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Impact of different MCC grades on processability and dissolution of IR tablet

Horster, Lutz[1]; Schmid, Alexander [1]

[1] Rottendorf Pharma GmbH, Ostenfelder Straße 51-61, 59320 Ennigerloh, Germany, lutz.horster@rottendorf.com

Introduction

Immediate release (IR) tablets with a G protein-coupled receptor antagonist should be manufactured using an existing dry granulation formulation that was focused on fast release. Filming on rollers of the granulator was observed and, depending on tooling curvature, filming on the punches during compression process. Slight increase of the level of extragranular lubricant did not completely resolve this issue.

The purpose of the work was to assess suitability of different grades of the intragranular filler microcrystalline cellulose (MCC) to overcome the filming issue. The fast release should not be impaired by the formulation adjustment.

Differently sized tablets with sticking defects on their surface.

Materials

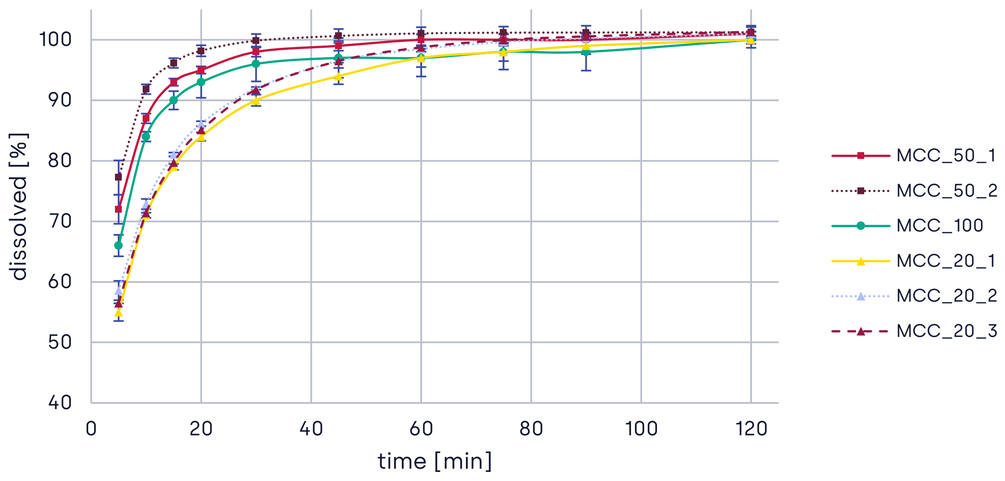
The tablet core composition consisted of approx. 30% customer-provided micronized API, small amounts of silica gel (SiO2), croscarmellose sodium (CMC), magnesium stearate (MgSt), 30% of spray-dried lactose-monohydrate and 30% of MCC (either Avicel PH 101 (MCC 50) or Avicel PH 203 (MCC 100) or Vivapur 105 (MCC 20). A non-functional coating was applied.

Methods

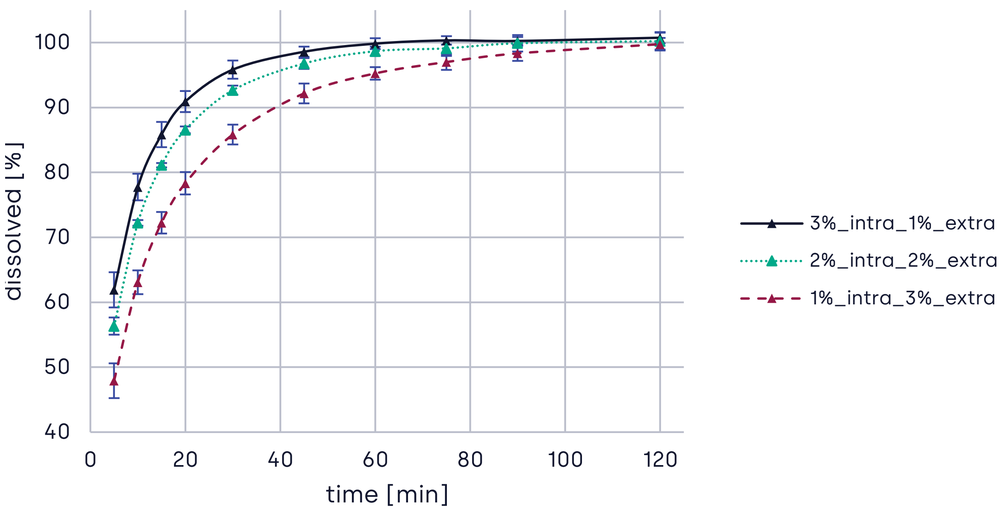
Pre-blends were prepared using a Comil (Quadro, CA) for de-agglomeration and a tumbling blender (L.B. Bohle, GE). The roller compaction dry granulation (RCDG) was performed with a Mini-Pactor (Gerteis, CH). Final blends were prepared using a tumbling blender. Those final blends were compressed to tablet cores using rotary presses T100 (Kilian, GE) or XL 200 (Korsch, GE) and three tooling depending on target dosage strength. The film-coating was performed using a BFC 50 drum coater (Bohle, GE).

Results & Discussion

RCDG process parameters had been set up based on an early RCDG DoE with the starting formulation (MCC 50). The process with a 1.0 mm screen led to bimodal PSD for all three MCC grades. The level of fines < 63 µm was slightly lower for the MCC 20 and MCC 100 (approx. 15%) than for the MCC 50 (approx. 20%). No filming was observed for the MCC 20 and MCC 100 during the granulation or subsequent tableting process. Tabletability for the MCC 100 was slightly lower compared to MCC 20 and MCC 50. This might be due its larger primary particle size. MCC 20 was therefore preferred option for future trials based on processability. Dissolution for the MCC 20 IR tablets revealed, however, a slight delay compared to MCC 50 and MCC 100 despite same tensile strength. Benefits from change to finer filler/binder grades have been reported previously (1). Delayed release, possibly due to change in porosity/hardness of the granules, are reported less.

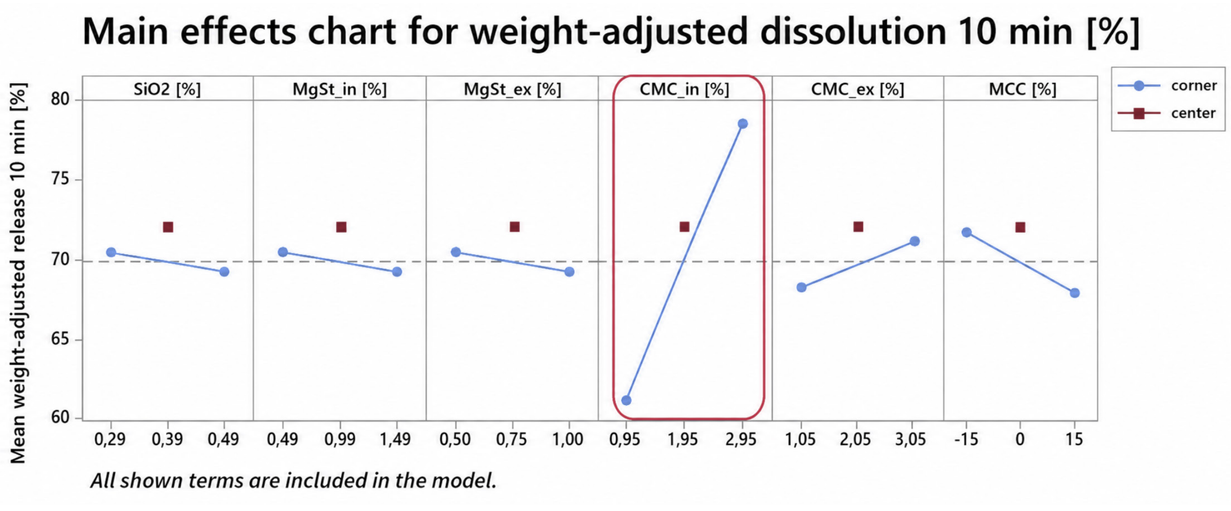


Release from IR tablets with MCC 50, MCC 100 and MCC 20; mean and SD (n=6).



Release from IR tablets with MCC 20 from formulation DoE with different ratio of intra-to-extragranular CMC: 4x n=3 for 3%:1% and 1%:3%, 3x n=3 for center point 2%:2%; mean and SD.

It was decided to continue with the MCC 20 formulation despite the delayed release. A 2^{6-2} formulation robustness DoE was performed to check robustness against possible batch-to-batch variability. The DoE revealed potential for accelerated dissolution by shifting part of CMC from the intragranular to the extragranular portion. This faster releasing option was chosen for future manufacturing.



Release from tablets after 10 min depending on DoE factors (19 runs incl. 3 center point runs).

Conclusion

Exchange of intragranular MCC 50 with finer MCC 20 avoided filming with this formulation more reliable than increase of extragranular lubricant. Disintegration and dissolution did however slow down with the finer filler/binder grade. A shift of extragranular portion of disintegrant could compensate for this effect and led to tablets with desired fast release.

References:

[1] Herting, M. G., Kleinebudde, P. Roll compaction/dry granulation: effect of raw material particle size on granule and tablet properties, Int J Pharm. 338, 110-118 (2007).

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