

# An approach to maximise drug loading for oral tablets via formulation and process design.

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## Introduction

Compound A is currently presented as an immediate release (IR) tablet at three tablet weights (300, 600 and 1200 mg), with the granulation step performed as a dry granulation (25%A). Such large tablet sizes produced when loaded at 25%A instigated a study to investigate increasing the drug loading from 25%A to 50%A and to subsequently reduce tablet size.

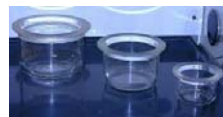
High Shear Wet Granulation (HSWG) was considered as an alternative process due to its differing agglomeration mechanism, which theoretically should allow for an increase in drug loading compared to the dry granulated blends. This study thus investigated a range of wet granulation formulations (different binders, disintegrants and diluent ratios) on a laboratory scale wet granulator and a single dry granulation at the higher drug loading of 50%A. Settings were taken from previous work to provide consolidated granules that will improve flow and to provide robust tablets. The aim of the project was to select suitable formulations for further process optimisation studies (granulation parameters, solvent ratio etc). Blends, granules and tablets were characterised with a range of techniques to determine optimal formulation(s) in terms of processing and *in vitro* drug release.

## Granule Properties

### Granulation

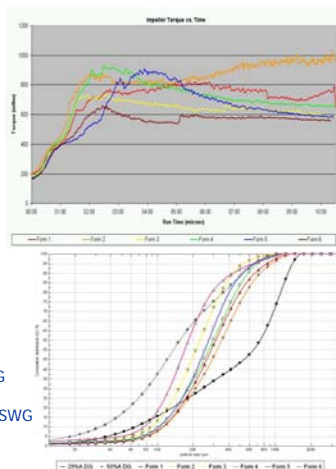
#### Equipment

- Pro-C-epT Mi-Pro (Belgium) was used for the HSWG batches.
- Bowl sizes range in volume from a 250mL bowl (~75g) to a 1.9L bowl (~0.8kg). For this work, a 900mL bowl was used
- The binder material (PVP/HPC) was added to the formulation dry, with solvent (de-ionised water) added to the granulation via a calibrated dropper (pictured)
- The process parameters included a solvent addition time of 2 minutes, a wet mass time of 8 minutes and an impeller speed of 383rpm
- A Gerteis Micropactor was used for the dry granulation step
- Batch sizes for all formulations were ~380g
  - The dry granulation process yielded ~100g of granules post milling (only middle 1/3 of ribbon was used to keep solid fraction constant)



#### Performance

- There is little difference between either of the formulations with the measured output.
- The only output showing any variability was granulator torque
- Most torque profiles peak between two and four minutes (at  $t = 2$ min, the solvent has been fully dispensed)
- The granulator torque of the Lactose formulation (Form 2) appears to continue rising as the granulation increases, due to slight over-wetting of the formulation

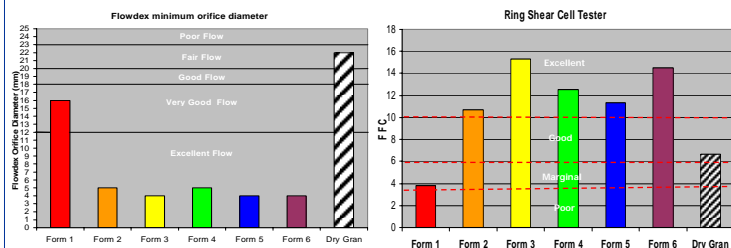


### Particle Sizing

- Sympatec HELOS (laser diffraction)
- The wet granulated batches had a very similar particle size distribution, with d50's clustered between 170-320mm
- Cumulative size range showed narrow span for HSWG batches, whilst DG batch had a wider span.
  - This accounts for the good flow observed for HSWG batches and poor flow for DG batch

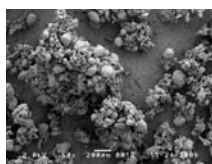
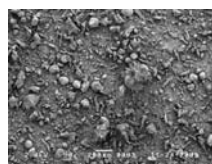
### Flow testing

- Two techniques were used to measure flow – the Flo-dex™ & the Schultz Ring Shear Cell tester
- Both tests indicated that all the wet granulated formulations (with the exception of Form 1) had "Excellent" flow c.f. fair/marginal flow for the dry granulation
- Flow for Form 1 was ranged between "marginal" and "good". This could have resulted from an unknown error during granulation



### Scanning Electron Microscopy (SEM)

- Granules scanned with a Topcon SM-300
- The SEM micrographs show that the wet granulation process produces rounded agglomerates with individual particle structure retained after milling, which accounts for the "excellent" flow recorded during flow testing
- Dry granulated material has been comminuted back to the starting blend under the same milling conditions



Dry Granulated

Wet Granulated (Form 5)

## Formulation

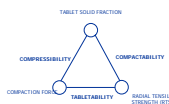
Six HSWG formulations were studied, with one excipient (binder, diluent or disintegrant) altered between each formulation to determine the affects of formulation variability. One dry granulated batch was also investigated.

Material	Form <sup>1</sup>	Form <sup>2</sup>	Form <sup>3</sup>	Form <sup>4</sup>	Form <sup>5</sup>	Form <sup>6</sup>	Dry Gran
Compound A	50%	50%	50%	50%	50%	50%	50%
MCC (Avicel PH101)	27.3%	27.3%	30.75%	27%	27.3%	27.3%	30.67%
Di-Calcium Phosphate Anhydrous (DCPa)	13.7%	-	10.25%	13%	13.7%	13.7%	15.33%
Lactose Anhydrous	-	13.7%	-	-	-	-	-
Sodium Starch Glycolate (Explotab®)	5%	5%	5%	5%	5%	-	3%
Croscarmellose Sodium (Ac-Di-Sol®)	-	-	-	-	-	5%	-
Polyvinylpyrrolidone (PVP - Kollidon® K30)	3%	3%	3%	5%	-	3%	-
Hydroxypropylcellulose (HPC - Klucel® EXF)	-	-	-	-	3%	-	-
Magnesium Stearate	1%	1%	1%	1%	1%	1%	1%
TOTAL	100%	100%	100%	100%	100%	100%	100%

## Tablet Properties

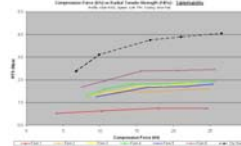
### Compaction Simulation

The six HSWG formulations and dry granulation were tested with an EHS compaction simulator, mimicking the tableting profile of a Killian RX51 tablet press using 8mm flat faced tooling. Three parameters – Compactionability, Compressibility and Tableability were investigated. Tablet hardness was measured as Radial Tensile Strength (RTS) instead of crushing strength to remove the influence of tablet geometry.



### Tableability

- Tableability is the relation between tablet hardness and the compression force used to make the tablet
- Most of the formulations make strong tablets, with the exception of Form 1
  - This is possibly due to the lower porosity of the granules of this form<sup>1</sup>
- Form 6 of the provides the strongest tablets of the HSWG batches
- Dry granulation provides much stronger tablets at lower compression force

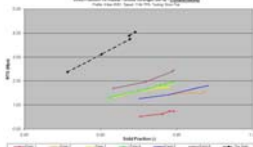


### Compressibility

- Compressibility is the relation between the tablet solid fraction (SF) and the compression force
- Most of the HSWG formulations approach a limiting solid fraction of 0.95 as the compression force increases, with the exception of Form 2 & Form 5.
  - Higher SF achieved for Form 2 & 5 could be due to higher inherent compressibility of component excipients.
- Dry granulation produced cores with lower SF than HSWG batches at same compressive force, which could possibly improve dissolution performance

### Compactionability

- Compactionability is the relation between tablet hardness and the core SF
- As expected, the core hardness increases as the solid fraction increases
- Form 6 (with Ac-Di-Sol®) has a higher tablet hardness at a lower solid fraction
- Dry granulation performs best with strong cores at a lower SF.



Of the seven formulations, only five were able to form suitable tablets for use with the tablet testing techniques described below (Form 1 produced low strength cores, whilst inadequate dry granulated material was available to produce cores for further testing). Tablets were created with oval shaped commercial tooling.

### X-ray Microtomography (μCT)

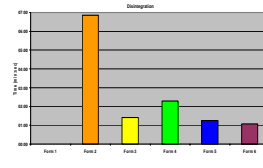
- Analysed with a Skyscan 1072 X-ray Microtomograph
- Tablets supported in a custom mount made from polystyrene (x-ray transparent).
- The resultant shadow images were reconstructed and analysed with software provided by the manufacturer (CTAn)
- Tablet core volume could be accurately measured, and hence the solid fraction. Form<sup>2</sup> (containing lactose) had the highest SF (~95%) and Form<sup>4</sup> (5% PVP) the lowest (~85%).



### Dissolution & Disintegration

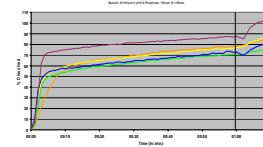
#### Disintegration

- Testing was conducted with a standard disintegration tester (Erweka) with 2mm screens and retaining disks. Disintegration medium was Milli-Q water (37°C ± 2 °C)
- Most tablet cores disintegrated quickly with the tablet breaking up and dissolving in <3 mins
- The Lactose (Form 2) cores disintegrated via surface erosion, possibly due to high core solid fraction



#### Dissolution

- USP Apparatus 1 (Baskets)
- pH 6.8 Phosphate buffer was used (drug product dissolution is high in pH 2 HCl and thus pH 6.8 used as more discriminating).
- The formulation containing Ac-Di-Sol® as the super-disintegrant performed well, keeping within the required release guidelines
- The remaining formulations released at a slower rate, due to the poor performance of Explotab® in the wet granulation process



## Conclusion

The feasibility of achieving high drug loadings of Compound A was assessed using a laboratory scale high shear wet granulator and roller compactor. Characterisation of granules/cores produced from these formulations indicated a decrease in mechanical strength of cores derived from the HSWG material c.f. dry granulated material, however most HSWG formulations were able to produce strong cores (RTS ≈2MPa). Flowability of the HSWG granules was also significantly higher than for granules produced via roller compaction/milling and for this reason HSWG would be chosen the granulation method of choice. Croscarmellose Sodium (Ac-Di-Sol®) was shown to be the preferred disintegrant for HSWG products and Form<sup>6</sup> was selected for further testing.

### Acknowledgements

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