Opportunities for Mixer Torque Rheometry

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Abstract

The process of wet granulation is widely used in the production of solid dosage formulations in the pharmaceutical industry. Because of the diverse nature of pharmaceutical materials, granulation is often employed as an intermediate process to enhance flow and compaction properties and improve the final product performance. Since the properties of a wet granule have a critical effect on the resultant dry granule, tablet, extrudate, or spheroid, a quantitative measurement of the rheological properties or consistency of a wet granule is valuable. The Consistency of the wet mass is a function of the distribution of the granulating liquid in the available pores and voids between the powder particles. The Consistency of a wet mass has been shown to be related to the end product properties. The Mixer Torque Rheometer (MTR-3) is a unique tool that allows a quantitative description of wet granulations. As well as offering useful practical applications quantitative descriptions can be essential in the context of modern pharmaceutical regulations.

Key words: Granulation, wet mass, consistency, Mixer Torque Rheometer, MTR, quantitative description.

Introduction

Wet granulations are a useful precursor to many solid dosage formulations and as such are widely used in the pharmaceutical industry. Because of the diverse nature of pharmaceutical materials, granulation is often employed as an intermediate process to enhance flow and compaction properties and improve the final product performance. The properties of a wet granule have a critical effect on the resultant dry granule, tablet, extrudate, or spheroid, therefore a quantitative measurement of the rheological properties or consistency of a wet granule can be valuable. The consistency of the wet mass is a function of the distribution of the granulating liquid in the available pores and voids between the powder particles. The consistency of a wet mass has been shown to be related to the end product properties.

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There are several challenges in making a good granulation amongst which are:

•*Material selection and interactions between component:.* The influence of different formulation components both alone and in different ratios can be quantitatively assessed very quickly and basic formulation development studies can proceed at a rate that was previously not possible.

•*Source/batch variation of components:* Some widely used formulation components such as microcrystalline cellulose are made from natural materials. There can be variations between batches that can be impossible to recognise easily and quickly. These minor changes can have significant effects on items such as yields in production. The Mixer Torque Rheometer can help detect and resolve such issues.

•*Processing end point determination (mixing requirement):* This perennial problem with in the pharmaceutical production. The MTR-3 can offer possibilities to assist in the determination of mixing end point

•*Scale-up to production:* The MTR can provide a reliable, quick and quantitative method of comparison of the material produced in scale up development work.

The above items can affect the properties of a granulation that in turn can affect the properties of the final product performance. Standardising of product performance is vital with in today's international pharmaceutical industry. In many cases, even though wet granulation is widely practised in the pharmaceutical industry sensory tests are still widely used to determine the qualities of wet granulations. An example of this is the "hand squeeze" test. With this test an experienced plant operator or formulator squeezes the material with the hand and makes a subjective assessment on the qualities of that particular wet mass. There is no doubt that these tests have been useful in the past but they do lack objectivity and preciseness. With such test it is impossible to compare granulations that are similar or are in different locations in space or time. The limitations on such a system is obvious and it the lack of a quantitative characterization is unacceptable in today's highly regulatory climate. It is to overcome this clear lack of information that the Caleva Mixer Torque Rheometer can be an invaluable aid.

Key features of the Instrument

Mixer Torque Rheometer (MTR) uniquely offers a means of characterizing the rheological behaviour of wet granulations by correlating the consistency with a numerical value.
Mixer Torque Rheometry is widely used in the pharmaceutical industry as the structure of the wet granulation is not compromised. Consequently the technique gives highly representative and indicative measurements. The MTR is suited to laboratory, production and quality control environments and may be operated in a range of containment regimes. The instrument is rapid in use and simple to operate. The MTR design is based on techniques developed and applied within academic research and practical industrial environments, primarily with wet granulations within the pharmaceutical industry.

Principle of Operation

The Mixer Torque Rheometer (MTR) comprises a mixing bowl containing two horizontal, contra-rotating mixing blades. The secondary blade rotates at twice the speed of the primary blade. Since the bowl pivots about the primary drive shaft, the action of mixing a wet powder mass generates a torque, which is detected via a torque arm by a loadcell. The torque generated is directly related to the Consistency of the wet powder mass in the bowl.

Data manipulation

During each logging period (a typical experiment will have 10 to 20 logging periods of 20 seconds each) the torque is sampled at 100Hz. This is a relatively large amount of data and it is usually summarised by a calculation of the 'Mean Line Torque' value. 'Mean Line Torque' is defined as the arithmetic mean of all raw data points in a data set (logging period).

Prior to each measurement of wet powder mass the MTR mixing bowl is run empty and the torque is measured. This 'Base Line Torque' is subtracted from all subsequent 'Measured Torque' figures to eliminate any slight variations in the bowl assembly. The result of this calculation gives a 'Corrected Mean Line Torque' value, which may also be referred to as 'Consistency' or 'pseudo viscosity'.

Control

The MTR is controlled via a Graphical User Interface (GUI) resident on a PC. The GUI enables experimental methods to be created and stored and allows experimental data to be stored and manipulated.

Applications

Mixer Torque Rheometry may be applied in the research, formulation development, process development, and process control areas of pharmaceutical granulation.

1. Research

Investigations have been carried out into the granulation process. Many materials studied using the Mixer Torque Rheometer have exhibited an increase in measured torque values with increasing binder content, rising to a maximum, thereafter decreasing as a slurry is produced as shown in FIG.I. This behaviour is consistent with the differing states of liquid saturation in an assembly of particles.

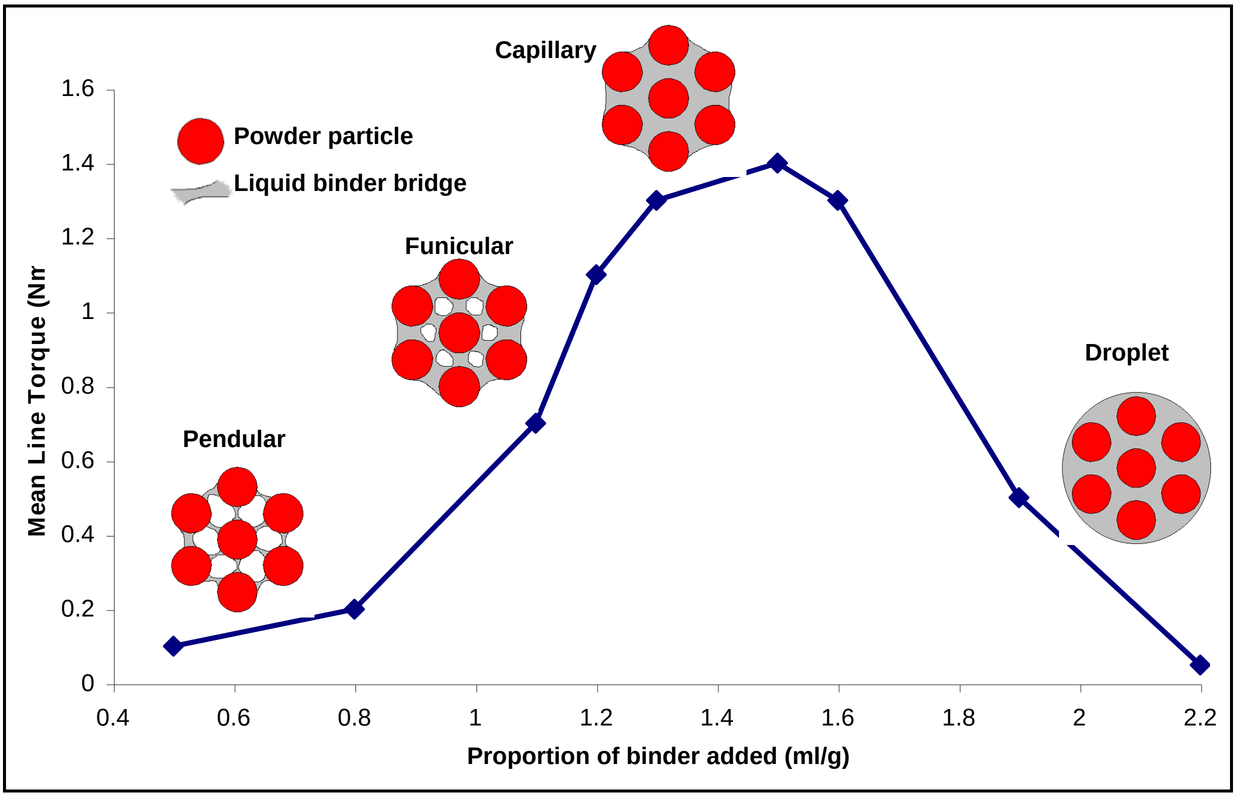

FIG.I. States of liquid saturation in an assembly of particles.

2. Formulation Development

The excipients used in a formulation may be varied to improve the product performance. The MTR may be used to analyse the effects of these variations rapidly and on a small scale by use of the Multiple Addition Test, as shown in FIG.II. The Multiple Addition test allows the operator to add binder to the dry powder in the mixing bowl in user defined increments, a user defined mixing and data logging period follows each addition. The chart shown in FIG.II also gives an indication of the reproducibility of the results that may be achieved on this instrument, despite it being a quantitative measurement technique.

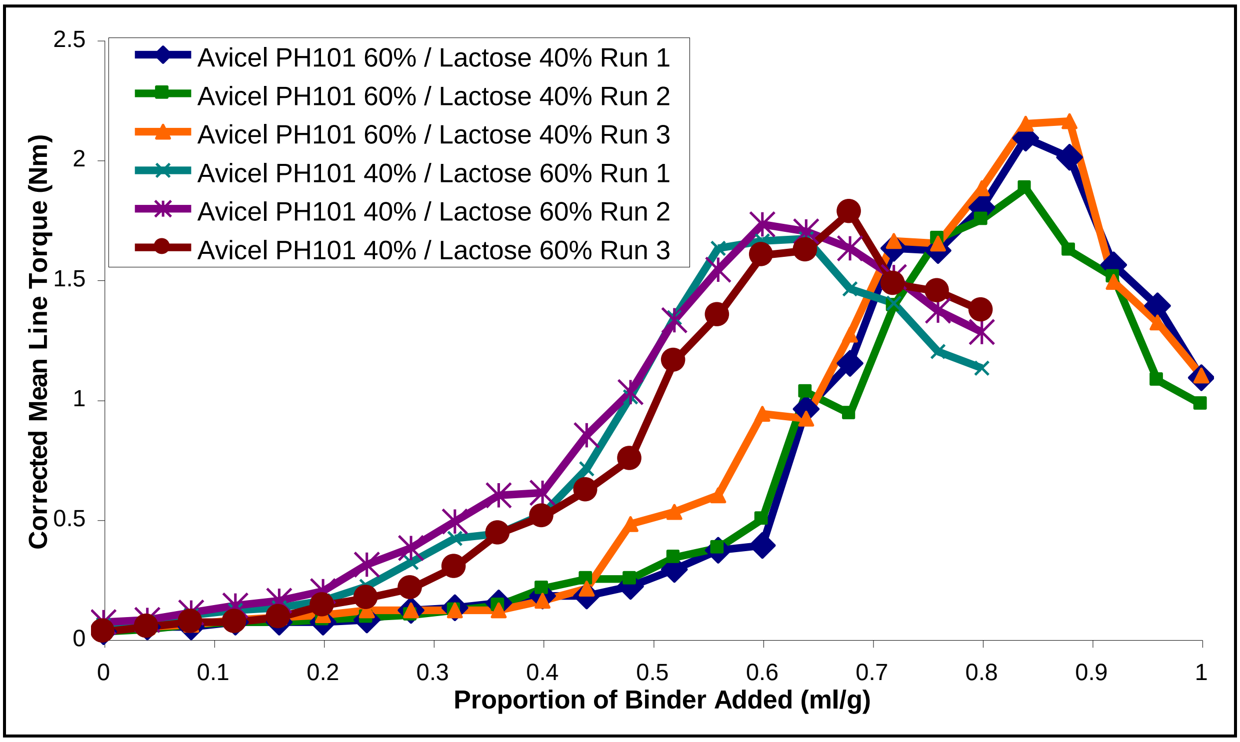

FIG.II. MTR Multiple Addition Tests for Avicel PH 101 / Lactose Mixes

Since the technique of Mixer Torque Rheometry is quantitative it is recommended that any experiment be carried out in triplicate as shown in FIG.II. An average of these results may then be taken to eliminate any spurious individual results and smooth the torque / binder ratio profile as shown in FIG.III.

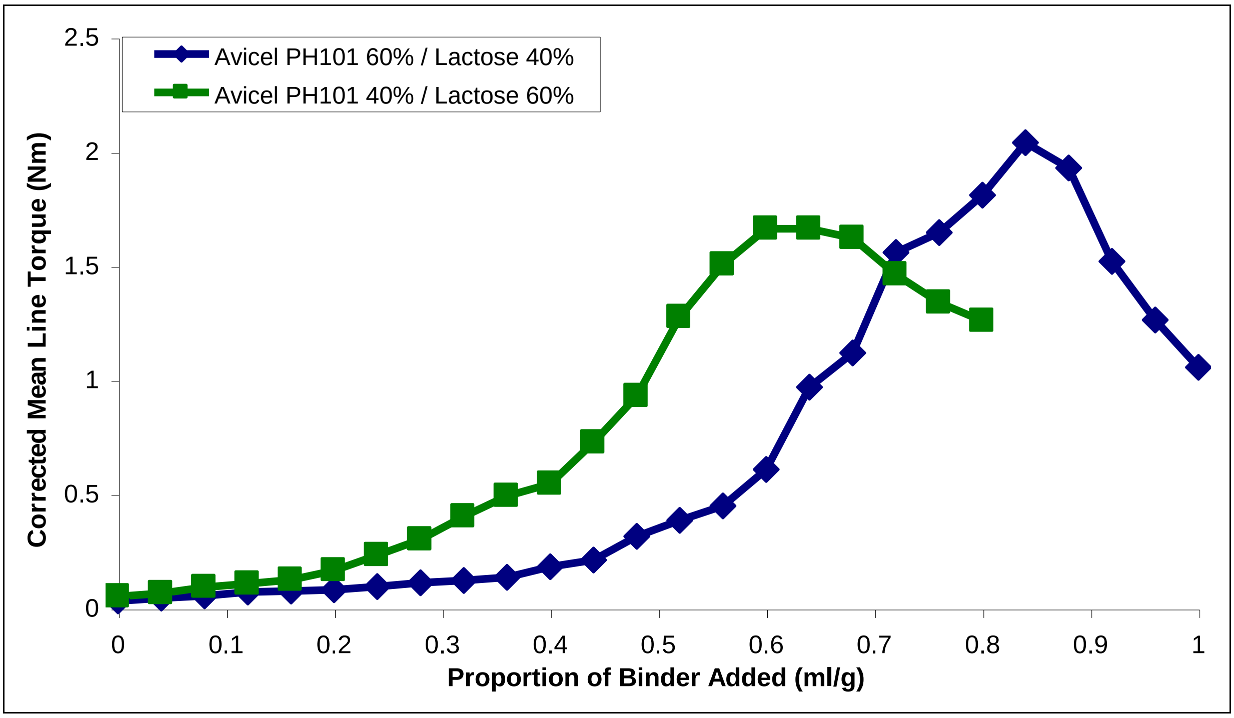

FIG.III. MTR Multiple Addition Tests for Avicel PH 101 / Lactose Mixes (Averaged).

Avicel PH101 is often used in wet granulations as it forms a strong granule and is not particularly sensitive to over-mixing and over-wetting.

There are three key differences between the consistencies of the two mixes shown in FIG.III. The blend with the higher proportion of Avicel exhibits a higher maximum torque response. It is therefore considered to be a stronger granule. It can be observed that this maximum torque response occurs at a higher binder ratio in the blend with the higher proportion of Avicel. Therefore these results indicate that the mixture requires more binder to achieve the strongest granule. Since the blend with the higher proportion of Avicel displays a higher torque response it follows that the peak is also broader. Therefore the formulation is more likely to be successful on a larger scale because it is less sensitive to over-wetting.

The MTR also enables binder – substrate interactions to be analysed. For example it has been shown that substituting different polymer binders or altering the concentration of polymer binders has an effect on the rheological behaviour of a granulation. These observed differences may be correlated with other binder substrate interaction phenomena to assist in the binder selection process. The MTR may also be used to detect changes in the rheological behaviour caused by source and batch variations of excipients.

The Multiple Addition Test rapidly gives an approximate indication of the optimum binder ratio (ratio that produces the strongest granule) for any given formulation. However, what is observed in the results shown in FIG.III. may not be a true indication of the binder ratio / torque profile. There are two reasons why this may be so:

No account has been taken for the rate of binder distribution. It is possible that the experiment has not allowed for sufficient time between binder additions for all the binder to be effectively distributed. In this instance the formulation will appear to yield the strongest granule at a higher binder ratio than in reality it does if mixed for a long period.

No account has been taken for the effect of prolonged mixing time. The MTR, by design, is a very high shear mixer. After prolonged mixing the granulation may become overworked, and may be prone to losing moisture through evaporation.

3.Process Development

The MTR may be employed as a process development tool offering savings in both time and resource usage. Mixing time is a critical parameter in the granulation process, particularly when processing with high shear granulators. The MTR may be used to examine the role of various material parameters in order to assess their influence on the required granulation end point. The type or concentration of polymer in a binder solution may be varied during formulation development, as this will influence the mixing time through the effect of viscosity on binder distribution. This in turn will effect the mixing time required to distribute the binder effectively. The MTR offers the ability to observe the subtle differences in the rheological behaviour of wet granulations caused by varying the binder solution concentration, type, and the binder – powder ratio by use of the Variable Mix Time Test. An example of some Variable Mix Time Test results is given in FIG.IV.

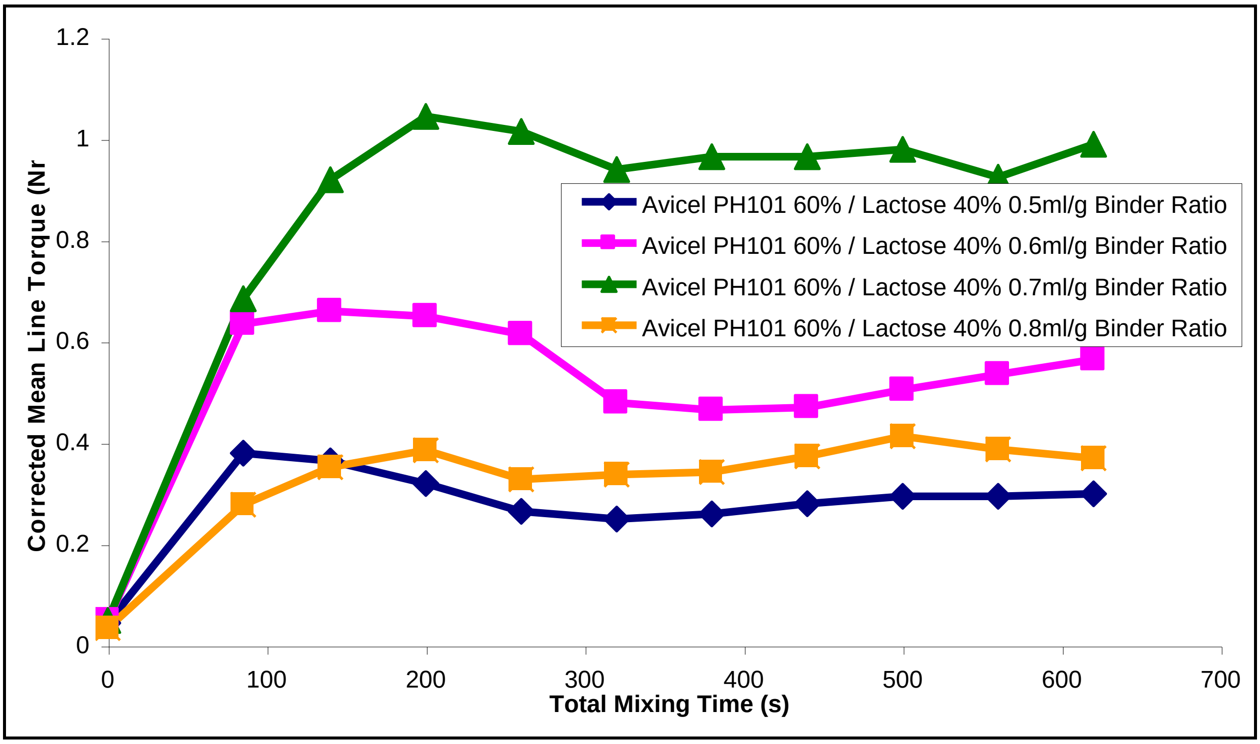

FIG.IV. Variable mix time test results. The binder ratios used in the tests were based on predictions made using the data reported in FIG.III.

0.5 ml/g
Dry mixture, gives relatively low torque value. The available binder is quickly distributed such that the maximum torque reading achieved occurs immediately after the binder addition. Granules are too dry for extrusion but may be suitable for compaction.

0.6 ml/g
Slightly dry mixture, initially behaves similarly to the theoretical optimum binder ratio. Maximum torque reading achieved occurs soon after the binder addition. Granules may be dried for compaction and are most likely to be suitable for extrusion.

0.7 ml/g
Theoretical optimum binder ratio (highest torque response). A strong granule gives a high torque reading. The torque does not reduce significantly even after prolonged mixing, therefore this material is not particularly sensitive to over-mixing. The resultant granule will be slightly too wet for extrusion, the optimum granule for extrusion is typically lower than this maximum torque response.

0.8 ml/g
Slightly over-wet mixture, the torque is lower than the theoretical optimum binder ratio mixture. The torque value gradually increases with prolonged mixing, this may indicate that the mixture is drying out. The resulting granule may be overworked and the mechanical properties may be poor. Note that the Multiple Addition Tests shown in FIG.III. indicated that this formulation at this binder ratio would still be below the optimum binder ratio. The

Variable Mix Time Test results shown in FIG.IV., however, indicate that in reality this formulation at this binder ratio is over-wet.

Process Control and Predictive Scale-up Strategies

The MTR is ideally suited for monitoring the Consistency of wet masses produced with production scale mixers because it uses such small sample sizes. The MTR Consistency Test measurement may be used to indicate the equivalence of rheological properties of mixes, even between granulators of different size or design. Ultimately the Consistency measurement may be regarded as a pseudo viscosity term, which can form part of a predictive scale up strategy based on dimensionless numbers.

Conclusions

The Caleva Mixer Torque Rheometer has significant potential to be an invaluable tool in all aspects of pharmaceutical granulation. It is rapid and simple to use and generates simple and reproducible results that accurately describe the properties of a wet mass in a way that is significantly more acceptable than that current “hand squeeze test”. The commercial equipment is currently available to all scientists working in this field.

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