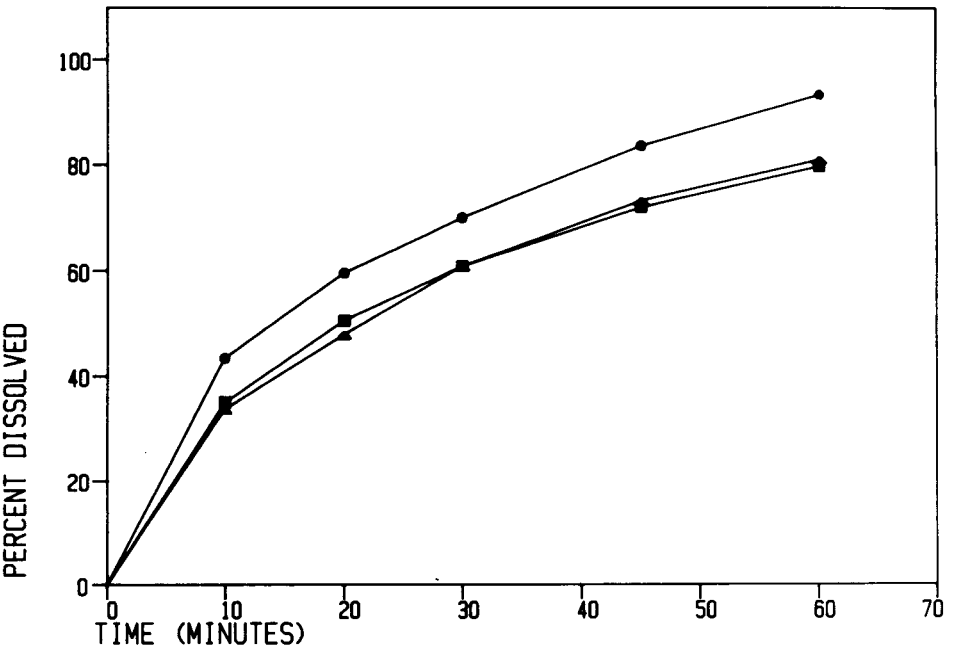

FIGURE 10

Percent drug released vs. time showing the effect of granulating liquid level in 16/30 mesh granules of 5% hydrochlorothiazide and 95% microcrystalline cellulose.
Key: ● 44 percent
■ 50 percent
▲ 55 percent

of the 16/30 mesh fraction of granules was monitored as a function of the granulating liquid level. The data shown in Figure 10 indicate that increasing the granulating liquid level up to 500 ml (50 percent) in this case results in a small decrease in dissolution. Further increase in the liquid level does not affect the dissolution.

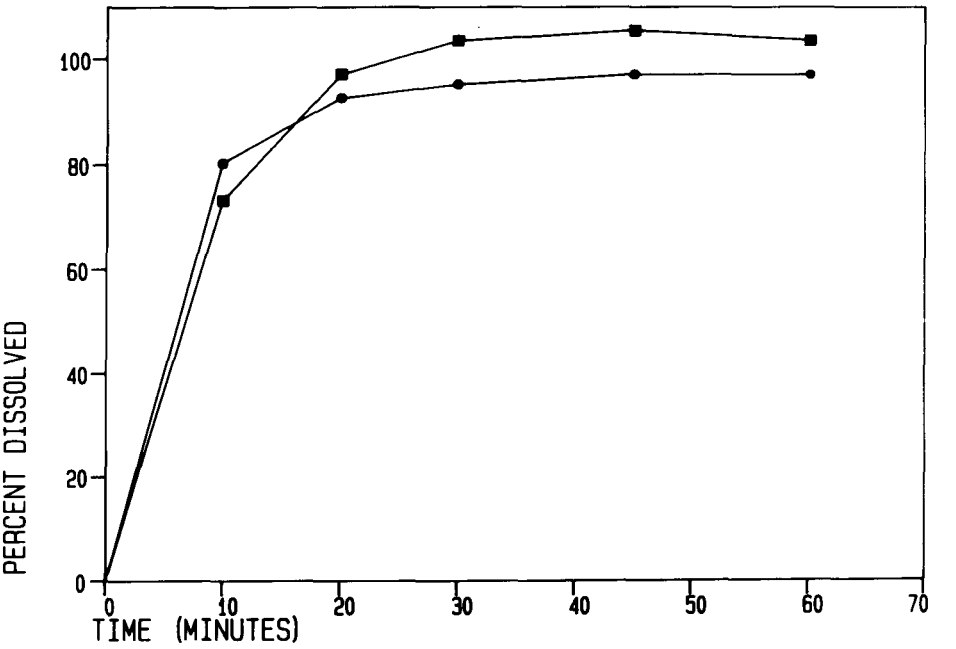

FIGURE 11

Percent drug released vs. time from tablets of 6 kg hardness containing 5% hydrochlorothiazide and 95% microcrystalline cellulose.
Key: ■ granulated product
● direct compression blend

Hydrochlorothiazide/Lactose

In order to demonstrate that the observations made earlier were more generally applicable, similar experimentation was performed with lactose based formulations. Tablets of 6 kg hardness were prepared from the direct compression and the granulated systems. From the dissolution profiles shown in Figure 11 it is apparent that granulation was not detrimental to dissolution in these formulations.

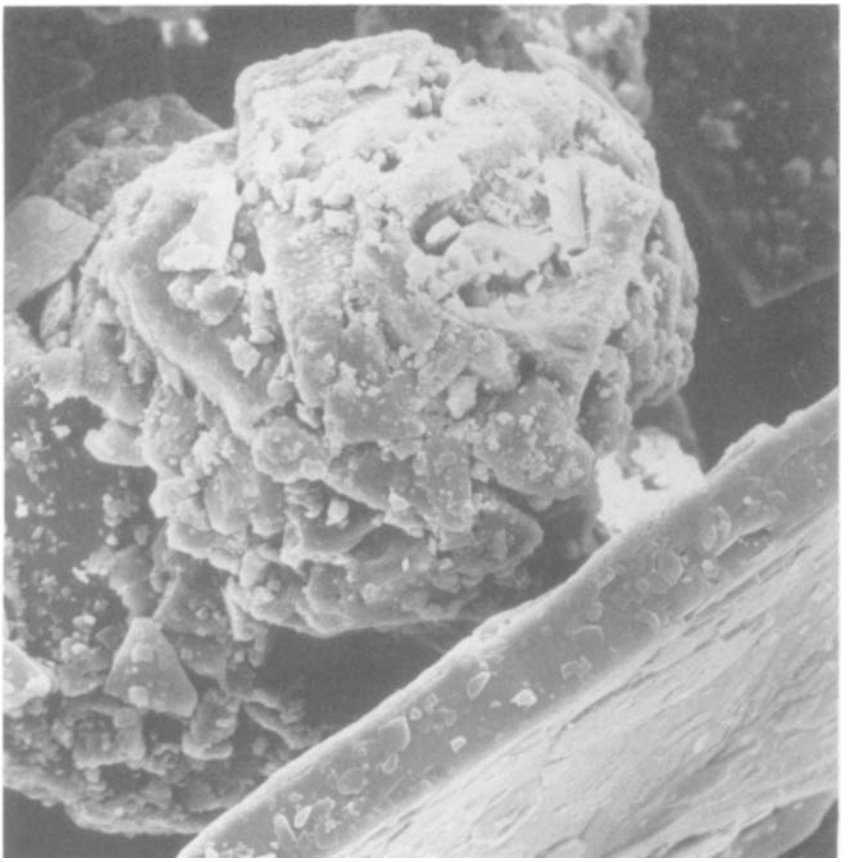

FIGURE 12

Scanning electron micrograph of direct compression mixture containing 5% hydrochlorothiazide and 95% lactose, magnification: 600X

Figures 12 and 13 indicate that when the hydrochlorothiazide:lactose mixture was granulated with water, the physical change observed (in the scanning electron micrographs) was somewhat different from that seen in the microcrystalline system (Figures 1 and 2).

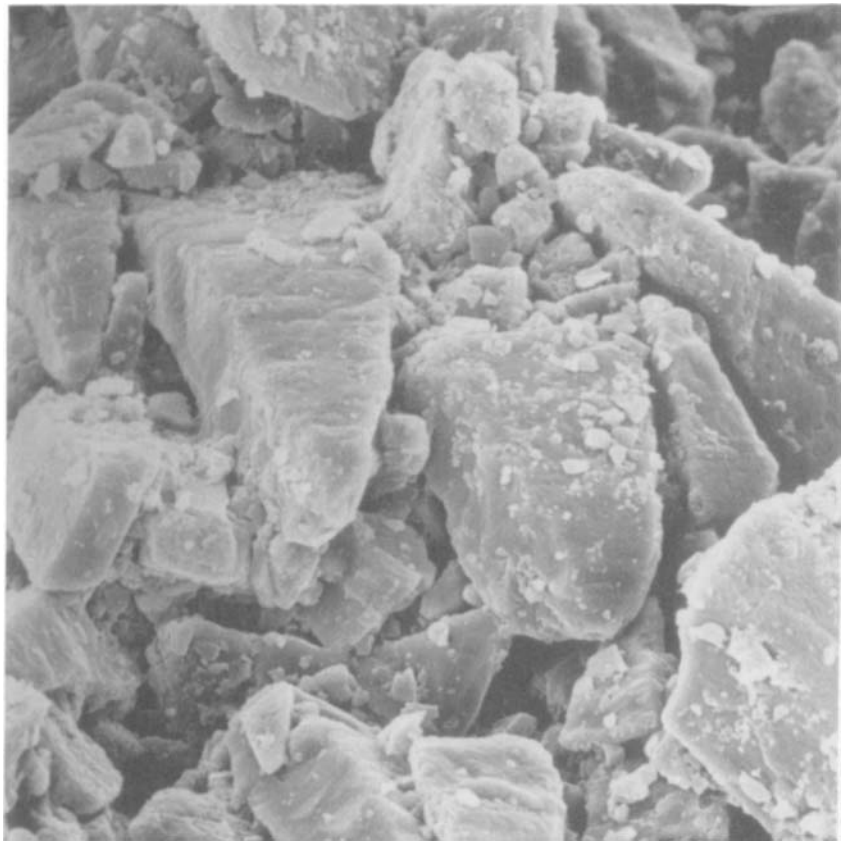

FIGURE 13

Scanning electron micrograph of granulated product prepared from 5% hydrochlorothiazide and 95% lactose with 18% water, magnification: 600X

CONCLUSIONS

Contrary to the general belief that the granulation process retards drug release, the data presented here indicate that the granulation process does not adversely affect dissolution of the binary systems studied.

As expected, aqueous solubility of the drug compound is an important factor affecting the release of drug.

The time of wet mixing affects the dissolution pattern. Increasing the time of wet mixing produces a decrease in dissolution up to a certain point. Mixing beyond that point produces only a small decrease in dissolution.

Increasing the granulating liquid level produces a gradual decrease in dissolution up to a maximum liquid level. Above that level the formation of granules does not take place and a slurry results.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support and assistance of FMC Corporation in providing scanning electron micrographs.

REFERENCES

1. H. Rumpf, in "Agglomeration," ed., W.A.Knepper, Wiley-Interscience, N.Y., 1962, p.379.
2. D.M. Newitt and A.L. Papadapoulos, Proc. Fert.Soc., 55 (1959).
3. P.J. Sherrington and R. Oliver, in"Granulation," ed., A.S. Goldberg, Heyden, Philadelphia (1981).

4. W. Jetzer, H. Leuenberger and H.B. Sucker, Pharm. Tech., 33 (1983).

5. S. Malamataris, B. Baie, and N. Pilpel, J.Pharm. Pharmac. 36, 616 (1984).

6. A. Panaggio, C.T. Rhodes and J.B. Schwartz, Pharm. Acta. Helv., 59, 37 (1984).

7. M.A. Zoglio, H.E. Huber, G. Koehne, P.L. Chan, and J.T. Carstensen, J. Pharm. Sci., 65, 1205 (1983).

8. D. Ganderton and B. Selkirk, J. Pharm. Pharmac., 22, 345 (1970).

9. E.N. Hiestand, J. Pharm. Sci., 55, 1325 (1966).

10. P. York, Int. J. Pharm., 6, 89 (1980).

11. W.O. Opakunle and M.S. Spring, J. Pharm. Pharmac., 28, 806 (1976).

12. A.A. Chalmers and P.H. Elworthy, J. Pharm. Pharmac., 28, 228 (1976).

13. A.A. Chalmers and P.H. Elworthy, J. Pharm. Pharmac. 28, 234 (1976).

14. W.L. Davies and W.T. Gloor, Jr., J. Pharm. Sci., 60, 1869 (1971).

15. W.L. Davies and W.T. Gloor, Jr., J. Pharm. Sci., 61, 618, (1972).

16. W.L. Davies and W.T. Gloor, Jr., J. Pharm. Sci., 62, 170 (1973).

17. B.M. Hunter and D. Ganderton, J. Pharm. Pharmac., 25, Suppl., 71P (1973).

18. E.J. Mendell, Manuf. Chem. & Aerosol News, 43 (1972).

19. W.O. Opakunle and M.S. Spring, J. Pharm. Pharmac., 28, 915 (1976).

20. A.M. Marks and J.J. Sciarra, J. Pharm. Sci., 57, 497 (1968).

21. A. McKenna and D.F. McCafferty, J. Pharm. Pharmac., 34, 347 (1982).

22. H.M. Unvala, "Influence of the Wet Granulation Process on Compression and Dissolution," MS Dissertation, PCP&S (1985)

23. D.M. Newitt and J.M. Conway-Jones, Trans. Instn. Chem. Engrs., 36, 422 (1958).

24. D.S. Alleva, "The Wet Granualtion Process: Kinetics and Mechanism of Granule Formation," Ph.D. Dissertation, PCP&S (1984).

25. H. Whitaker and M.S. Spring, J. Pharm. Pharmac., 29, 191 (1982).