



Mixer Torque Rheometer Studies to Minimize Drug Utilization for Extrusion / Spheronization Formulations

Authors Ronald Vladyka and Jason Oliver
 Cardinal Health Pharmaceutical Development
 14 Schoolhouse Road
 Somerset NJ, 08873

Introduction

During the development of a controlled release dosage form, extrusion spheronization is a common technology to prepare drug loaded pellets. These pellets are coated with functional polymer systems to achieve a sustained release profile. One of the beneficial features of extruded spheronized pellets is the ability to prepare high, greater than 75%, drug loaded particles. During the development of prototype samples a large number of batches may be needed to determine the optimal granulating fluid level to prepare pellets with favorable physical characteristics. Because of the large number of batches, active substance can easily be consumed rapidly. This becomes a major concern when the drug substance is in short supply.

The use of the mixer torque rheometer (MTR) as an upfront analytical tool can greatly reduce the number of development batches and conserve valuable API. This equipment has been shown to be an excellent tool for the evaluation of wet granulated systems and as a scale-up tool for high shear granulations (1). The objective of this study is to apply the MTR to determine the optimal granulation fluid level for two formulated systems using API with low and high solubility. With the use of the MTR it will be determined if drug utilization can be kept to a minimum when developing an extruded / spheronized product.

Methods

Two formulated systems containing either Diltiazem (aqueous solubility of 420 mg/ml) or Ketoprofen (aqueous solubility of 0.294 mg/ml) were dry blended with microcrystalline cellulose (Avicel PH 101, FMC BioPolymer) and methylcellulose A15 LV (Methocel, Dow Corp). Diltiazem HCl accounted for 75% of the formulation while the Ketoprofen represented 80%.

The granulation characteristics of these two systems were evaluated by using the MTR (Caleva Ltd-Figure 1)(2). A multi-addition profile was utilized to model the granulation process. Drug substance and excipients were dry blended. A 20 gram sample of this dry blend was utilized in these studies. Two grams of granulating fluid (DI Water) for the Ketoprofen formulation and 0.75 grams for the Diltiazem were added in multiply additions over 10 wet massing intervals. Each wet massing interval consisted of a two-and-a-half minute mixing period and a 20-second data logging (collection) period with the MTR operating at 50 rpm. Mean line torque and average amplitude were the two parameters of interest that were monitored during the granulation process.

One kilogram confirmation prototype batches were produced for each formula. Prototype batches for each of the formulas were prepared using both the mean line torque and average amplitude maximum fluid levels. The granulation process was conducted in a planetary mixer (Hobart). A Nica radial extruder with a 1.0 x 1.0 mm screen and Nica spheronizer were used to prepare the pellets. All pellets were dried in a forced hot air oven (Blue M). The pellets were evaluated for particle size distribution by sieve analysis (RoTap) and two-dimensional aspect measurements (MEJII Stereomicroscope).

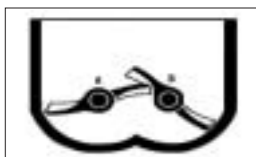


FIGURE 1
View of mixer torque rheometer bowl showing intermeshing paddles. **A**=drive shaft, **B**= subsidiary shaft

Results and Discussion:

Mixerer Torque Rheometer

The data collected for the MTR batches (average amplitude and mean line torque) were plotted and used to determine granulating fluid levels for the 1 kg prototype batches. It is well known that the maximum mean line torque value represents the capillary phase of a wet granulation. During the capillary phase all pores become filled with granulating fluid (3). Luukkonen et al. have demonstrated with excipient granulations that optimum extruded / spheronized pellet properties are achieved when the granulation is in the capillary state (4) or maximum mean line torque. Because of these findings the fluid level at the maximum mean line torque was evaluated. Additionally, a second value was investigated in these studies. It was determined in earlier studies that the average amplitude may also provide some useful information. Thus, average amplitude was monitored during the granulation process evaluation.

Ketoprofen

The MTR results indicate two different fluid levels for the Ketoprofen formulation (Figure 2). The maximum mean line torque occurs with approximately 70% granulating fluid, while the maximum average amplitude is reached when only 50% of the granulating fluid has been added to the batch. Both of these granulating fluid levels were evaluated in the 1 kg prototype batches and the resultant pellets' properties were determined. The pellets prepared with the maximum mean line torque value resulted in not greater than 49.2% of the pellets with in the <1180, > 590 micron particle size range. These pellets were very large in size, thus indicating an over wet system. (Table 1.) The fluid level corresponding to the maximum average amplitude yielded 82.0% of the pellets having a particle size <1190, > 590 microns and an aspect ratio of 1.12.

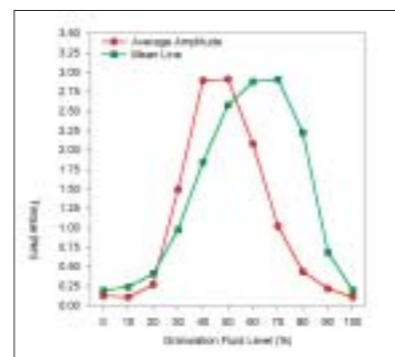


FIGURE 2
MTR Data for 80% Ketoprofen Batch

Particle Size	80% Ketoprofen Formula	75% Diltiazem HCl Formula
14 mesh (1410 µm)	8.0%	13.6%
16 mesh (1190 µm)	3.7%	8.7%
18 mesh (1000 µm)	26.6%	16.3%
20 mesh (840 µm)	30.0%	30.7%
25 mesh (710 µm)	15.4%	18.2%
30 mesh (590 µm)	10.0%	10.6%
<30 mesh (<590 µm)	6.3%	1.9%
Aspect Ratio:		
Mean (n=10)	1.12	1.21

TABLE 1
Pellet particle size distribution and aspect ratio

Diltiazem HCl:

As with the Ketoprofen formulation the Diltiazem system yielded two different fluid levels for the maximum mean line torque and average amplitude (Figure 3). The prototype 1 kg batch made with a 30% granulating fluid level, representing the maximum mean line torque, resulted in an over wet system in which no usable pellets were prepared. The batch produced with a fluid level corresponding to the maximum average amplitude, 22%, yielded 75.8% of the pellets having a particle size <1190, > 710 microns and an aspect ratio of 1.21 (Table 1).

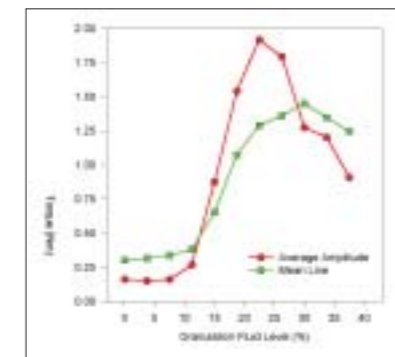


FIGURE 3
MTR Data for 75% Diltiazem HCl Batch

Conclusions:

The use of the mixer torque rheometer utilizing the appropriate output measurement can determine the optimal granulating fluid level to prepare higher quality pellets. Based on the results of this study the use of maximum average amplitude is a better predictor of granulating fluid level than maximum mean line torque. The average amplitude measurement may represent a formulated system in which the granulating fluid can be held within the granulation and can compensate for fluid migration during the extrusion / spheronization process. Unlike the capillary phase that excess at the maximum mean line torque value the granulating fluid may have the potential to migrate during the extrusion / spheronization process and result in increased surface wetting and thus an over wet system. Additional studies are currently ongoing to further understand and model this theory of water migration.

Utilizing the most appropriate tools (mixer torque rheometry) and techniques (maximum average amplitude measurements) will allow the best use of drug substance. In our study, only 15 to 16 grams of drug was used for each formulation to determine the optimal granulating fluid levels. Based on the results of the MTR data larger batches can then be prepared with the confidence that quality pellets will be made. These quality pellets can then be used for coating trials and the development of a controlled release dosage form.

References:

- Hancock et al, 1992. Int. J. Pharm. 83, 147-153.
- Rowe and Parker, 1994. Pharm. Technology 3, 74-82.
- Hancock et al, 1994. Int. J. Pharm. 102, 167-176.
- Luukkonen et al, 1999. AAPS Annual Meeting, New Orleans.