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RESEARCH PAPER

The Use of Mixer Torque Rheometry to Study the Effect of Formulation Variables on the Properties of Wet Granulations

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ABSTRACT

Mixer torque rheometry was used to investigate the rheological behavior of wet granulations with different concentrations of drug, binder, and water. An experimental design was employed to systematically study the effects of the three formulation variables on the torque profiles of the wet masses over time. Under comparable conditions, increasing binder and water concentrations tended to produce higher wet mass consistencies. Friability of the dried granules was measured as an indication of the strength of the granules. A reduced quadratic model in terms of each of the three variables was found to satisfactorily predict granule friability. Granule friability decreased with increases in the binder level and increased slightly with increasing drug concentration. An inverse relationship was seen between granule friability and the amount of water added to the formulation, especially at lower drug concentrations. Mixer torque rheometry is a useful method for studying the properties of wet granulations when minimal amounts of drug are available for the development of a wet granulated formulation.

Key Words: *Granule friability; Mixer torque rheometry; Wet granulation*

INTRODUCTION

This paper investigates the potential use of mixer torque rheometry for the optimization of binder levels in a wet granulated product and the effects of formulation factors on the properties of the resulting granules. Torque monitoring has been used at commercial scales for monitoring wet mass quality and especially for process end-point detection. Granulation processes can also be monitored

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indirectly using motor power consumption or a motor load analyzer (1,2). In smaller granulation equipment, however, it is difficult to use power consumption for sensitive monitoring of the changes in the wet mass. At the small research and development scale, limited amounts of drug are available for development of a wet granulated formulation and process. In these situations, direct measurements of the torque on the mixer caused by the imposition of a shear field on the material in the mixer can be more readily obtained. These measurements could potentially be more sensitive to the changes occurring in the wet mass during granulation (3,4). Rheological monitoring of wet granulation processes by torque rheometry has been reviewed by Parker et al. (5). A mixer torque rheometer could potentially help to characterize mixing kinetics and identify the correct range of binder and binder-activating fluid in the formulation (6,7). The mixer torque rheometer used in this study continuously measures the reaction torque of the mixing bowl via a torque arm fixed to the bowl, resting on a calibrated load cell (8). The torque on the bowl is generated in response to the movement of the mass of powder mixed by the blades in the bowl. This method has been claimed to be a more direct measure of the torque in the bowl (5).

A mixer torque rheometer may be used to monitor granulation processes in one of three ways. In the single addition method, a mixture of powders is blended for a predetermined amount of time in the torque rheometer bowl after the addition of granulating fluid. Data is then logged to measure the consistency of the wet mass. This method is typically used for testing the effects of different binder ratios. A variation of this is the multiple addition method in which the binder is added in increments and measurements are taken after each addition. This method suffers from the disadvantage that after each binder addition, the mass is mixed for a different length of the total mixing time. In a second application of torque rheometry, samples are withdrawn from a large batch made in a high shear mixer granulator and the consistency of the wet mass is measured to help determine the end-point of the granulation process; this is more relevant to production monitoring. A third method, called the variable mix time method, involves investigation of the mixing kinetics by logging the data at specific times after the addition of the binder. This method was selected for the present study because it can also be used to obtain the equilibrium torque level after a predetermined amount of mixing time.

The final objective of controlling wet mass properties is to produce dried granules of reproducible quality downstream in the process. In a pharmaceutical tabletting process, for example, the quality of the granules will significantly affect the characteristics of the compacted final product. Granule friability was used in this study as a measure of the strength of the granules and was correlated to the formulation factors studied.

EXPERIMENTAL

Materials

A practically water-insoluble (~0.04 μg/mL) compound in preclinical development stage, hereinafter referred to as SC-A, was obtained from Pharmacia chemical compound file and used as a model drug. Lactose monohydrate 310 was obtained from Foremost Farms, Baraboo, WI. Microcrystalline cellulose (Avicel PH101) and croscarmellose sodium (Ac-Di-Sol) were obtained from FMC Corporation, Princeton, NJ. Low viscosity hydroxypropyl methylcellulose (Pharmacoat 603) and Polysorbate 80 were obtained from Shin-Etsu Chemical, Tokyo, Japan, and Sigma Chemical Co., St. Louis, MO.

Formulation Rationale and Experimental Design

The general composition of the lactose-based formulation used in this study is shown in Table 1. The amount of drug in the granulation was varied between 5% and 70% to study its effect on the granulation process. Lactose, the primary diluent, was varied proportionally between 13.5% and 81.5% depending on the amount of drug in the formulation. The level of microcrystalline cellulose was held constant at 5%. Croscarmellose was added as an intragranular disintegrant at a constant level of 5%. Low viscosity hydroxypropyl methylcellulose was used as a binder at levels between 1% and 6% and was incorporated in the dry mix. Purified water, USP, containing a constant level of 0.5% polysorbate 80 was used as the granulating liquid. Purified water was varied between 30% and 50% of the dry powder blend. The total weight of each powder blend was 25 g. The three experimental

Table 1

Granulation Composition Summary

Components	Intragranular	Granulating Fluid	Range/Amount
1	SC-A	—	5.0–70.0%
2	Lactose 310	—	13.5–81.5%
3	Avicel PH101	—	5.0%
4	Ac-Di-Sol	—	5.0%
4	Pharmacoat 603	—	1–6%
5		Tween 80	0.5%
6		Distilled water	30–50% of batch

Table 2

Levels of Experimental Variables Studied

Factor	$-\alpha$	-1	0	$+1$	$+\alpha$
Drug (%)	5	18.18	37.50	56.82	70
HPMC (%)	1	2.01	3.5	4.99	6
Water (%)	30	34.05	40	45.95	50

variables studied were the effect of binder concentration in the powder blend, the effect of drug concentration in the powder blend, and the effect of the amount of water added during granulation. These three factors were varied according to a central composite design as shown in Table 2. These three independent variables were studied at five levels each to give a total of 15 distinct experiments. The central point of the design was repeated in triplicate for a total of 17 experiments (see Table 3).

Preparation of Granulates and Torque Measurements

The method used in this study consisted of measuring the torque on the mixing bowl to obtain a quantitative measure of the rheological properties of the wet mass. Torque measurements were made using a Caleva torque rheometer (Model MTR, Caleva, Dorset, UK) equipped with a microcomputer for data acquisition. The mixing bowl in the Caleva torque rheometer is mounted on ball bearings to allow free rotational movement of the bowl. A moment arm attached to the bowl, and perpendicular to the mixing blades, rests on a load transducer that measures the load on the mixing bowl. The moment arm is 100 mm in length from the bowl pivot point to the force transducer. In these experiments, the main blade rotated at a preset speed and the blades on a subsidiary shaft rotated at twice the speed of the main blade to provide shear to the material between the blades.

The main blades of the mixer torque rheometer were run at 50 rpm without any powder for 20 sec to obtain a baseline reading. The blends were dry mixed in a Turbula mixer (WAB Turbula, Basel, Switzerland) for 3 min prior to loading them into the torque rheometer. The rheometer was then run for 30 sec with dry powder, immediately after which the binder solution was added to the powder bed with a syringe as a bolus addition over 10 sec. After the beginning of addition of the binder, data was logged for 10-sec periods every 12 sec, for a total experimental duration of about 6 min. At the end of the experiment, the granulation was collected and sieved through a size 18 mesh (1000 μm) screen and then dried in a convection oven at 60°C for 3 days.

Granule Friability Measurements

Granule friability measurements for evaluating the strength of the granules were conducted by modification of a procedure used by Faure et al. (9). The granules were sieved through a 1000 μm sieve to remove any large agglomerates. The fraction that passed through the sieve was then sieved through a 140 mesh sieve to remove any fines below 106 μm. Two grams of the fraction retained on the 106 μm sieve was then placed on a clean 106 μm sieve along with 30 glass beads of approximately 5 mm diameter. The sieve was then shaken in a sonic sifter (ATM Sonic Sifter, Milwaukee, WI) for 5 min at

Table 3

Predicted vs. Actual Values of Granule Friability

Experiment Number	Drug (%)	Binder (%)	Water (%)	Actual Value	Predicted Value	Residuals
1	37.50	3.50	40.00	19.79	17.51	2.28
2	37.50	3.50	40.00	26.49	17.51	8.98
3	56.82	2.01	34.05	46.97	48.77	−1.80
4	56.82	2.01	45.95	37.69	38.79	−1.10
5	37.50	3.50	40.00	22.53	17.51	5.02
6	37.50	6.00	40.00	20.3	19.07	1.23
7	18.18	4.99	34.05	15.78	22.64	−6.86
8	37.50	1.00	40.00	68.35	66.71	1.64
9	70.0	3.50	40.00	21.094	22.77	−1.68
10	56.82	4.99	45.95	4.05	10.46	−6.41
11	18.18	4.99	45.95	1.89	−4.26	6.15
12	5.00	3.50	40.00	8.39	12.25	−3.86
13	37.50	3.50	30.00	24.86	33.02	−8.16
14	18.18	2.01	45.95	12.25	24.07	−11.82
15	18.18	2.01	34.05	61.28	50.97	10.31
16	37.50	3.50	50.00	4.68	2.00	2.68
17	56.82	4.99	34.05	23.85	20.44	3.41

a fixed amplitude setting in the sift/pulse mode. The amount remaining on the sieve was weighed and granule friability was calculated using the formula:

granule friability
= (starting amount on sieve
− amount remaining after 5 min)
× 100/(starting amount on sieve)

RESULTS AND DISCUSSION

Wet Mass Consistency Measurements Using Torque Rheometry

Two parameters for characterizing the wet mass can be obtained from a torque rheometer: the mean torque increase from baseline and the mean amplitude of the torque peaks. The mean torque is a measure of the resistance of the mass to mixing, and the differences in amplitude of the torque oscillations are an indication of the rheological heterogeneity of the mass (10). There is assumed to be a direct relationship between the measured parameters of torque and the viscosity of the wet mass in the mixer bowl (5). It is then possible to investigate the effect of the formulation components on the torque during mixing, which serves as a measure of the viscosity of the wet mass. Compared to liquid rheology, measurements made by mixer torque rheometry are complicated by the fact that the sample is compressed and expanded between the blades because of the changing gap between them. Ideally, these experiments should be repeated in triplicate to reduce the variability associated with differences in the initial wetting of the mass after the addition of the binder fluid. In this study, however, due to drug availability limitations, only a single experiment could be performed for each of the 15 different formulations. The central point of the experimental design was repeated in triplicate to obtain an indication of the variability in these experiments. The mean torque from all the experiments is shown in Fig. 1. Most formulations showed a very flat profile of mean torque vs. time except for formulations 6, 10, and 11. It appears that, in most cases, the binder distributed rapidly and the torque quickly reached an equilibrium value. In the case of formulations 6, 10, and 11, which had relatively high levels of binder and water, the equilibrium levels were reached after a slight delay and the final equilibrium torque was also correspondingly higher.

In order to look for systematic effects of the formulation variables on the wet mass consistency, the torque profile was reduced to a single quantity for use as a response from the experiment.

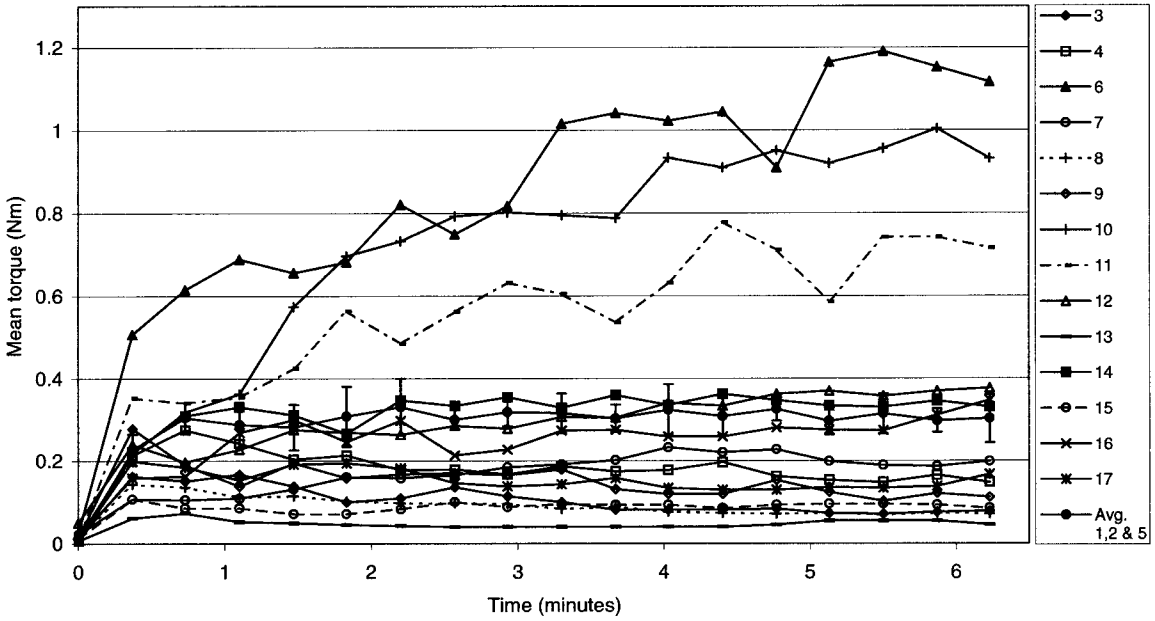

Figure 1. Mean torque from all the logged data points over the entire experiment.

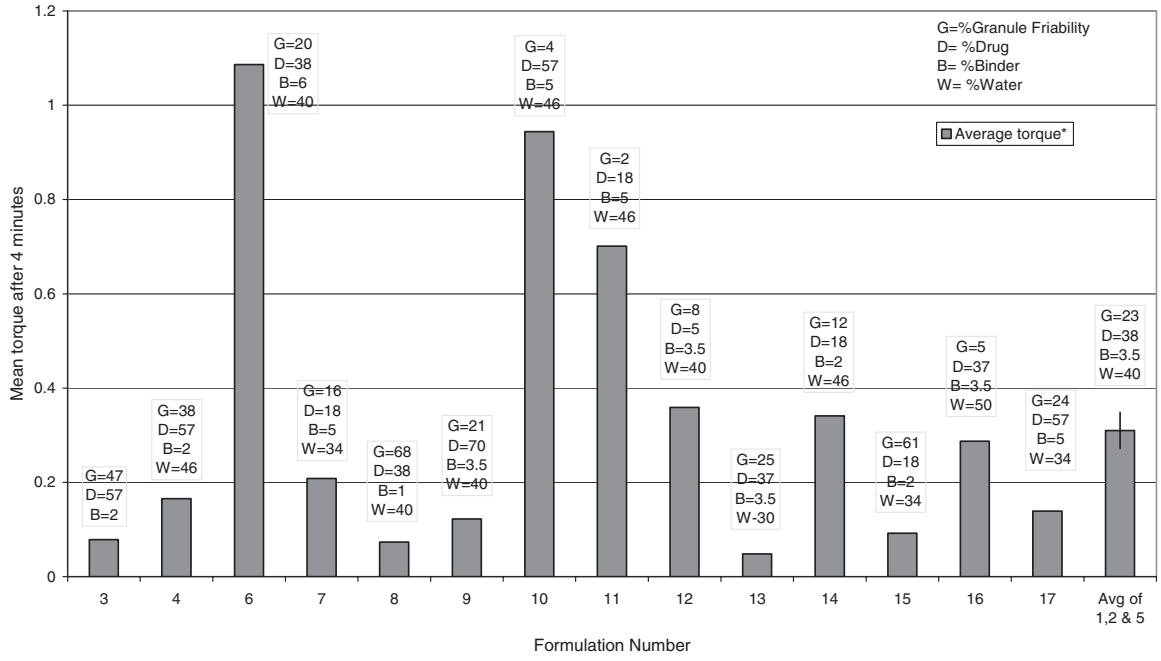

Figure 2. Average of the torque between 4 and 6.2 min for all formulations.

The torque values recorded between time points of 4 min after the start of the experiment until the end of the experiment were averaged for each formulation. Figure 2 shows these mean values along with the levels of the three variables and the corresponding granule friability of each formulation. It was assumed that this mean torque after 4 min was reflective of the equilibrium torque level after the

binder had distributed throughout the powder mass. No statistical correlation could be found between the mean equilibrium torque of the wet masses and the formulation variables studied. The percentage relative standard deviations of some data points from the replicated experimental center point were as high as 24%. This level of variability may not allow the detection of subtle differences in torque measurements arising from minor changes in formulation composition.

Effect of Formulation Variables

Graphical correlations between individual variables and the torque profiles were visible even though these trends could not be modeled by multiple regression analysis of all 17 experiments. Plots of mean torque vs. time of formulations 12, 13, and 16 with different amounts of water and the same amount of binder (3.5%) and drug (37.5%) are shown in Fig. 3. Formulation 13 with 30% water showed the lowest wet mass consistency, whereas formulations 12 and 16 with 40% and 50% water had torque profiles in the same range, with the formulation containing 50% water showing slightly lower torque levels. According to theory, the wet mass should show increasing viscosity (reflected by higher torque) with increasing levels of fluid (due to increasing wetting and binder activation), rising to a maximum and decreasing thereafter as a slurry is produced when excess water is added (11). The wet mass will go through initial pendular and funicular states in which lens-shaped rings of liquid are formed at the points of contact between some or all of the particles respectively. At the limit of the funicular state, all the pores become filled with liquid and the mass is now thought to be at the capillary state. Torque values are at a maximum in the capillary state, and decrease if additional liquid is added because of the formation of slurry at the droplet state. At 40% water, the torque may have reached a limiting value near the capillary state; at a higher water level of 50%, the material is presumably beginning to enter the slurry state, which results in a reduction of the measured wet mass consistency.

Figure 4 compares formulations with three different levels of binder at the same level of water (40%) and drug (37.5%). It is clear that under comparable conditions, higher amounts of binder produce higher wet mass consistencies. This is presumably due to the increased amount of binder available for activation by the granulating fluid, as well as greater viscosity of the interparticle liquid binder

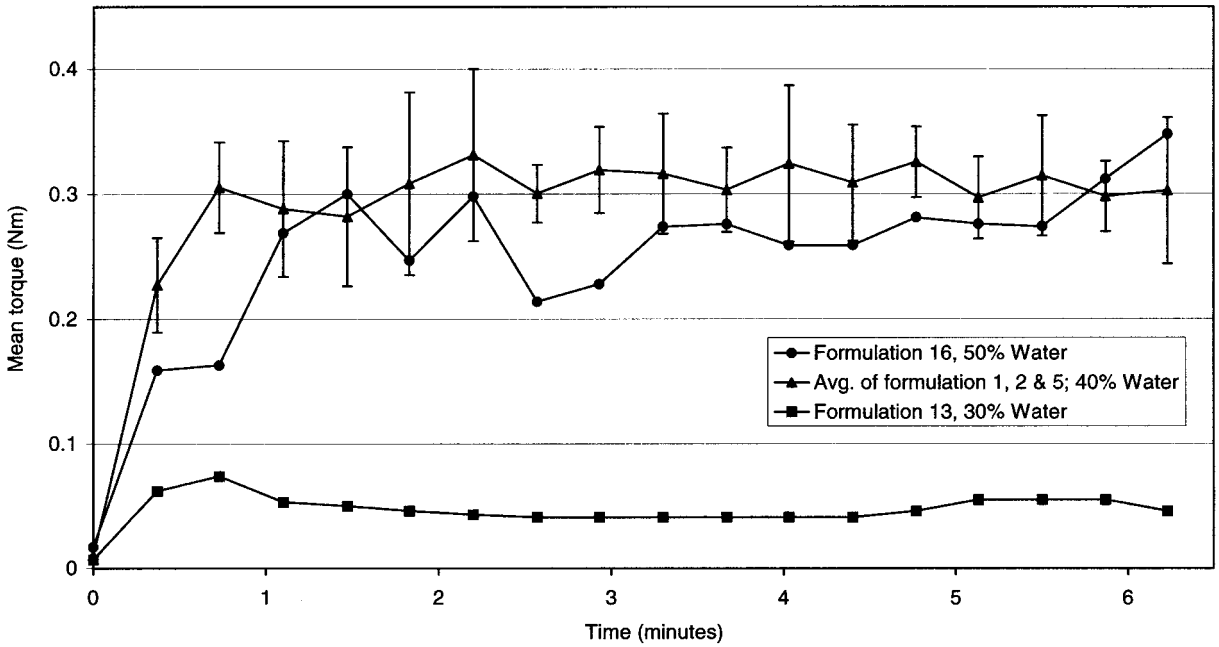

Figure 3. Mean torque at different water contents, 3.5% binder and 37.5% drug.

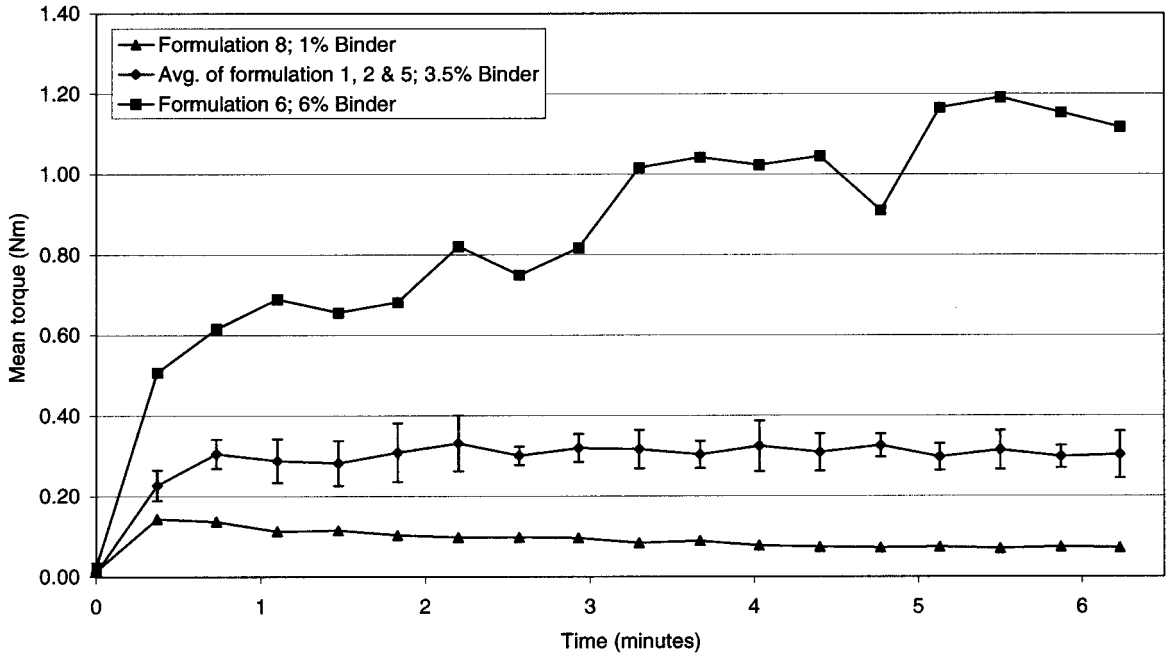

Figure 4. Mean torque for formulations with different binder contents at 40% water level.

bridges. Even though it is reasonable to expect interactions between water and binder content, they could not be discovered upon statistical analysis of the data from these experiments.

The effect of the amount of drug in the formulation at the same level of binder and water, on the viscosity of the wet mass is shown in Fig. 5. At 5% and 37.5% drug levels, there do not seem to be significant differences in the mean torque. At the 70% drug level, there was a reduction in the mean torque profile. At this high level of drug there may have been insufficient surfactant for wetting all the drug particles and distributing the binder fluid throughout the powder mass.

Effects of Formulation Variables on the Friability of Granules Produced in the Torque Rheometer

It is intrinsically assumed that wet mass properties will affect the quality of dry granules produced downstream in the process. While we were unable to discover predictive statistical correlations between wet mass properties and the formulation variables, an attempt was made to find such correlations between the dried granule friability and the formulation variables. An empirical model in terms of the independent experimental variables was fitted to the data from the 15 distinct experiments by least-squares regression using Design Expert vers. 5.08. The best-fitting model was a reduced quadratic equation in terms of each of the three variables (see Table 4). The *F*-test showed that the model was significant with $P < .0001$ (H_0 is that all the coefficients are equal to zero). The design had three replicates of the central point, and the total number of distinct experiments (15) was greater than the number of parameters in the model (5), which allowed the calculation of a lack-of-fit parameter. This was found to be insignificant with $P = .1606$ (Table 4). The adjusted *r*-squared of the final model was 0.8514.

The final equation in terms of actual factors and coefficients was:

$$\begin{aligned}\text{granule friability} = {} & 211.79 - 1.31 \times \text{drug} - 37.95 \\ & \times \text{binder} - 2.93 \times \text{water} \\ & + 4.06 \times \text{binder}^2 + 0.037 \\ & \times \text{drug} \times \text{water}\end{aligned}$$

The coefficients for the drug and the drug–water interaction term were significant only at the 15% confidence level ($P < .15$ level), but were still included

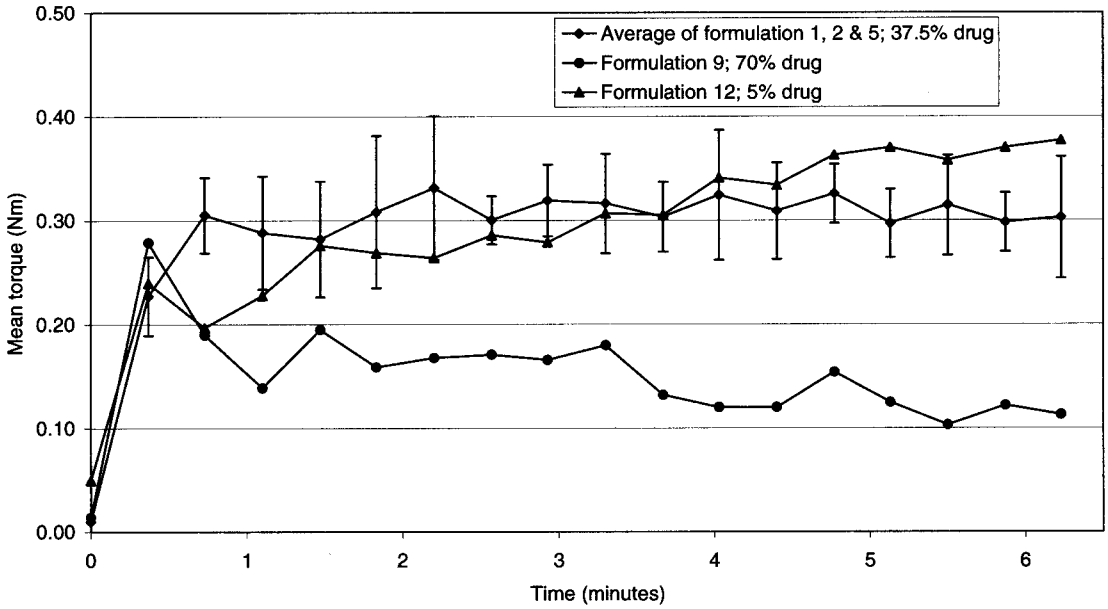

Figure 5. Mean torque of formulations with different drug contents.

Table 4

Coefficient Estimates and ANOVA for Reduced Quadratic Model

(a) Coefficient Estimates of the Model Parameters

Factor	Coefficient Estimate	Degrees of Freedom	Standard Error	t for H_0, Coeff=0	Prob > |t|
Intercept	17.51	1	2.42		
A-Drug	3.13	1	1.99	1.57	0.1441
B-Binder	−14.16	1	1.99	−7.12	< 0.0001
C-Water	−9.22	1	1.99	−4.64	0.0007
B^2	8.97	1	2.04	4.40	0.0011
AC	4.23	1	2.60	1.63	0.132

(b) ANOVA for Response Surface Reduced Quadratic Model

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-value	Prob > F
Model	5226.70	5	1045.34	19.34	< 0.0001
Residual	594.64	11	54.06		
Lack of fit	571.95	9	63.55	5.60	0.1606
Pure error	22.69	2	11.35		
Corr. total	5821.34	16			
Root MSE	7.35	R-squared Adjusted	0.8979		
Dep. mean	24.72	R-squared Predicted	0.8514		
CV	29.74	R-squared	0.7492		

in the equation to improve the correlation coefficient of the entire model. All other model coefficients were very significant with $P < .01$. Table 3 also shows the predicted values obtained from the model compared to those from the actual experiments. The studentized residuals vs. the predicted values show random scatter, indicating that the sizes of the residuals are independent of the predicted values (graph not shown).

Response Surface Plots of the Effects of Formulation Variables on the Granule Friability

A response surface and a contour plot of granule friability vs. the binder and drug concentrations at a constant water level of 40% (mid-point of the water range) are shown in Figs. 6a and 6b. The plot shows that granule friability decreases with an increase in the binder level as expected. At between 1% and 2% binder the granule friability is very high (ranging between 40% and 60%), while the friability reduces to less than 10% at higher binder concentrations and lower drug concentrations. Granule friability also appears to increase slightly with increasing drug concentration, though this may not be a very significant effect as seen from the analysis of variance (ANOVA) table for the coefficients of the different equation parameters.

Figures 7a and 7b show a response surface and a contour plot of the granule friability vs. drug and water concentration at the 3.5%, mid-range, binder level. There is an inverse relationship between granule friability and the amount of water added to the formulation, especially at lower drug concentrations. At higher water levels, there is a direct correlation between the amount of drug in the formulation and granule friability. At lower water levels the relationship is reversed and higher amounts of drug decrease the granule friability, although the extent of the effect is not as strong. This interaction between the drug and water levels may not be very statistically significant, as seen in the ANOVA table.

Figures 8a and 8b show a response surface and a corresponding contour plot of the granule friability vs. water and binder concentration at the middle range drug concentration of 37.5%. Granule friability generally appears to decrease with increasing amount of water at all levels of binder. Increasing levels of binder tend to decrease granule friabilities down to a limiting value in the mid-range of binder concentration. After this limiting value, granule friabilities appear to level off at a low value (or increase slightly).

CONCLUSIONS

In this study, torque measurements were not discriminatory enough to detect minor differences in formulation composition. However, general trends in the torque profiles were reflective of the composition of the formulation. Granule friabilities showed

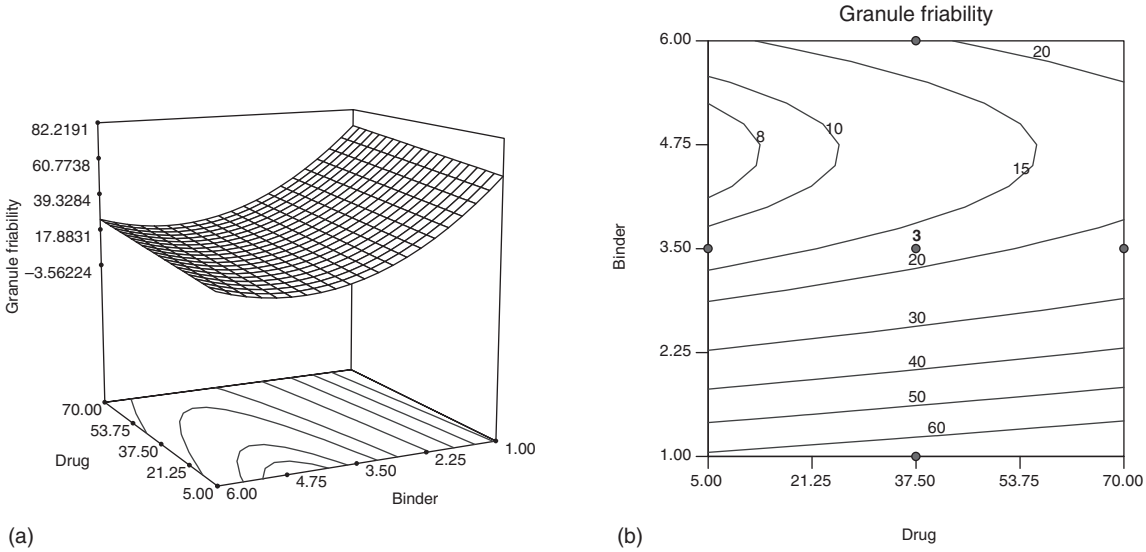

Figure 6. Granule friability as a function of binder and drug concentration.

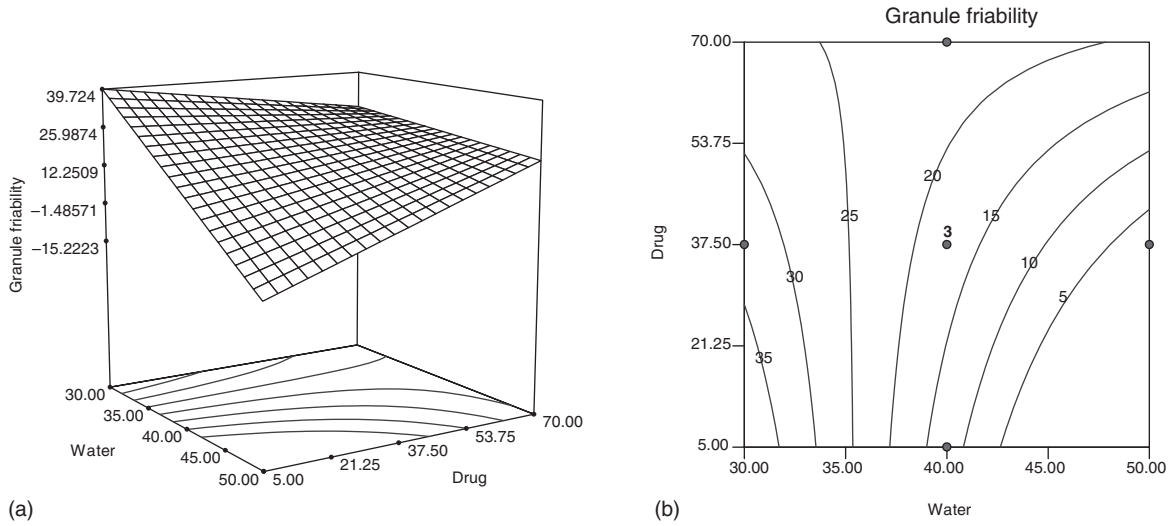

Figure 7. Granule friability as a function of drug and water level.

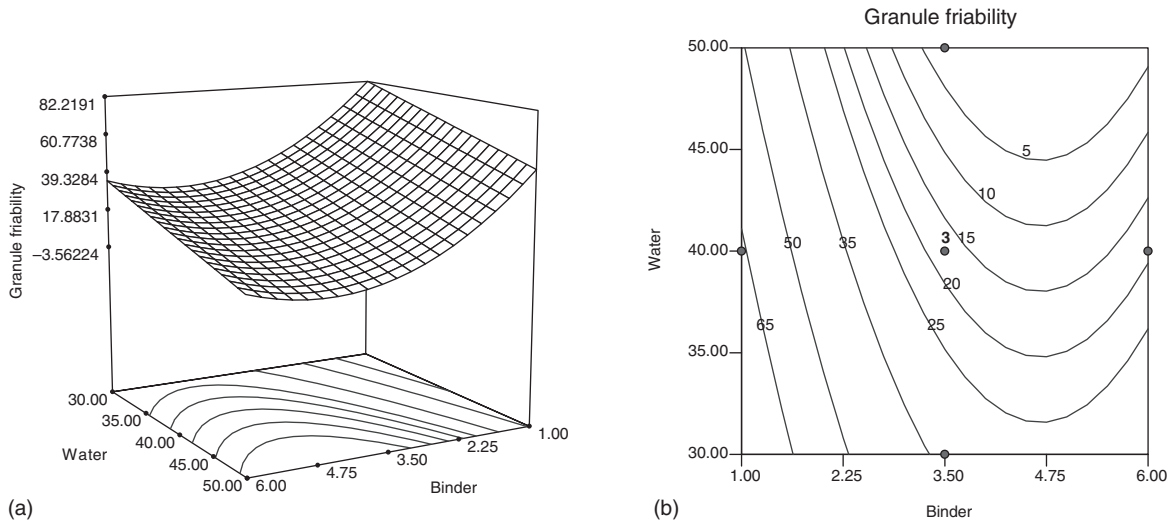

Figure 8. Granule friability as a function of binder and water level.

strong dependence on formulation variables, which could be modeled using an empirical equation in terms of the experimental factors. Some useful conclusions could be drawn from the data. For example, it may be unnecessary to exceed a threshold value of binder in the formulation since further increases may not increase granule strength any further. Moreover, increasing the binder may actually be detrimental to the formulation by making it overly sensitive to the level of water in the formulation or greatly increasing the density and reducing the compactability of the granules. Drug concentration does appear to have some effect on the granule strength, along with some evidence of an interaction between drug and water concentration. This indicates that, depending on the final dose of the chemical in the dosage form, there may be a need for slight modifications in the level of granulating fluid required for the process. It also suggests that major changes in bulk physical properties of different lots of a drug substance could potentially be detected by the use of mixer torque rheometry.

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