Developing a high API load IR tablet by switching from a wet to a dry granulation and DoE formulation

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PURPOSE

Manufacturing **high dose API tablets** can be challenging by both **wet and dry granulation** due to the impact of API properties on the granulation process, and in the case of roller compaction, its flow properties. The purpose of this work was to develop a three times higher strength (600mg) immediate release (IR) tablet from an already existing wet granulation formulation. The properties of granules and tablets made of two high dose formulations of the same API were compared by wet and dry granulation. The **dry granulation formulation** was selected for its ability to allow high API load and developed using a **QbD approach and Design of Experiments (DoE).**

OBJECTIVE(S)

The objective of this presentation is to discuss the difference between wet and dry granulation processes on granules and IR tablets critical attributes and parameters impacting formulations for roller compaction.

METHOD(S)

This work was performed in two steps by:
1 - comparing with the same API lot the existing 50% API wet granulation formulation manufactured in a high shear mixer to a 66% API baseline dry granulation formulation using a Gerteis mini pactor
2 - developing a dry granulation formulation at high API load (68 to 89%) by a fractional factorial formulation DoE with 4 factors, 2 levels and 18 experiments (including 3 center points). The four factors were concentrations of intra and extra granular microcrystalline cellulose, disintegrant (croscarmellose), and binder (HPMC 15).

For these two studies, tablets CQAs or granules / final blend characteristics impacting CQAs and defined during the preliminary risk assessment were evaluated.

Both studies used a Gerteis Minipactor™ for roller compaction, IMA synthesis 500™ for the compression at industrial scale and Styl'One™ compression simulator.

RESULT(S)

1- Baseline study : wet granulation versus dry granulation

No flow issues were faced during roller compaction despite the high API load. Coarser granules were obtained by roller compaction as shown in Figure 1.

Hausner ratio and Carr index of granules were similar between wet and dry granulation formulations (1.3 and 22 respectively i.e. passable flow). However the Flodex™ value obtained on the granules from the roller compaction main run was higher than for the wet granulation (26 versus 4 mm). However a proper flow was observed on the industrial tablet press (compression forces % RSD NMT 10% and tablet weight variation NMT 1%).

Despite the presence of bigger particles in the dry granules and higher API load, their compressibility was equivalent to those made by wet granulation (tensile strength close to 2MPa starting from compression pressures around 150MPa).

At an equivalent disintegrant concentration (2.9% and 3.5% of croscarmellose in wet and dry granulations formulations) the dissolution profile was quicker with dry granulation as shown in Figure 2.

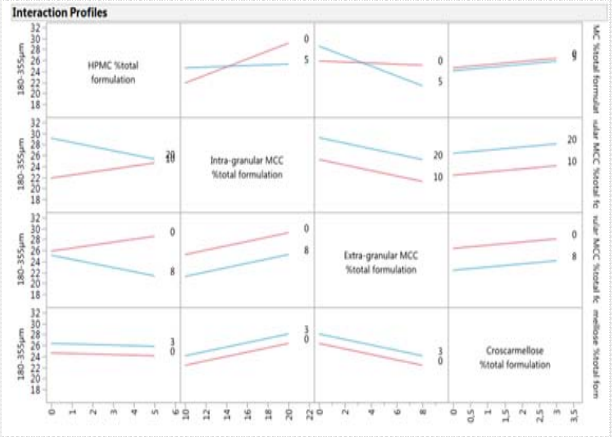

Figure 3: interaction of the four formulation factors on the target PSD fraction (180-355µm)

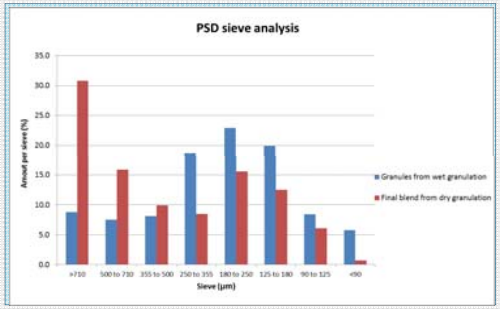

Figure 1: PSD by sieve analysis of granules made by wet granulation (9501EX) and final blend from roller compaction (9502EX)

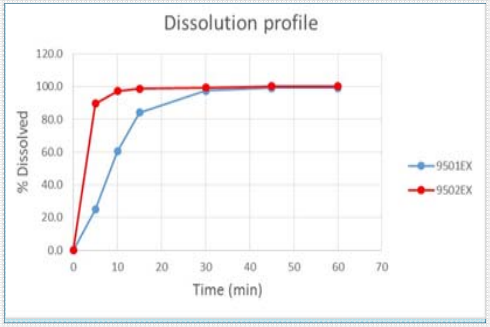

Figure 2: dissolution of tablets made by wet granulation (batch 9501EX) and dry granulation (9502EX)

2 – Formulation DoE by roller compaction

The binder HPMC 15 didn't play a higher binding role than microcrystalline cellulose ph102. As shown in Figure 3, microcrystalline cellulose ph 102 impacted the PSD positively to a higher extend when HPM C was absent. It also had a minor impact on the dissolution profile, much lower than the quadratic effect observed on the studied 0-3% range for croscarmellose.

Tensile strength was mainly driven by the API concentration as shown in Figure 4.

CONCLUSION(S)

Roller compaction allowed to increase the **IR tablet API load up to 75%** while keeping a tensile strength NLT 2MPa (Figure 4) .

HPMC 15 was removed from the dry granulation formulation as it didn't play a higher binding role than microcrystalline cellulose ph102 and had a minor impact on the dissolution profile.

Croscarmellose was used as a disintegrant for both wet and dry granulation with a faster dissolution by dry granulation when using an equivalent concentration as in wet granulation formulation. In order to reach a dissolution profile close to the one obtained by wet granulation, the disintegrant concentration was divided by three.

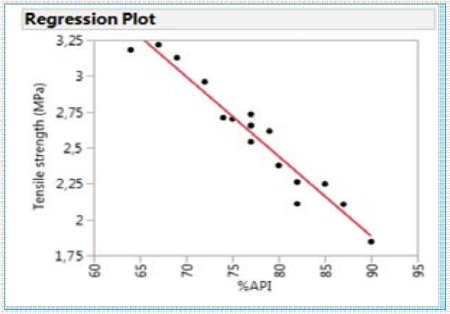

Figure 4: Tensile strength as a function of %API in roller compaction formulation (by compression simulation, 60ktab/h, compression pressure 200-250MPa)

REFERENCE

Systematical approach of formulation and process development using roller compaction
Yue Teng, Zhihui Qiu, Hong Wen
European Journal of Pharmaceutics and Biopharmaceutics 73 (2009) 219–229

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