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PHYSICAL ASPECTS OF WET GRANULATION IV - EFFECT OF KNEADING TIME ON DISSOLUTION RATE AND TABLET PROPERTIES

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ABSTRACT

The physical properties of sucrose-lactose-starch granulations containing a water soluble drug are characterized, and the relationship between granulation kneading time and each of these properties is examined. In addition, the effect of granulation kneading time on the properties of tablets prepared from the granules is examined.

INTRODUCTION

The flow properties of cohesive powders can often be improved by increasing the powder's average particle size. Although there are

several methods by which this particle size increase may be effected, one of the most popular methods in the pharmaceutical industry is wet granulation. Briefly, the wet granulation process involves kneading a granulating paste (e.g. starch paste) with a dry powder to form large agglomerates. The agglomerates are then screened and excess moisture is removed by drying.

One difficulty encountered in wet granulation is judging the so-called "granulation endpoint", i.e. the kneading time required to obtain optimum granule properties. Insufficient kneading time may result in an uneven distribution of the granulating paste throughout the dry powder and less than optimal agglomerate growth,[1] while excessive kneading time results in the formation of dense, nonporous granules.[2] Traditionally, granulation endpoint detection has been qualitative, for example, an operator will feel the granulation to see if it is ready. Recent attempts have been made to make endpoint detection more quantitative, for example, by monitoring the rotation rate of the mixer impeller or the growth of the granules during mixing.[3,4]

Previous papers in this series have examined the effect of kneading time on various mechanical and physical properties of a sucrose-lactose-starch granulation.[1,2,5] Data from these studies indicate that the kneading times required to produce granules having optimum mechanical properties and granules exhibiting a maximum dissolution rate (for a water soluble dye) are not equal. The present work examines this problem further for two different granulation batch sizes, using a water soluble drug (Dyphylline) as a model substance. In addition, the effect of granulation kneading time on several tablet parameters is examined.

TABLE 1

Formulae Used to Prepare the Sucrose-Lactose-Starch Granulations

	4 Kg Batch	30 Kg Batch
Dyphylline	80.0 g	600.0 g
Lactose	2139.0 g	16043.0 g
Sucrose	1306.0 g	9795.0 g
Corn Starch	456.0 g	3420.0 g
Starch Paste	350.0 ml	2700.0 ml
	(18.4 g corn starch)	(138.0 g corn starch)

EXPERIMENTAL

Wet granulations containing 2% Dyphylline (7-(2,3 dihydroxypropyl)theophylline) were prepared according to the formulae shown in Table 1. Dry powders were premixed for 3 minutes in either a Model M-20-6 (4 Kg batch) or a Model FM-100 (30 Kg batch) Littleford-Lodige blender, the required amount of starch paste was added, and the mixture was kneaded for 1, 3, 5, 7, 9, or 13 minutes. The wet granules were removed from the blender, processed through a number 6 screen in an oscillating granulator (F.J. Stokes Machine Company, Philadelphia, PA), and dried in a fluid bed drier (Aeromatic A.G., Basel, Switzerland) having an inlet air temperature of 42°C and an air velocity of 380 cfm. Drying was discontinued when the outlet air temperature reached 35°C.

Each dried granulation was characterized in terms of its particle size distribution (sieve analysis), apparent and tap densities, and

flow rate. The latter parameter was determined by measuring the amount of time required for 100 gm of the granulation to empty from a funnel having a 0.71 cm diameter orifice. Granule dissolution testing was performed at 27°C in a rotating basket apparatus, using 900 ml of distilled water as the dissolution medium. The dissolution of Dyphylline from the granules was monitored by measuring the UV absorbance of the medium at 272 nm as a function of time.

Tablets were prepared on a Stokes Model F tablet press from samples of the 4 Kg batch size granulations lubricated with 1% magnesium stearate. The position of the lower punch remained fixed throughout the course of the work. Tablet hardness was measured with a benchtop hardness tester (Dr. K. Schleuniger & Co., Switzerland). Tablet dissolution testing was carried out in a manner analogous to that employed for the granules, except that a paddle apparatus was used.

RESULTS AND DISCUSSION

The physical characteristics of a granulation are, to a large extent, determined by the mixer used to prepare the granulation.[6] This presents problems in the scale-up of formulations from the laboratory scale to the pilot plant and production scale. Previously, the sucrose-lactose-starch granulations that are the subject of this series of papers were prepared in a mixer having a capacity of approximately 30 Kg. This mixer was also used in the present work; however, granulations were prepared in a mixer having a capacity of approximately 4 Kg as well. The particle size distributions at various kneading times for granulations prepared in both mixers are shown in Figures 1 and 2. The distributions differ at short kneading

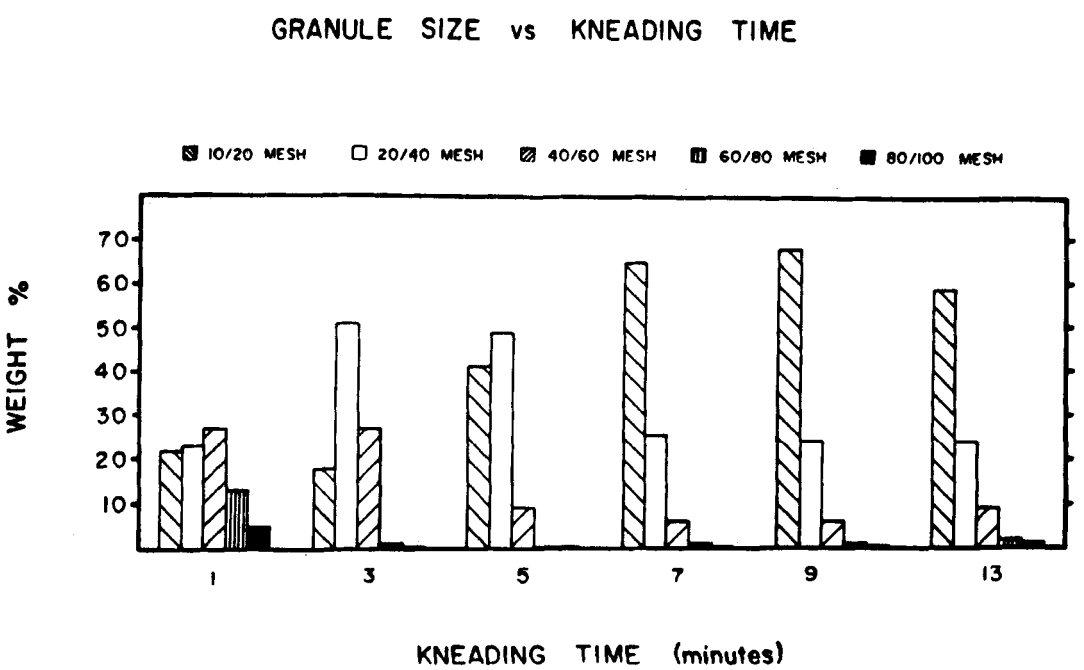

FIGURE 1

Size distribution (weight percent) at various kneading times of typical granulations prepared in the small Lodige mixer.

times, with somewhat faster agglomerate growth occurring in the smaller, more intense mixer. As kneading time is increased, however, the particle size distributions for both batch sizes become nearly identical. Earlier work with the large mixer showed that the particle size distribution of a granulation kneaded in excess of 5 minutes is not so much determined by the mixer as it is by wet screening the granules through a number 6 sieve, which acts as an extruder.[2] It is likely, therefore, that any difference in particle size distribution, and hence mixer shear properties, between the 4 Kg and 30 Kg batches is masked by the wet screening process at long kneading times.

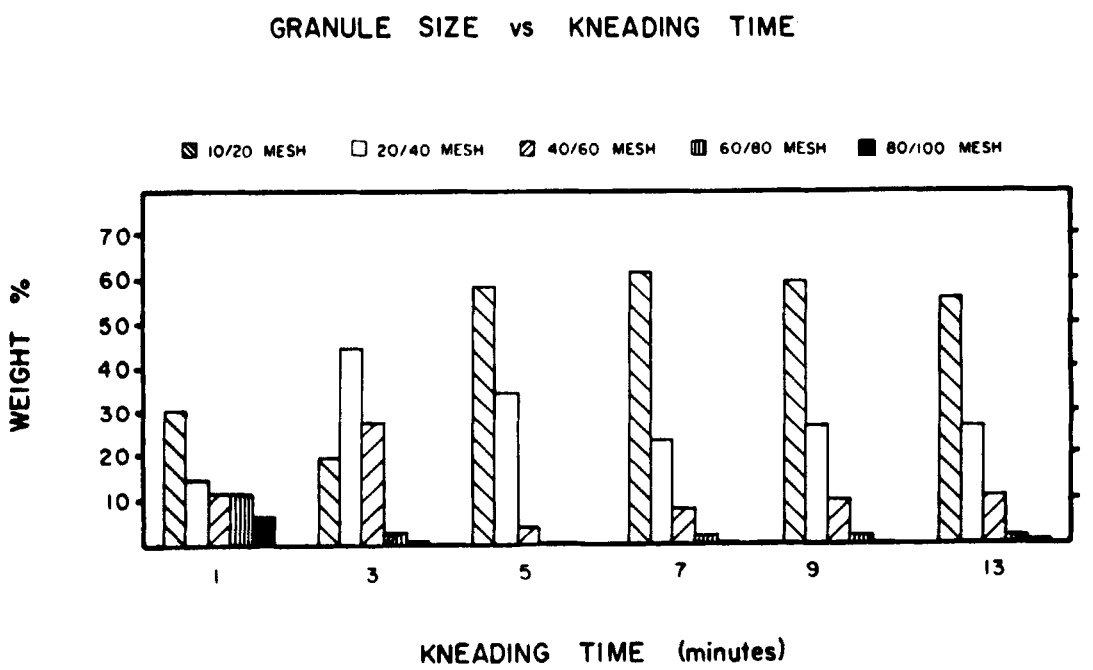

FIGURE 2

Size distribution (weight percent) at various kneading times of typical granulations prepared in the large Lodige mixer.

Since the particle size distributions of the granulations changed as a function of kneading time, their bulk densities would be expected to change with kneading time as well. Apparent density and tap density values for both batch sizes at various kneading times are reported in Table 2. The apparent and tap densities for both batch sizes exhibit maxima; however, the maxima for the 4 Kg batch occur at approximately 3 minutes while those for the 30 Kg batch occur at approximately 5 minutes, again reflecting the different shear properties of the mixers. The kneading time required to maximize the apparent and tap densities of granulations prepared in the large mixer is consistent with kneading times required to produce granules in the

TABLE 2

Apparent and Tap Densities of the Sucrose-Lactose-Starch Granulations as a Function of Granulation Kneading Time

Small Lodige Mixer

Kneading Time (min)	Density (g/cc) Apparent	Tap
1	0.56	0.70
3	0.62	0.75
5	0.61	0.73
7	0.54	0.68
9	0.54	0.66
13	0.55	0.69

Large Lodige Mixer

Kneading Time (min)	Density (g/cc) Apparent	Tap
1	0.58	0.72
3	0.60	0.70
5	0.61	0.73
7	0.55	0.66
9	0.57	0.69
13	0.58	0.70

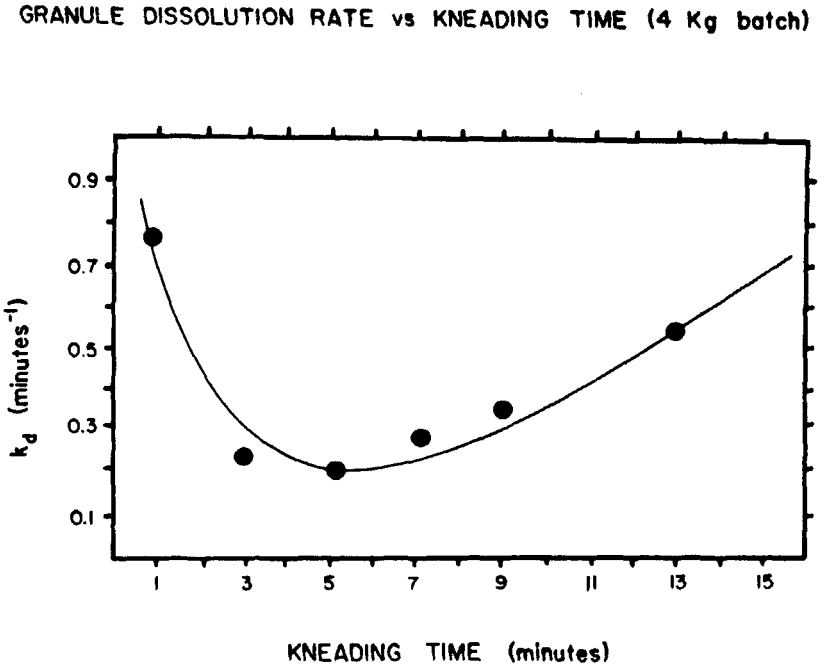

FIGURE 3

Plot of the dissolution rate of Dyphylline from granules versus the kneading time used to prepare the granules in the small Lodige mixer. Testing was performed using a basket rotation speed of 50 rpm.

same batch size having optimum Pilpel hardness and pore specific surface area.[2,5]

Like other granule physical properties, the dissolution rate of Dyphylline from granules exhibits an extremum when plotted as a function of kneading time. The plots of dissolution rate versus kneading time for Dyphylline-containing granules from the 4 Kg and 30 Kg batches are profile-wise very similar, as can be seen from Figures 3 and 4. Earlier work with a 30 Kg batch showed that the pore volume of the sucrose-lactose-starch granules was minimized after 8-10

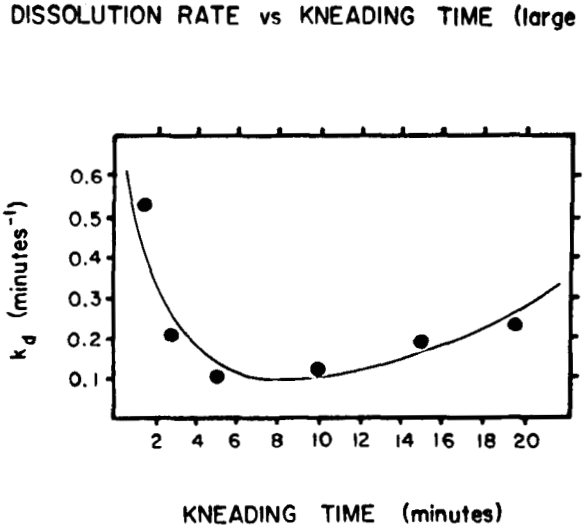

FIGURE 4

Plot of the dissolution rate of Dyphylline from granules versus the kneading time used to prepare the granules in the large Lodige mixer. Testing was performed using a basket rotation speed of 50 rpm.

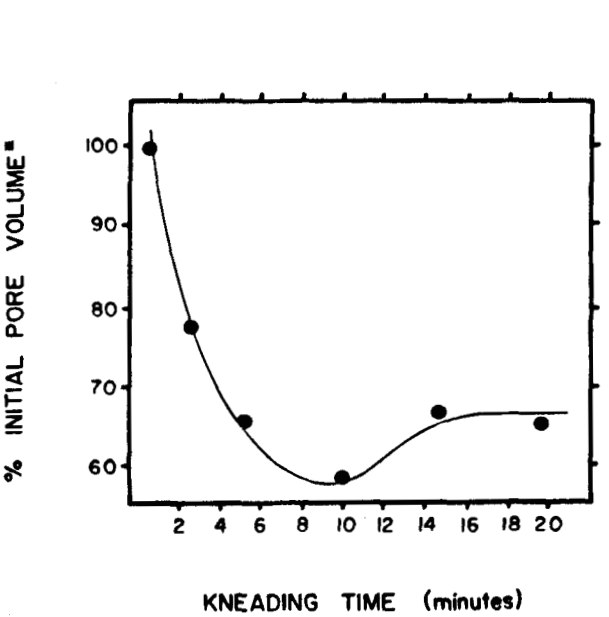

FIGURE 5

Change in granule pore volume (expressed as the percent of the initial pore volume) as a function of kneading time for granulations prepared in the large Lodige mixer (data are from ref. 5).

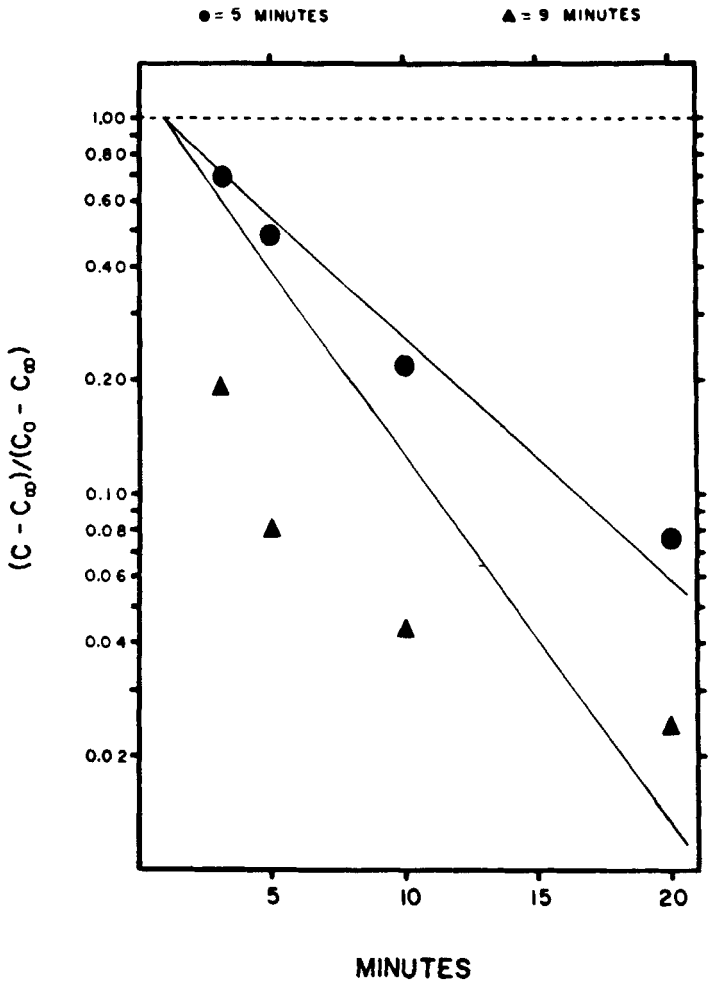

FIGURE 6

σ-plot of Dyphylline dissolution data obtained from granules kneaded for 5 (●) and 9 (▲) minutes in the large Lodige mixer.

minutes of kneading (Figure 5),[5] which is in good agreement with the kneading time required to minimize the dissolution rate of Dyphylline from the granules produced in the present work. This agreement not only indicates that the dissolution rate of the drug is related to the porosity of the granules, but also that the mechanism of the

TABLE 3

Linearity of σ^{-}-plots Constructed from Granule Dissolution Data

Kneading Time (min)	Correlation Coefficient
1	- 0.992
3	- 0.991
5	- 0.992
7	- 0.981
9	- 0.844
13	- 0.966

dissolution process changes as a function of kneading time. This may be seen more clearly by constructing σ^{-}-plots from the granule dissolution data, as shown in Figure 6. A dissolution process whose rate is limited by the diffusion of liquid into and diffusion of dissolved drug out of the granule, such as would occur through granule pores, will exhibit a linear profile when plotted in this fashion.[7] As shown by the curves in Figure 6 and the data in Table 3, the linearity of the σ^{-}plots decreases with decreasing granule porosity, suggesting that a process other than diffusion (e.g. erosion) becomes increasingly important in the dissolution of drug from granules as the kneading time used to prepare the granules is increased.

Previous workers have demonstrated that the flow rate of a granulation is dependent on the diameter of the granules.[8] As mentioned earlier, the particle size distributions of the granulations prepared in the present work changed as a function of kneading time. It would be expected, therefore, that the flow rate of the granulations would change as a function of kneading time as well, and

GRANULE FLOW RATE vs KNEADING TIME

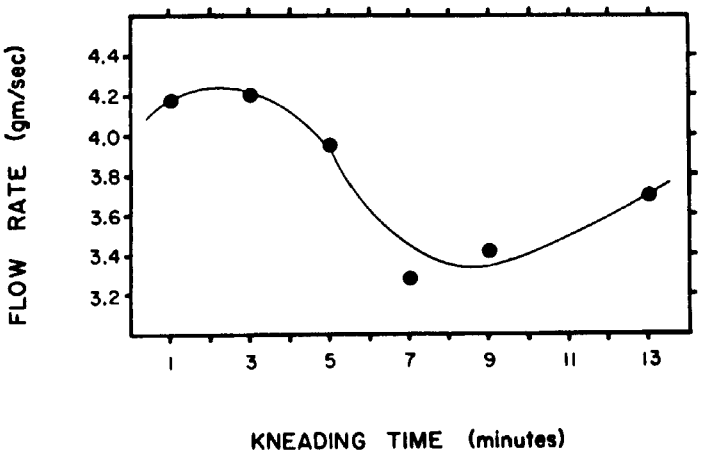

FIGURE 7

Plot of granule flow rate versus the kneading time used to prepare the granules in the small Lodige mixer.

TABLET WEIGHT vs KNEADING TIME (4 Kg batch)

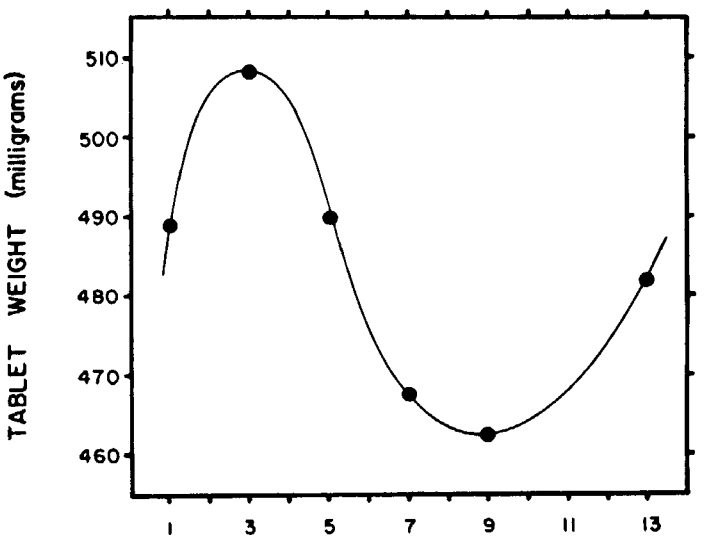

FIGURE 8

Plot of tablet weight versus the kneading time used to prepare the granules from which the tablets were compressed.

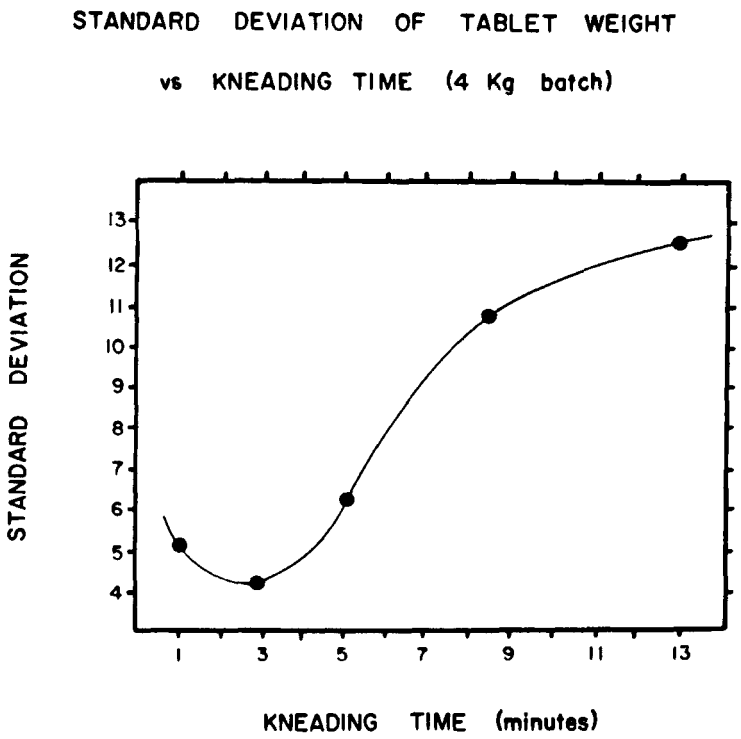

FIGURE 9

Plot of the standard deviation of tablet weight versus the kneading time used to prepare the granules from which the tablets were compressed.

this is what is observed (Figure 7). Not surprisingly, the weight of tablets prepared from the various granulations parallels the trend in the granulation flow rates, with the maximum tablet weight (Figure 8) and the minimum tablet weight variation (Figure 9) occurring at a kneading time of approximately 3 minutes. The latter property has also been shown to be dependent on granule diameter.[9] Deviation in tablet properties such as hardness is also minimized in tablets prepared from granulations kneaded for approximately 3 minutes (Figure 10). All of these findings reflect the importance of powder or granule flow in determining the properties of the finished tablet.

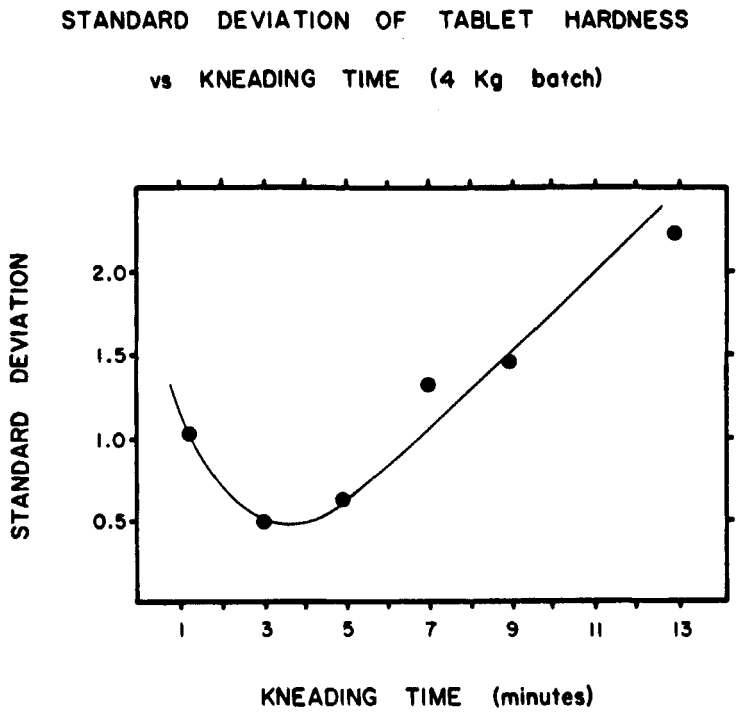

FIGURE 10

Plot of the standard deviation of tablet hardness versus the kneading time used to prepare the granules from which the tablets were compressed.

The dissolution rate of Dyphylline from tablets prepared from the various lubricated granulations passes through a minimum when plotted as a function of granulation kneading time (Figure 11), as did the dissolution rate of Dyphylline from granules. Although the kneading time required to minimize the dissolution rate of Dyphylline from granules and tablets is approximately the same, the magnitude of the dissolution rate from granules is approximately three times greater than the dissolution rate from tablets. The slower dissolution of Dyphylline from tablets may be attributed, in part, to the addition of

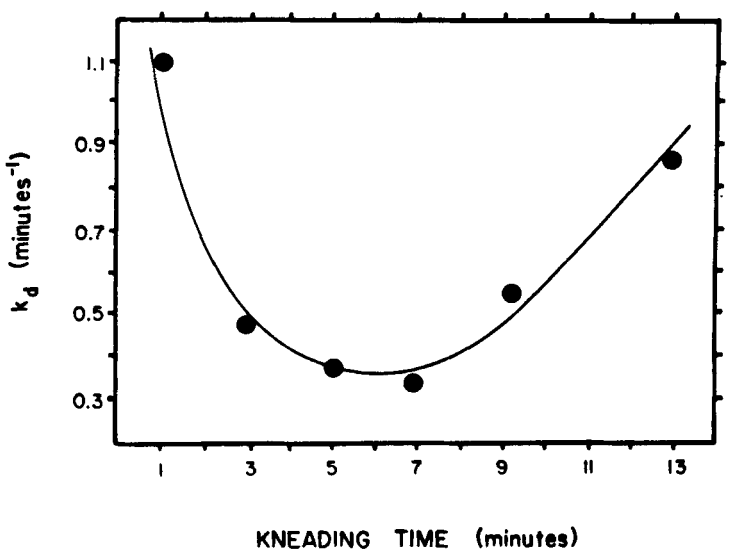

FIGURE 11

Plot of the dissolution rate of Dyphylline from tablets versus the kneading time used to prepare the granules from which the tablets were compressed. Testing was performed using a paddle rotation speed of 50 rpm.

magnesium stearate to the tablet formulations.[10-12] However, the major reason for the slower dissolution is that a disintegration step has been introduced into the dissolution of drug from the tablets, i.e., the tablets must first disintegrate to granules before dissolution can begin.[13] The dissolution rate of drug from the granules produced by disintegration of the tablets apparently does not exhibit as great a kneading time dependence as the dissolution rate from the original granules, since although the dissolution rate of drug from tablets exhibits a minimum, the linearity of σ^{-}-plots

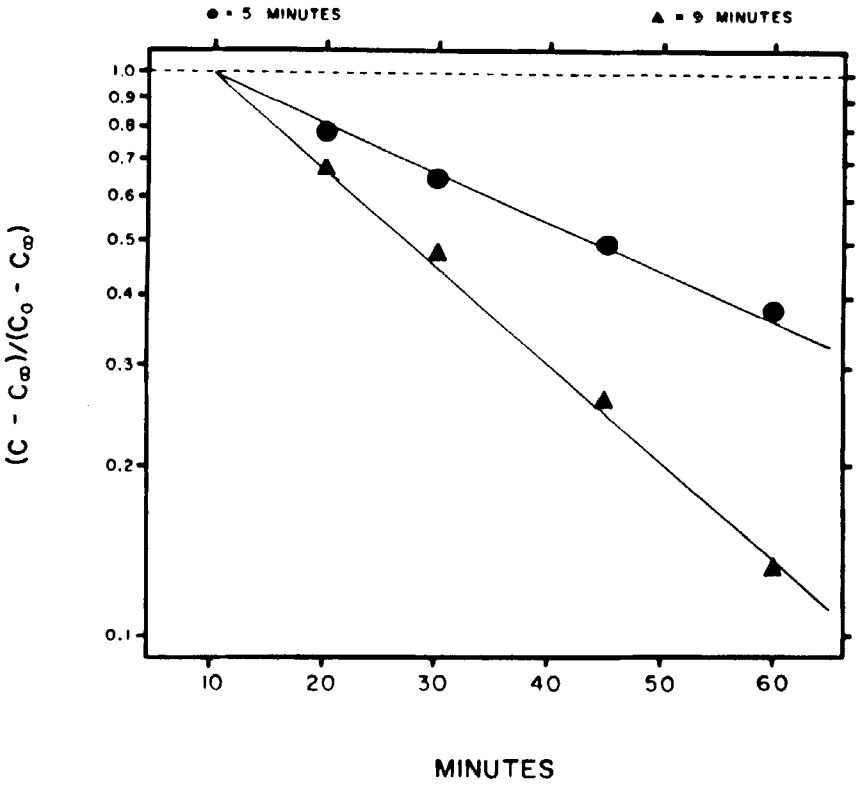

FIGURE 12

σ⁻-plot of Dyphylline dissolution data obtained from tablets compressed from granules kneaded for 5 (●) and 9 (▲) minutes in the small Lodige mixer.

TABLE 4

Linearity of σ⁻-plots Constructed from Tablet Dissolution Data

Kneading Time (min)	Correlation Coefficient
1	- 0.999
3	- 0.997
5	- 0.998
9	- 0.999
13	- 0.999

constructed from the tablet dissolution data does not decrease with increased granulation kneading time (Figure 12, Table 4). The lack of kneading time dependence exhibited by the dissolution of Dyphylline from tablets could again be due to the different shear properties of the mixers, since the granules used to prepare the tablets and the granules that were tested directly were prepared in the small and large Lodige mixers, respectively. It is also possible that the linearity of the σ-plots obtained from tablet dissolution data reflects structural changes in the tabletted granules, the most likely structural change being increased porosity due to granule fracture during compression.

CONCLUSIONS

The physical characteristics of a wet granulation are dependent on the type of mixer used to prepare the granulation, presumably because a high shear mixer is able to distribute the granulating paste more efficiently than a low shear mixer. The properties of a granulation are also dependent on kneading time. In the present work, several physical parameters, including the apparent and tap densities of the granules and the dissolution rate of Dyphylline from the granules, were found to exhibit extrema when their values were plotted as functions of kneading time. The changes observed in the dissolution rate of drug from the granules parallels changes observed previously in granule porosity, suggesting that the dissolution process is dependent on the diffusion of liquid into and dissolved drug out of the granules via the pores. The diffusion dependence decreases as kneading time is increased, as evidenced by the decreased linearity of the data when plotted in σ-fashion.

The dissolution of Dyphylline from tablets prepared from the various granulations appears to be less dependent on kneading time than dissolution from granules; however, the dissolution rate of Dyphylline from tablets does exhibit an extremum when plotted as a function of kneading time, with the maximum rate occurring at either very short (< 2 minutes) or very long (> 9 minutes) kneading times. These times do not correspond to the kneading time required to obtain optimum tablets, i.e., tablets which have minimum weight and hardness variation. It appears that a satisfactory balance between maximum tablet dissolution rate and optimum tablet properties may be achieved by using an intermediate kneading time, in the present case from 2 to 5 minutes.

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