Development and Scale-up of a Modified Release Bilayer Tablet based on Compaction Simulation

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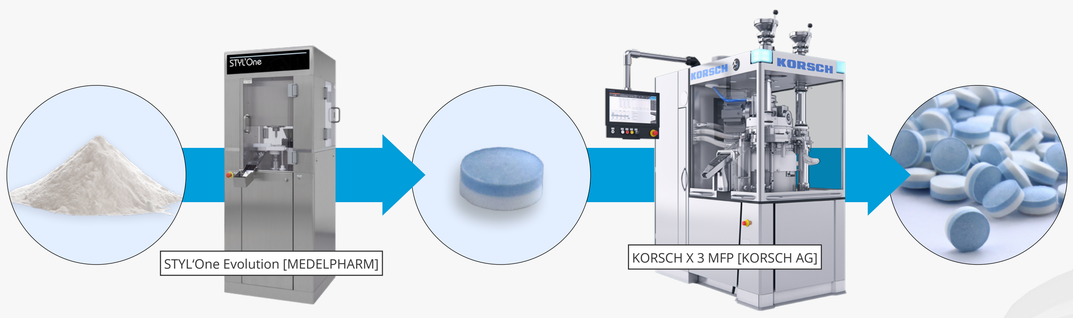
INTRODUCTION

Drug delivery systems with modified drug release have become an increasingly important branch of drug research in recent years due to their numerous advantages. In this context, preparations with only once-daily administration can increase patient compliance and reduce side effects. Multilayer tablets as dosage form can offer different active pharmaceutical ingredient (API) release profiles while combining different active ingredients in just one tablet. The aim of the present work was to develop a bilayer tablet with fast and prolonged release of the API diclofenac based on compaction simulation and subsequent transfer to a production rotary press.

MATERIALS AND METHODS

Trade Name	Composition	Function
Kollidon® SR [BASF]	PVA/PVP	Prolonged release layer
Kollitab™ DC 87 L [BASF]	Lactose monohydrate, PEG-PVA, grafted copolymer, crospovidone, SSF	Immediate release layer
Diclofenac sodium [BASF]		API



RESULTS

FORMULATION DEVELOPMENT

Parameters to investigate for tablet formulation development can be the following:

Particle size

- D10, D50, D90, Distribution Span (DSP)
- Bulk density (DBU)
- Tapped density (DTA)

Flowability

- Carr index (CAR)
- Hausner ratio (HAR)
- Angle of repose (AOR)

Tabletability

- Compressibility (CPR)
- Compactibility (CMP)
- Tensile strength at varying compression pressures (TST 100, 150, 250)

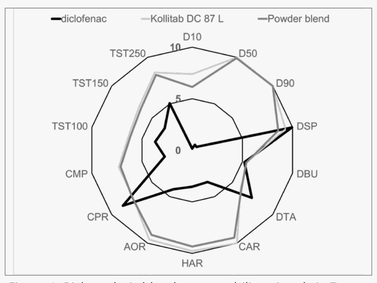


Figure 1: Risk analysis blend processability wizard via ZoomLab® of diclofenac, Kollitab® DC 87 L and the immediate release layer (0=insufficient, 10= excellent)

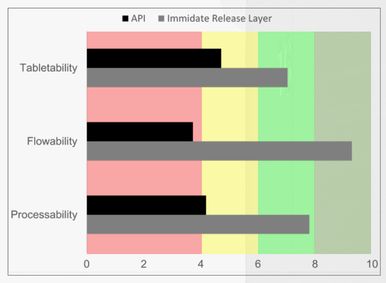


Figure 2: Overall ZoomLab® ranking for API and final immediate release formulation properties (0=insufficient, 10= excellent)

PROCESSABILITY

Adjustment process parameters

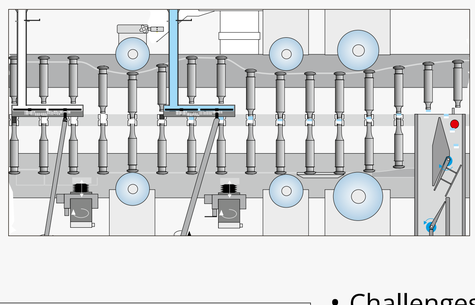
- Layer position selection
- Tamping force
- Pre compression force
- Main compression force
- Compression speed
- Ejection forces

API dissolution

- Tablet disintegration
- Tablet porosity
- Influence of excipients

Final formulation selection

- Processability: Acceptable ejection force (<1500 N)
- Quality: Sufficient tablet hardness (>150 N)
- Required dissolution profile (immediate release followed by sustained release



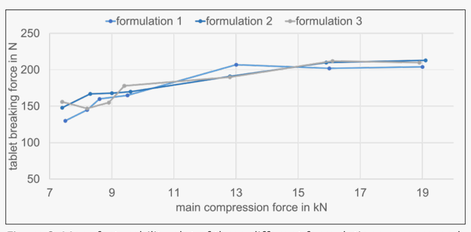


Figure 3: Manufacturability plot of three different formulations compressed on the STYL'One Evolution with the X 3 simulation profile at 20 rpm simulated speed. Tamping and pre compression force fixed at 1 kN. n=10 (average)

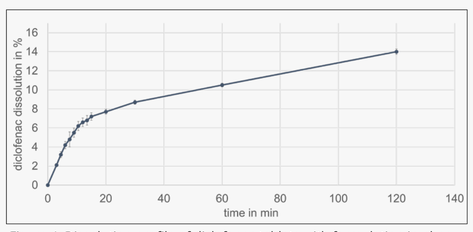


Figure 4: Dissolution profile of diclofenac tablets with formulation in phosphate buffer (pH 6.8) at 37 °C (± 0.5 °C) with paddle speed at 75 rpm. n=6 (average±STD)

Layer 1
75 mg diclofenac sodium + 167. 5 mg Kollidon® SR + 7.5 mg magnesium stearate
Layer 2
25 mg diclofenac sodium + 125 mg Kollitab® DC 87 L

SCALE-UP

Mechanical properties

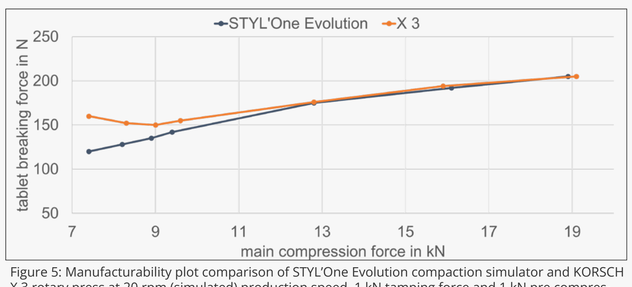


Figure 5: Manufacturability plot comparison of STYL'One Evolution compaction simulator and KORSCH X 3 rotary press at 20 rpm (simulated) production speed, 1 kN tamping force and 1 kN pre compression force for both presses. n=10 (average)

API dissolution

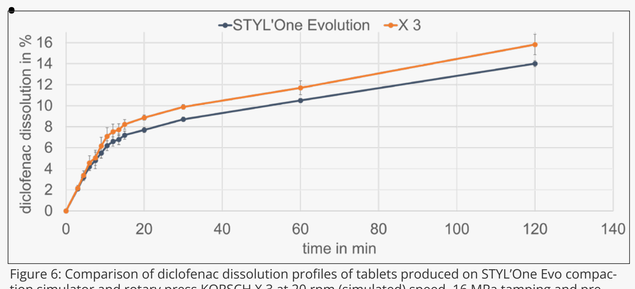


Figure 6: Comparison of diclofenac dissolution profiles of tablets produced on STYL'One Evo compaction simulator and rotary press KORSCH X 3 at 20 rpm (simulated) speed, 16 MPa tamping and pre compression pressure and main compression pressure at 300 MPa. n=6 (average±STD)

- Challenges in production predicted by compaction simulation (high ejection stress)
- Similarity of dissolution profiles given (f2-Test)
- No statistical differences between mechanical tablet parameters produced by compaction simulator and rotary press

CONCLUSION

- Formulation development of an immediate and prolonged release bilayer tablet was successful
- Combination of digital formulation development and compaction simulation did minimize required API quantity and time
- The compaction simulator STYL'One Evolution was able to predict challenges and final tablet parameters on production scale

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