Wet granulation to improve flow properties of mefenamic acid oral formulations.

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Introduction

Wet granulation (WG) is one of the processing routes used for manufacturing tablets as it can be used to enhance the flow and compaction properties of a formulation.[1] In wet granulation, granules are formed by wetting the powder mixture with a granulating fluid before drying and granulating.

A Mixer Torque Rheometer (MTR) can be used to quantify the optimum amount of fluid required to granulate a powder. Using small batch sizes, it is possible to perform investigations to assess the changes in a formulation as it wets.[2] In previous work with direct compression the formulation had challenging flow properties in tabletting leading to fill weight inconsistencies.

The aim of the investigation is to determine the optimum granulation fluid proportions and then assess the effects of changing processing method to wet granulation on flow properties and tabletability.

Materials and methods

One powder blend was prepared (*Table 1*) for granulation end point determination using an MTR, (Caleva, Dorset, UK) (Fig. 1). A multiple addition experiment was performed using the test parameters listed in *Table 2*.

Table 1: Formulation composition

Material	Formulation 1
Mefenamic acid	**33.3**
Avicel PH102®	**46.6**
Lactose fast flo 316	**15.5**
Vivapharm PVP K30®	**3.0**
Super disintegrant (SSG)	**5.0**
Magnesium stearate	**0.5**

Magnesium stearate was added to the final formulation after granules were prepared.

Fig. 1: Image of MTR

Table 2: MTR test parameters

Test parameter	Description
Binder	**Vivapharm PVP K30® (present in the blend as a powder)**
Granulating fluid	**Water**
Speed	**50 rpm**
Mix time	**20 seconds**
Log time	**10 seconds**
Number of additions (steps)	**50**
Binder addition at each step	**1 ml**

Once the granulation end point test was complete the data was plotted, and the torque normalised to find the optimum binder ratio. Granules were then made at this level (0.8 ml/g binder ratio) and dried for 40 minutes at 60°C.

A Schultze Shear Cell was used to determine the flow properties of the powder blend and the granules. The test was performed at 4000 Pa normal force in duplicate. Both the blend and the granules were then compressed using a Phoenix Compaction Simulator (Brierley Hill, UK) using a Korsch XL 100 press simulation at 40 rpm with 10 mm flat face tooling and a 375 mg fill weight. The compaction simulator was used to accurately record the punch pressure. Tensile strength was calculated using the out of die measurements of the compacts.

Results- Optimum Binder Ratio

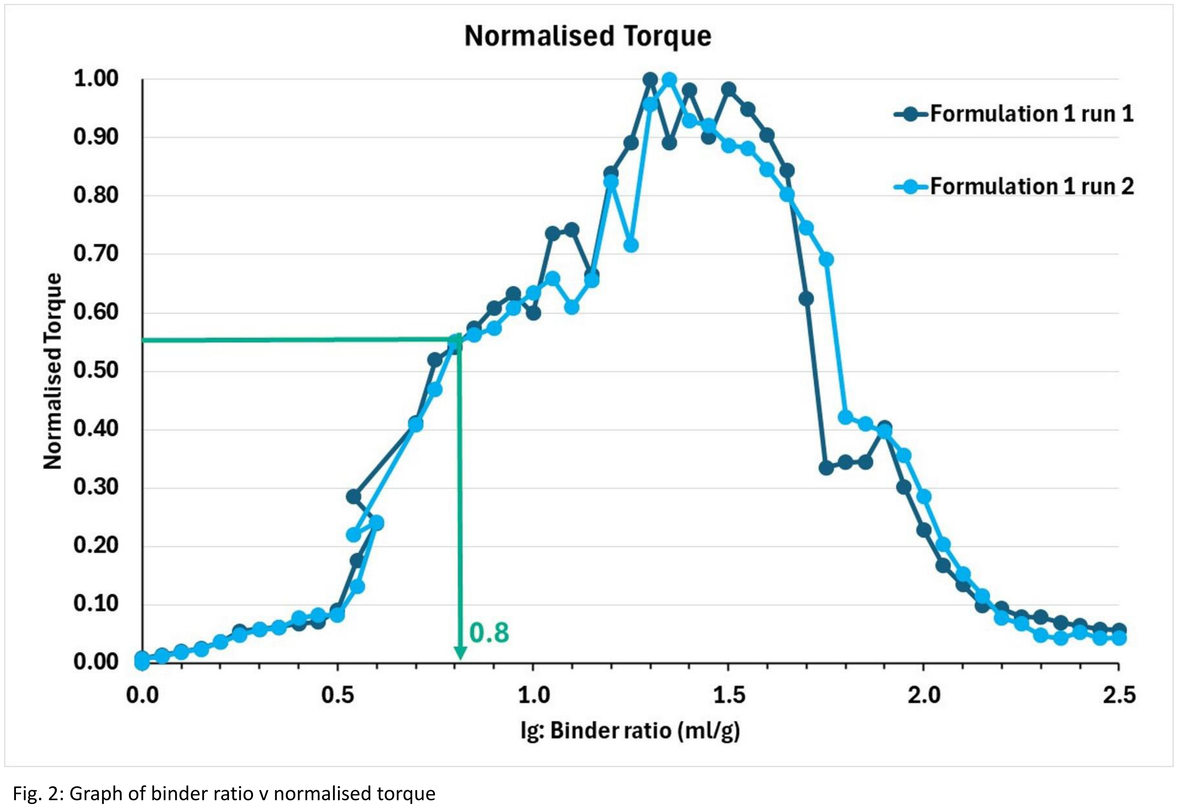

Fig. 2: Graph of binder ratio v normalised torque

Results- Flow and compaction

Once the data was plotted the granulation end point was chosen using a theory proposed in a paper by Uemura where 0.56 of the normalised torque is chosen to get the binder ratio.[3] In this case it gives a binder ratio of 0.8 ml/g (Fig. 2).

Flow testing was performed on both the powder blend and the granules at 4000 Pa to compare differences in flow properties the results are shown in *Table 3*.

Table 3: Shear cell results

Material	FFC 1	FFC 2	Average
Formulation 1 DC	9.44	9.04	**9.24**
Formulation 1 WG	16.72	16.99	**16.86**

Results from the shear cell show that flow is significantly improved when the formulation is wet granulated compared to the powder blend. The DC formulation showing 'Easy flowing' flow properties and the wet granulated formulation showing 'Free flowing' flow properties.

The tensile strength of the resulting compacts were calculated and shown compared to punch pressure Fig.3.

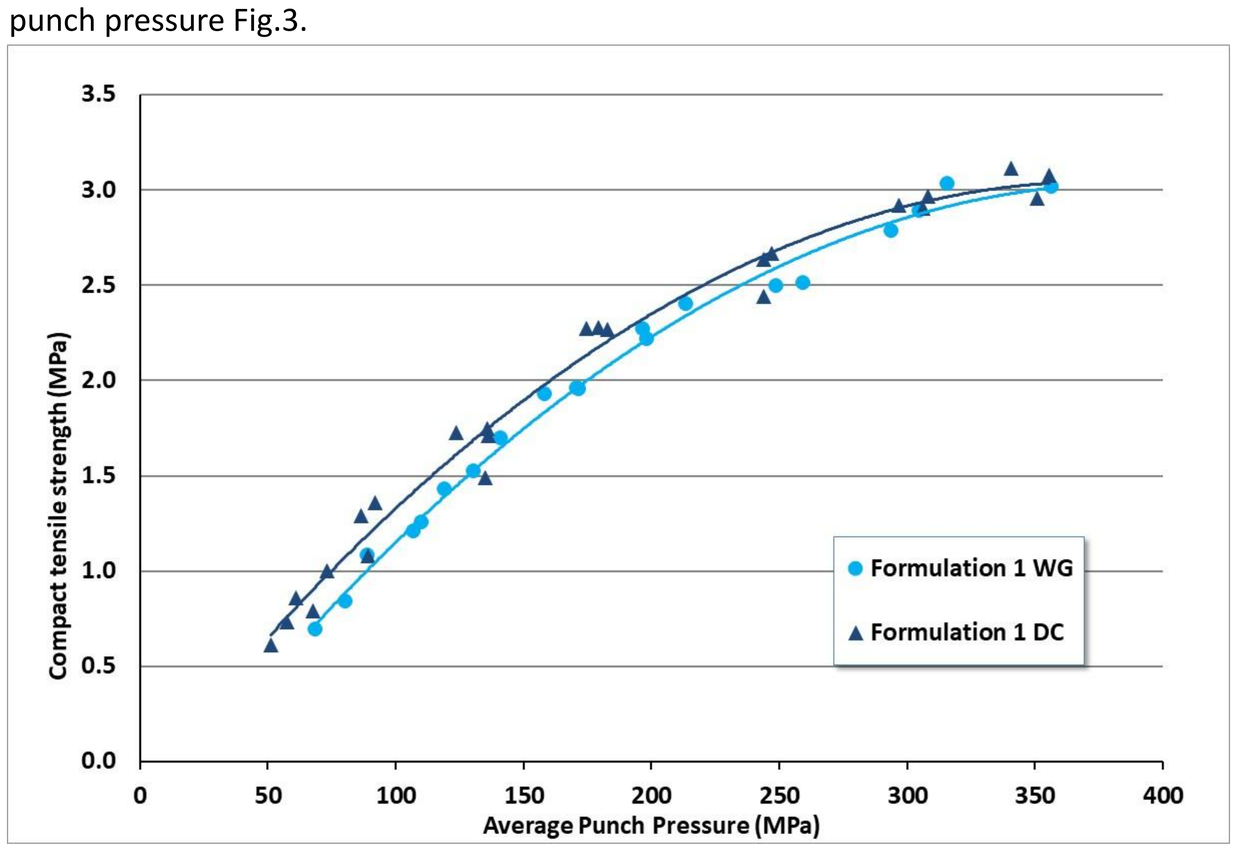

Fig.3: Comparison of Tabletability for Formulation 1 from DC and WG methods.

Formulations need a minimum strength of 1.7 MPa to be considered suitable for scale up to commercial production.[4] Both processing routes are successful in achieving this. WG shows slightly lower tablet strength than for DC.

The flow properties have been significantly improved as the DC formulation needed to be manually filled as a consistent fill weight could not be achieved whereas the WG granules could be hopper filled.

Conclusions

The MTR was used successfully to predict a binder ratio using the proposed value by Uemura of 0.56 ratio of normalised torque.

The resulting granules showed a significant improvement in flow properties with the formulation going from 'Easy flowing' to 'Free flowing'.

This change in processing route meant that the WG formulation was not as challenging to tablet compared to DC. The Direct compression blend had to be manually filled into the die as a consistent fill weight could not be achieved. This would not be suitable for scale-up to production.

The formulations both produced tablets with a suitable tensile strength and changing processing route to WG did not significantly reduce the tensile strength.

References

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