# THE SPHERONIZATION CHALLENGE

caleva
CASE STUDY

A CASE STUDY


## The Challenge

Amongst our recent "Challengers" was a major pharmaceutical, biotech & nutraceutical manufacturer with an extensive portfolio of products. For reasons of confidentiality we do not name them.

One of our Production Extruder & Spheronizer Systems for manufacturing on a large-scale was used in trials by the manufacturer, but the pellets produced were not acceptable. As the product was already registered the composition could not be changed as we required.
The only changes permitted were to vary:

- The amount of binder addition
- The operational parameters of the manufacturing process

# Two key conditions were observed at the customer site

- There was no way to measure the consistency of the material during or after granulation.
- The granulation did not appear to be very homogeneous.

In our experience, at the development stage, the granulation parameters are often underestimated and the importance and the influence of this process on the final product outcome is often overlooked.

Our investigation examines this idea and a “road map” was created which allowed the customer to move forward to manufacture an acceptable product.

## Materials

Premix samples were supplied by Customer

Liquid for the binder addition

## Equipment

Caleva Mixer Torque Rheometer

Caleva Multi Lab

## Subject Matter Expert

Dr Steve Robinson B.A. PhD.

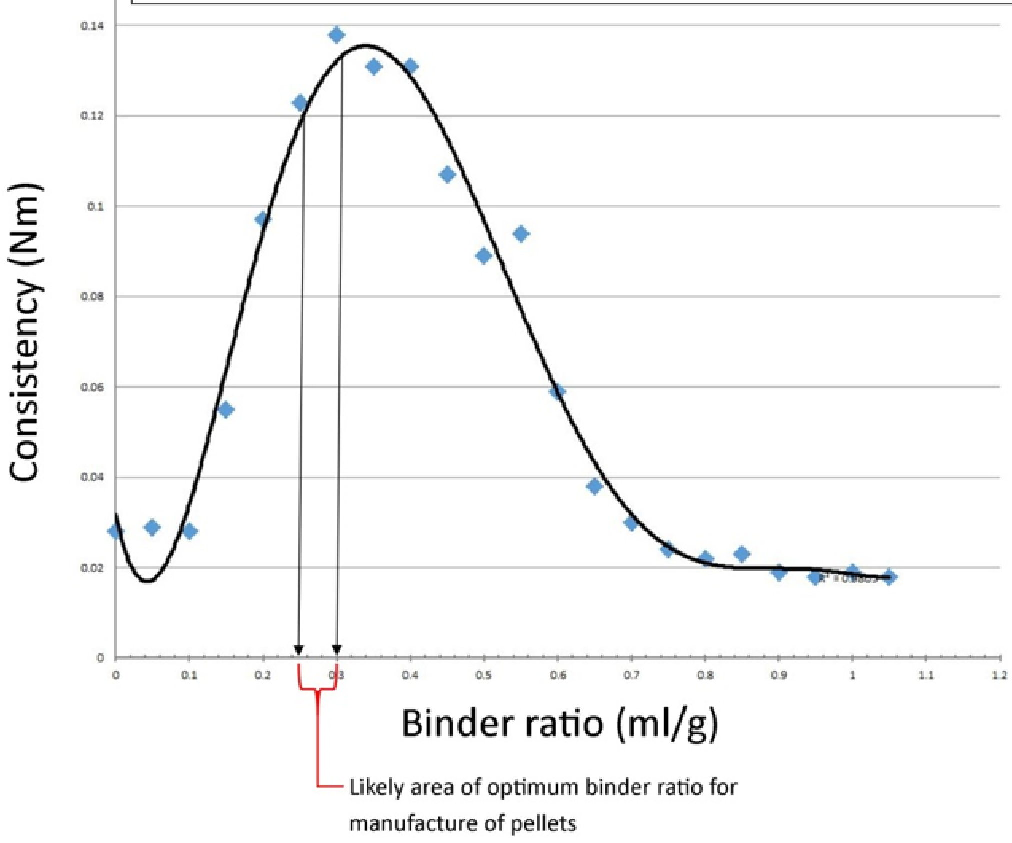
# A series of trials to understand the importance of granulation

## Trial 1 - Determine liquid binder

A preliminary multiple addition test was run using the MTR. This was to determine the optimum amount of liquid binder for the formulation. A figure of about 0.25 ml/g of the binder mix was suggested by the results obtained from the MTR. However, at this figure the consistency (or cohesiveness) of the formulation as measured by the MTR was very low (about 0.15 Nm – this is low compared to many formulations that can easily, and do regularly, go as high as 2 to 4 Nm). However, this figure was accepted for the trials as it was in close agreement to the figures generated by the manufacturer during their own trials. The graph shows that the optimum binder ratio is likely to be between 0.23 to 0.3 ml/g.

### Summary results from the initial Multiple Trial to choose a starting point for the optimum binder content ratio.

Figure 1. Results from a preliminary Multiple Addition (MA) trial to establish an optimum zone for the appropriate binder content in ml/g



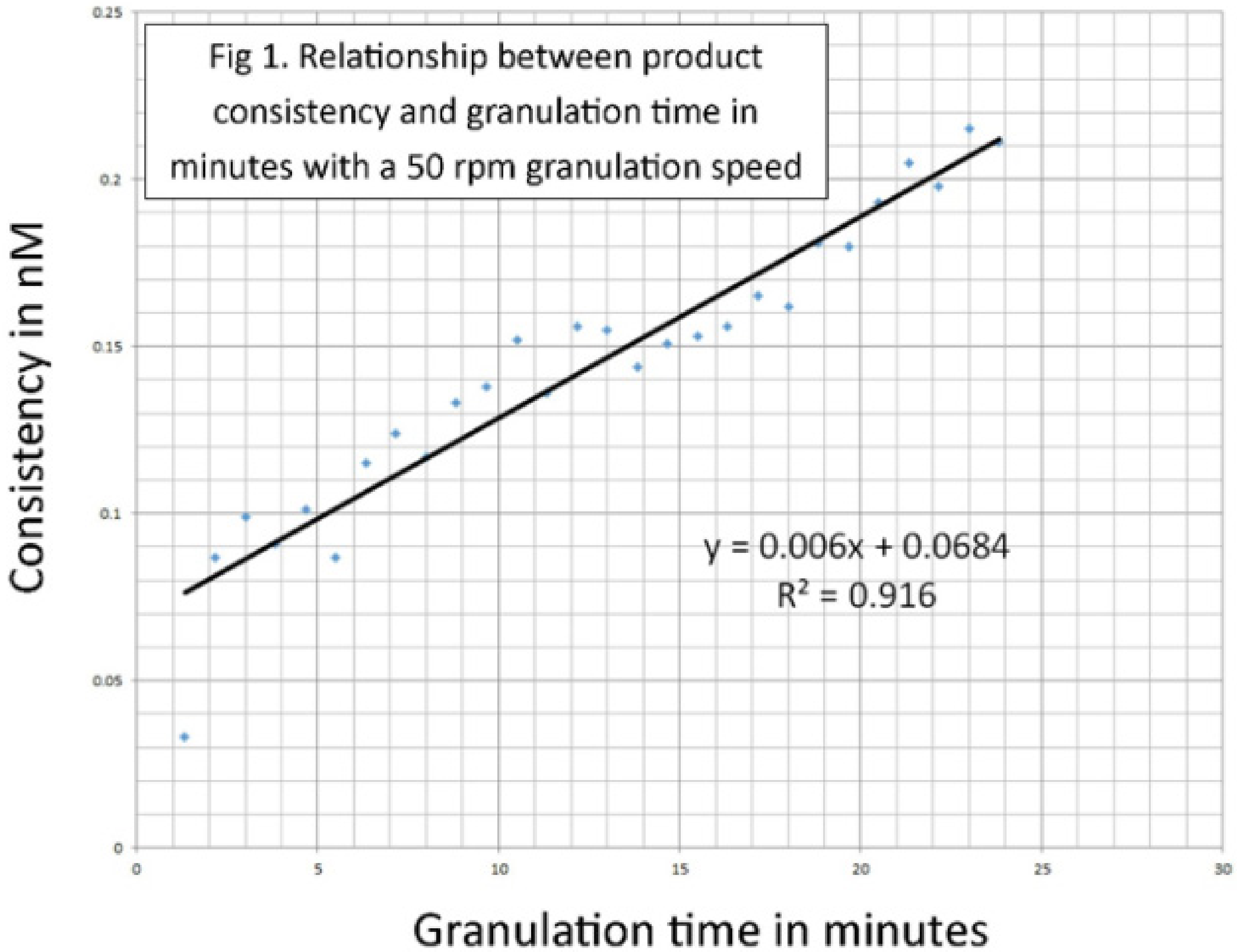

Note that this result was taken from **one trial** and it is normally recommended that **three trials** are completed and the mean of the three trials used for the binder ratio determination.

Such a graph is an indication, but possibly not a definitive result as the effect of "mix time" is considered in these multiple addition trials. It is recommended that an additional set of trials are used if possible making use of a screen extruder and larger spheronizer.

## Trial 2 - Additional granulation

A second trial was run using the Caleva Mixer Torque Rheometer to examine the proposition that additional granulation might improve the consistency of the product, as on occasion this has found to be the case in previous experiments with different products.

A sample of 20 g of premix was added to the MTR bowl with 5ml of binder. The MTR granulator was run at 50 rpm and the consistency measured periodically.




## Results

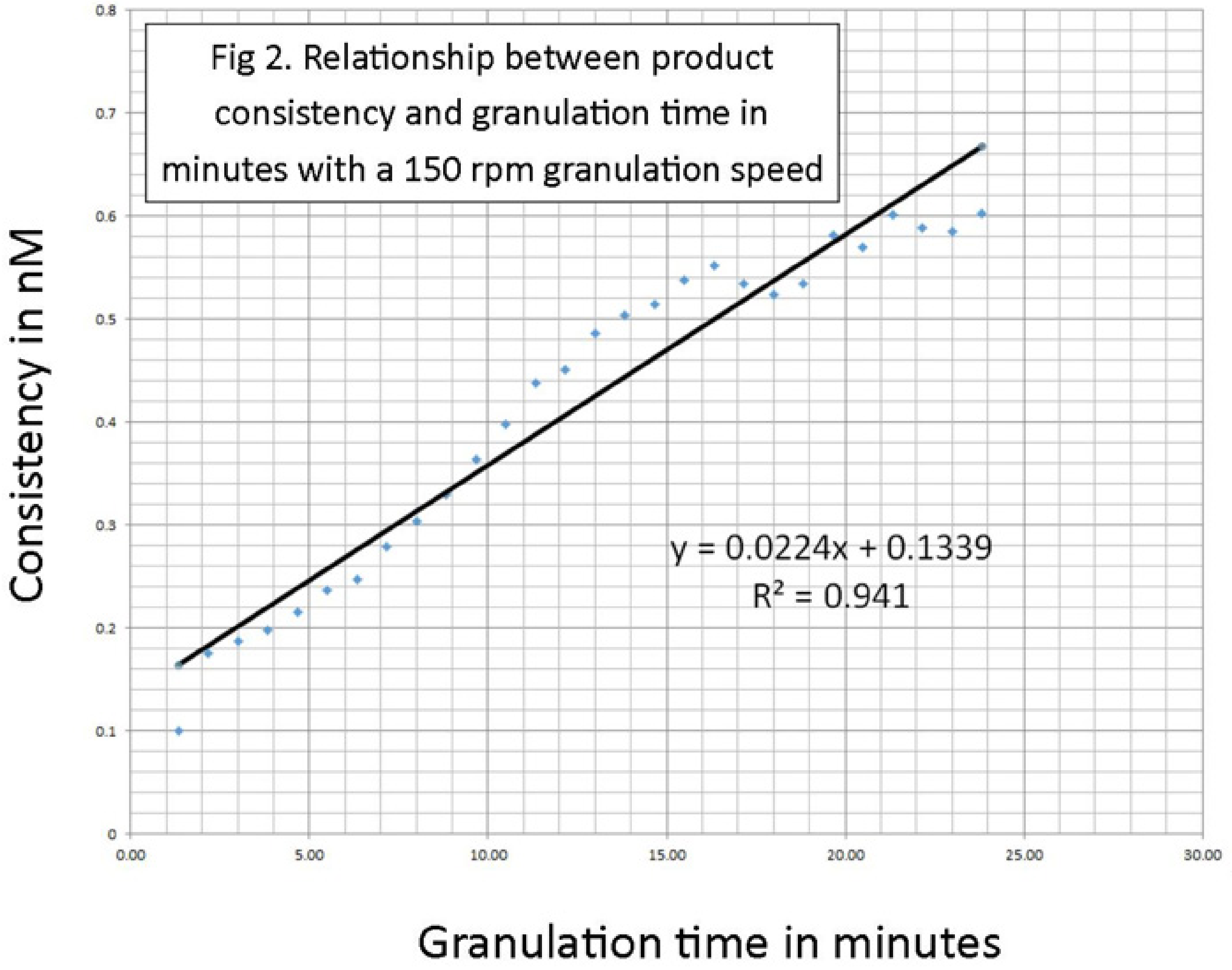
Figure 1 clearly shows that with continuing granulation, the consistency of the formulation continued to increase throughout the whole granulation period (about 25 minutes). There was no indication that the maximum level had been reached. This reached a higher figure than the one reached during the Multiple Addition test (0.215 Nm compared to 0.15 Nm) and presumably (although no measurements have been made) with the standard formulation developments that we have been testing. The higher level of consistency obtained suggested that there would be a good chance that the resultant material would be more suitable for extrusion and spheronization and make it easier to handle and removed some of the stickiness problem that had been troublesome.

## Trial 3 - Effects on consistency after trial 2

As there was no clear limit on the consistency level reached, a subsequent trial was planned to look at the effect of additional granulation on the consistency of the formulation.

An increase in the 25-minute granulation time would not be ideal.

Trial 1 above was repeated but with a mixing speed of 150 rpm (compared to 50 rpm in the first trial). A 25 minute granulation time was also used to see if a limit could be reached with an increased blade revolution speed. The results are shown in Figure 2 below.




## Results

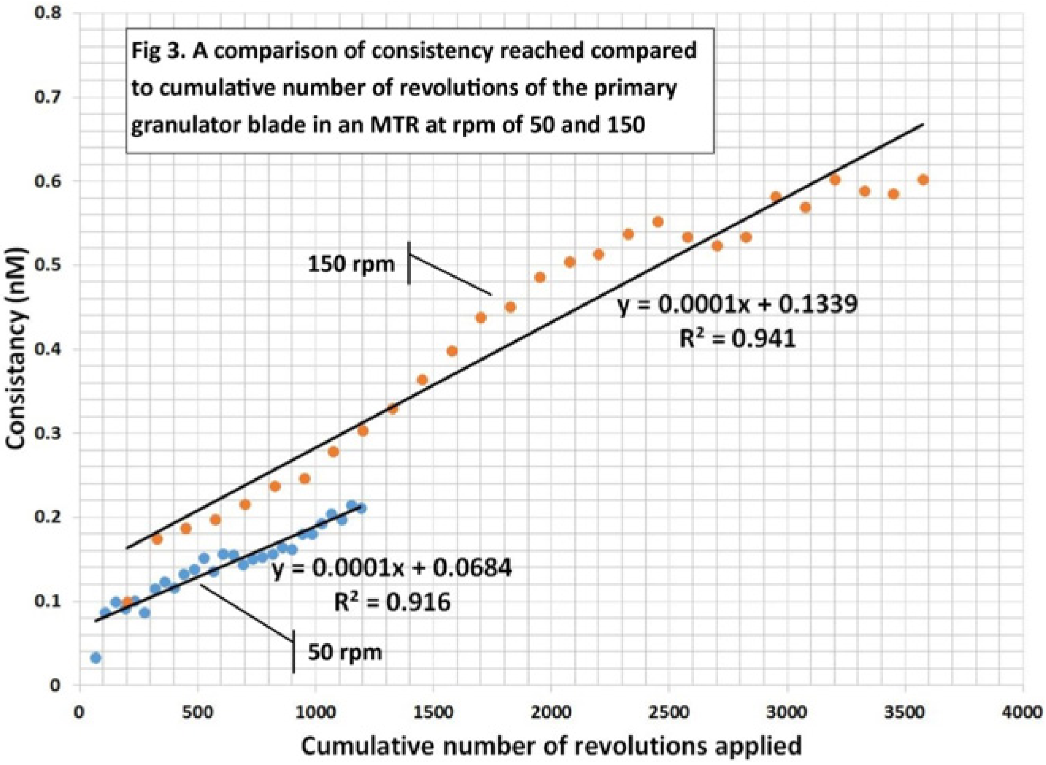
On the graphs the results look similar but the difference in scales should be noted.
Once again, with the more aggressive granulation no peak was reached. The increase appeared to be linear to a maximum of about 0.6 Nm.

Again, significantly higher than the consistency generally used in the formulation process.

A subjective and qualitative assessment of the resultant granulation showed that the material extruded more easily and felt drier and less sticky during spheronization than the ones experienced in the large-scale trials despite having the same amount of binder liquid.

## Data Comparison

Figure 3 shows the data on the same graph, for an easy comparison of consistency related to the **number of revolutions (and not time)** at different blade rotation speed.




## Comparison of the results indicates several points

- At both speeds there is a clear linear relationship between the number of revolutions and the product consistency measured and this reaches levels that are unlikely in the granulation techniques being used in the current trails at the customer site.
- There is an indication (but no clear proof) that the speed of the blade will generate a higher consistency level in the formulation, but it is highly likely that both speeds generate a consistency that is above what is being used in the current manufacturing process.
- The rate of increase is the same for both blade speeds but the faster blade seems to reach a higher initial level with fewer revolutions. This is not explained but could be due to a more aggressive premixing of the product before the binder liquid is added but this would require additional experimental work.
- There is a suggestion that at about 3,000 revolutions of the primary blade the rate of increase in consistency is beginning to slow but additional trials would be necessary to confirm this. It is not clear from this single trial.
- Despite the comment above there is no clear evidence in any of the results that any the maximum consistency has been reached. However, for our purpose it was assumed that the increase obtained was enough to move to extrusion and spheronization trails with this granulation parameter.

**In addition to the above, it was quite evident from a qualitative (and subjective) physical examination of the formulation that after a significantly more aggressive granulation, the material was easier to work with and had lost the “wet and sticky” feeling that we had seen in the larger scale samples.**

## General conclusions from the MTR trials

As the results showed that a more aggressive granulation led to a higher level of consistency and increasing the plasticity of the formulation, this suggests that the extrusion and spheronization process would benefit from this, making the product easier to manage.

A set of two trials were completed using the Caleva Caleva Multi Lab to investigate the effect of a significantly more aggressive granulation on the extrusion and spheronization of the formulation. These are shown below as trials 4 and 5.

## Trial 4 - Follow up trials using the information generated by the MTR trials

Trials were completed using the Caleva Multi Lab

### Materials

- 20 grams of the premix provided by the manufacturer
- 5.0 ml mix of water and prepared binder containing 0.0268 g of PG (0.134% in the formulation)
- The binder solution was at 90 to 95 dig C when added by a syringe.

### Granulation

- The granulator was run at 150 rpm for 25 minutes
  (Number of revolutions =~ 3750)
- The mixing bowls and blades were soaked in boiling water and dried before use so that they were quite warm during the granulation. Temperature measurements were not taken.

### Extrusion

- The material was extruded through the CML small screw extruder running at 90 rpm with a 1 x 1 mm hole dies.

### Spheronization

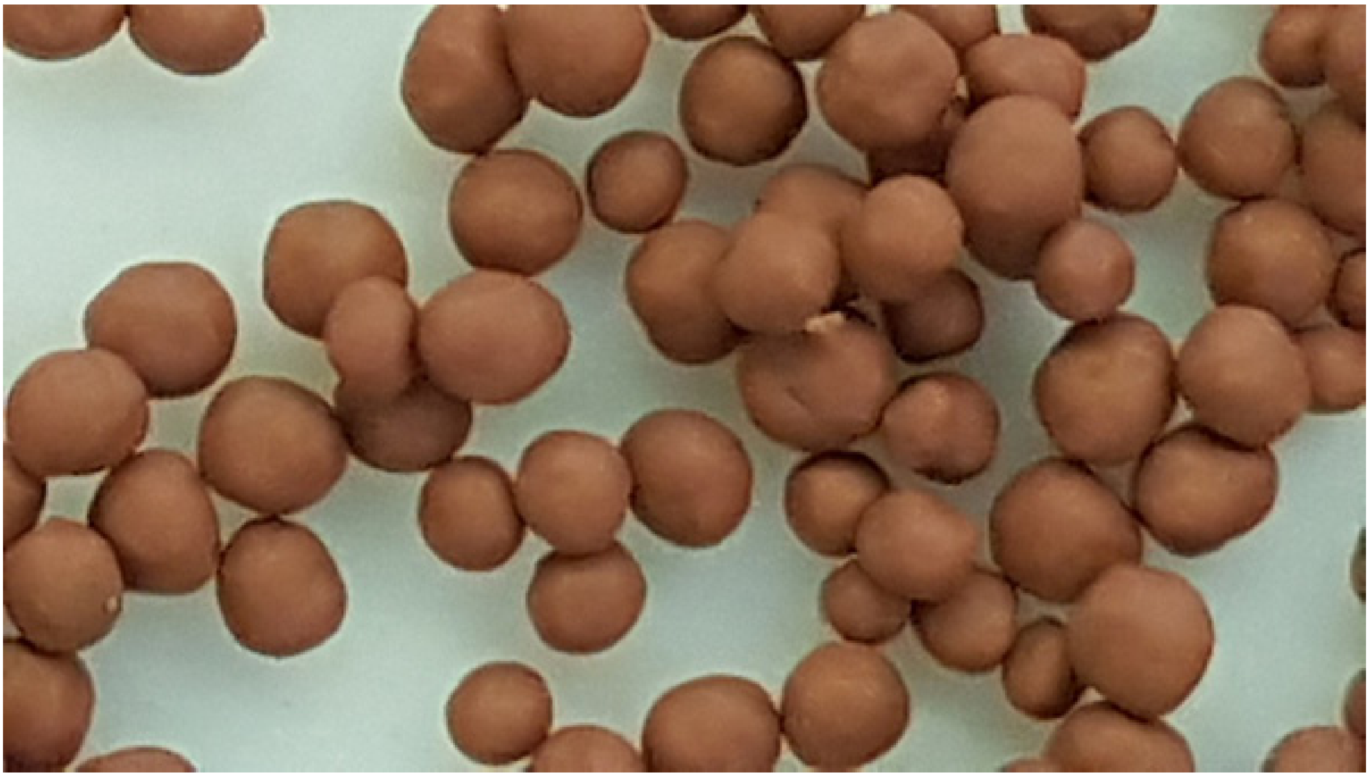
- The extrudate produced were spheronized in an 85 mm diameter bowl at 2500 rpm for 8 minutes (20.000 revolutions).

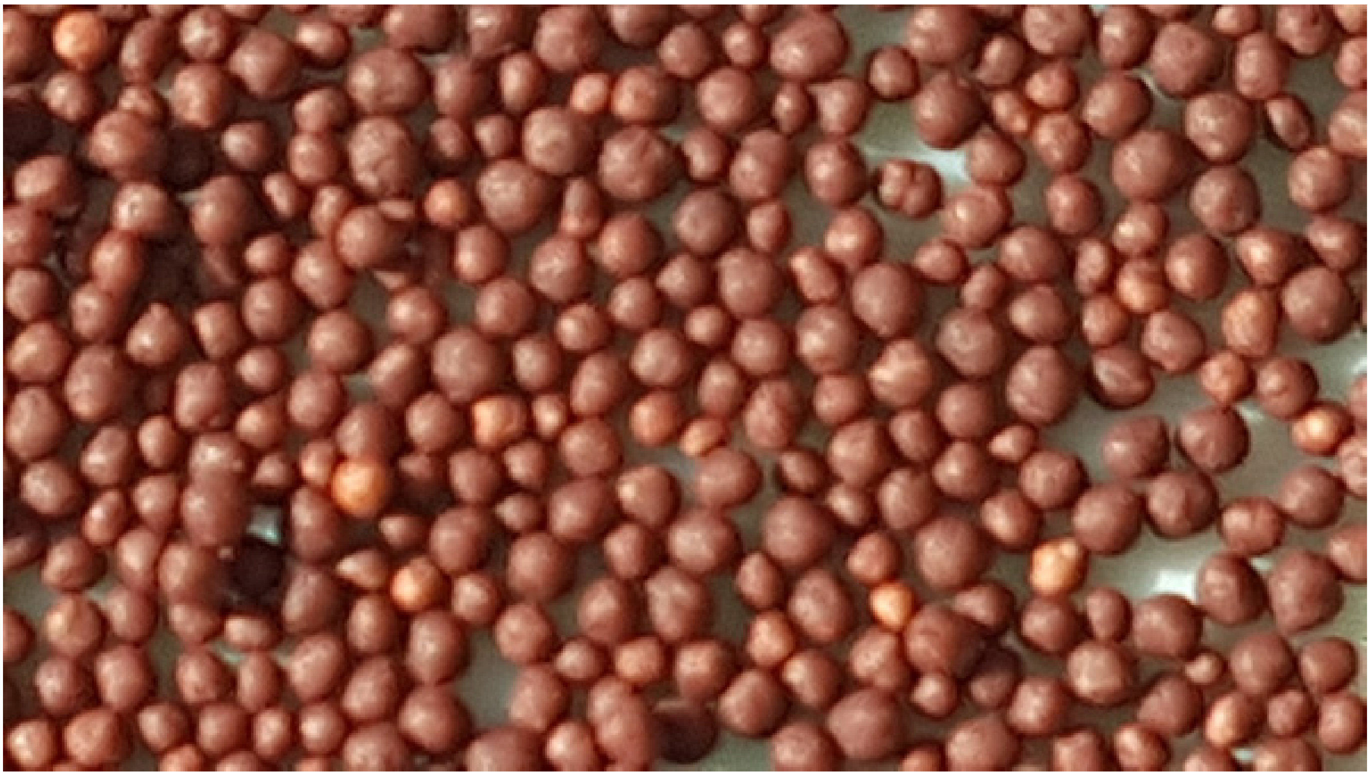
### Results

- The extrusion and spheronization worked well with no evidence of the stickiness that was previously experienced

## Trial 4 - Images of pellets after spheronization and before drying

Pellet samples after spheronization and **before drying**. No sieving, no selection.





# Trial 4 - Closeup images of pellets with measurements

Close up images of pellets with measurements. No sieving, no selection.

The measurements shown on specific pellets are:

- R = Diameter of the circle drawn around the pellet diameter in mm.
- G = Circumference in mm of the circle drawn around the pellet.
- A = Area of the circle drawn around the pellet.


**A follow up Trial 5 was completed to see if the processing time could be reduced.**

### Trial 5 - Can the process time be reduced?

A trial fundamentally similar to Trial 4, but modified to see if the process time could be reduced.

#### Material

20 grams of premix provided by the manufacturer was added to the CML
5.5 ml mix of water and prepared binder

#### Granulation

The granulator was run at 240 rpm for 15 minutes.
(Number of revolutions =~ 3600 revs (compared with 3750 in trial 4))

The mixing bowls and blades were soaked in boiling water and dried before use so that they were quite warm during the granulation.

#### Extrusion

The material was extruded through the CML extruder running at 90 rpm with a 1 x 1 mm hole dies.

#### Spheronization

The extrudate produced were in an 85 mm diameter bowl at 4500 rpm for 4 minutes (18,000 revolutions compared to 20,000 in Trial 4).

#### Results

The extrusion and spheronization worked well with no evidence of the stickiness that is being seen at the customer site.

## General Conclusions

The granulation parameters clearly need adjustment

- A more aggressive granulation gives a formulation that is easier to manage and can produce good pellets on a lab scale using the CML.
- None of the three processes (Granulation, Extrusion and Spheronization) show any difficulty.
- There is no evidence of the problematic stickiness.
- The process time is longer than we would ideally want it to be.

If you are interested in working with Caleva to develop your formulation, then don't hesitate to contact us here:

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