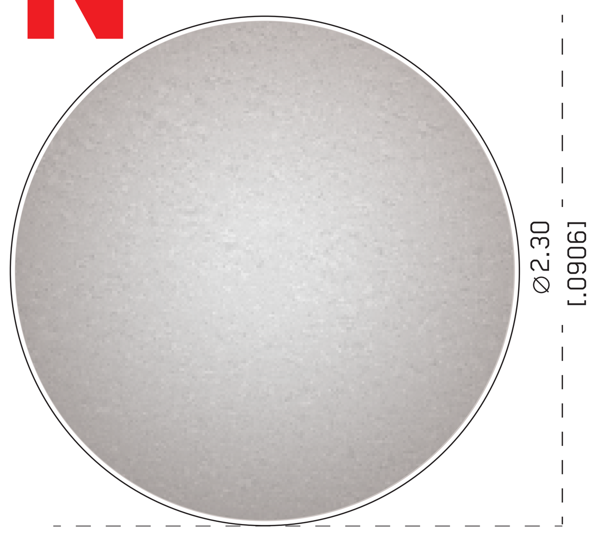
OPTIMIZATION OF A MINI-TABLET COMPRESSION PROCESS

Schmid, Alexander.[1]
Sonsalla, Tina-Sophie.[1]
Look, Jennifer [1]

[1]Rottendorf Pharma GmbH,
Ostenfelder Straße 51 – 61,
59320 Ennigerloh, Germany
alexander.schmid@rottendorf.com



I PURPOSE

In this study a direct blend formulation, initially developed for adults, was transferred to a pediatric mini-tablet formulation using a 2.3 mm multi-tip compression tooling.

Mini-tablets are tablets with a defined size of 2 – 3 mm [1]. The manufacturing process poses many challenges due to this small size of this dosage form. The compression in particular deals with sticking, trapping & breaking of the tablets, electrostatic charging or excessive wear of the compression tooling.

During the first trials several issues were observed, especily defective tablets (see Figure 1) and an uncontrolled ejection of tablets (see Figure 2). Broken or defective tablets can relate to issues with content uniformity, tablets which are not ejected properly reduce the yield and cause problems during the compression process. As different optimizations to formulation and process parameters did not lead to a sufficient improvement, the tablet scraper remained as a main root cause for the broken tablets. Since there was no ready-to-use solution available, different optimizations with focus on a newly designed customized tablet scraper were performed in cooperation with Korsch.

II MATERIALS / METHODS

Material

The final blend for the compression of the mini-tablets was manufactured in a direct blend approach containing API (12%), Cellulose, Mannitol, Croscarmellose-Sodium and Sodium Stearyl Fumarate. The mini-tablets (biconvex round tablet, diameter of 2.30 mm, cup depth of 0.26 mm, overall weight of 10 mg, thickness of 1.9 mm)

Equipment

The final blend was manufactured in a blend-mill-blend approach, using a free fall blender and a conical-mill with a 991µm sieve. The lubricant was sieved through a 250 µm hand sieve. For the compression a Korsch XL 200 rotary tablet press was used, equipped with a EU-D multi-tip tooling (14 separate pins per punch) from Natoli made out of M340 steel.

Since the standard Korsch XL 200 tablet scraper was not working for such small tablets, in a first step a 3D-printed prototype was developed together with Korsch, which was further improved to a GMP stainless steel scraper (see Figure 3).

Solution / technical development

As a first step, the gap between the tablet scraper and the die table had to be decreased. This resulted in a desired reduction of observed defects. However, it was still noticed that tablets are "caught" in front of the tablet scraper and were not able to leave the rotating die table. This was mainly caused by the small size and the low tablet weight due to missing centrifugal forces. This observation lead to the conclusion that the tablets need to be actively forced into the direction of the discharge chute. The idea was to guide the tablets with compressed air and a slightly different angle of the scraper. To enable these features, a 3D-printed prototype was developed together with the Korsch AG (see Figure 3).

III DISCUSSION & RESULTS

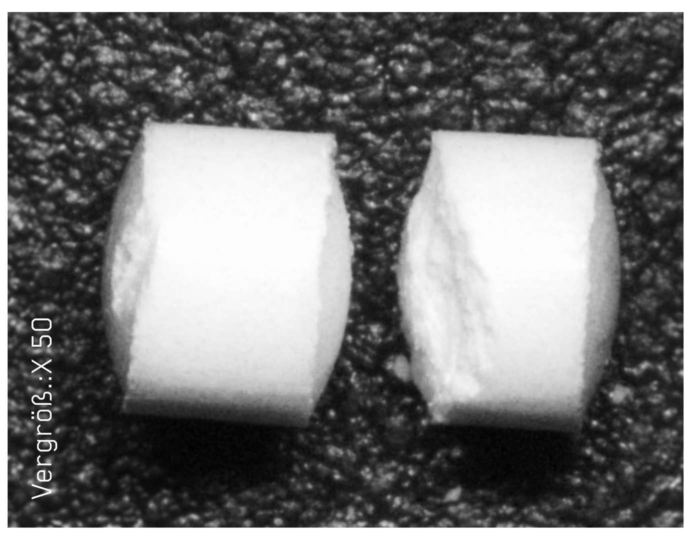


Figure 1 | Defective mini-tablets manufactured with the standard scraper

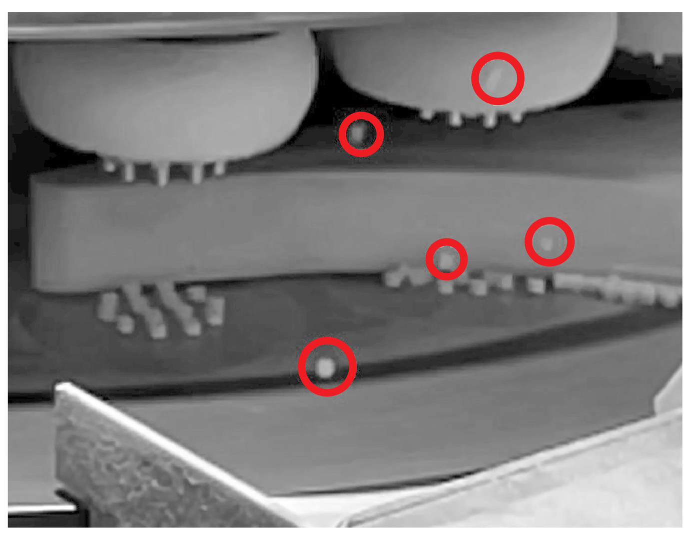


Figure 2 | Uncontrolled ejection of mini-tablets

Problem Description

During the first manufacturing campaign with the 2.3 mm multi-tip tooling, using the standard Korsch XL200 tablet scraper, it could be noticed that severe issues during the tablet compression occurred. The manufactured tablet cores were trapped in a gap between the die table and the tablet scraper. In addition, the ejected cores were not guided away from the rotor into the chute (see Figure 2) and continued to collide with newly ejected cores. Consequently, the tablets broke during ongoing rotation of the tablet press and were not properly discharged from the tablet press (see Figure 1).

Tablet Scraper Version	Compressed air [bar]	Defects [%] Visual appearance sample n=100
Standard scraper	n.a.	24
Protoype Tablet Scraper Standard Angle	1	7
	3	1
Protoype Tablet Scraper Adapted Angle	1	1
	3	0

Table 1 | Comparison of different tablet scrapers & adjustments

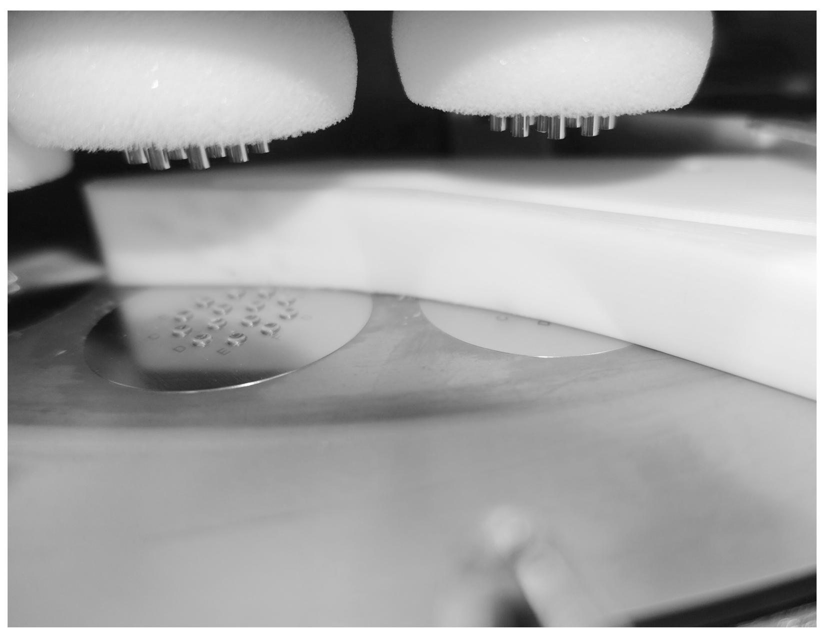


Figure 3 | 3D-printed prototype tablet scraper

This prototype was tested and modified during subsequent compression trials. By the adaption of the compressed air pressure and the overall angle of the tablet scraper, it was possible to completely eliminate the previously observed defects (see Table 1 & 2).

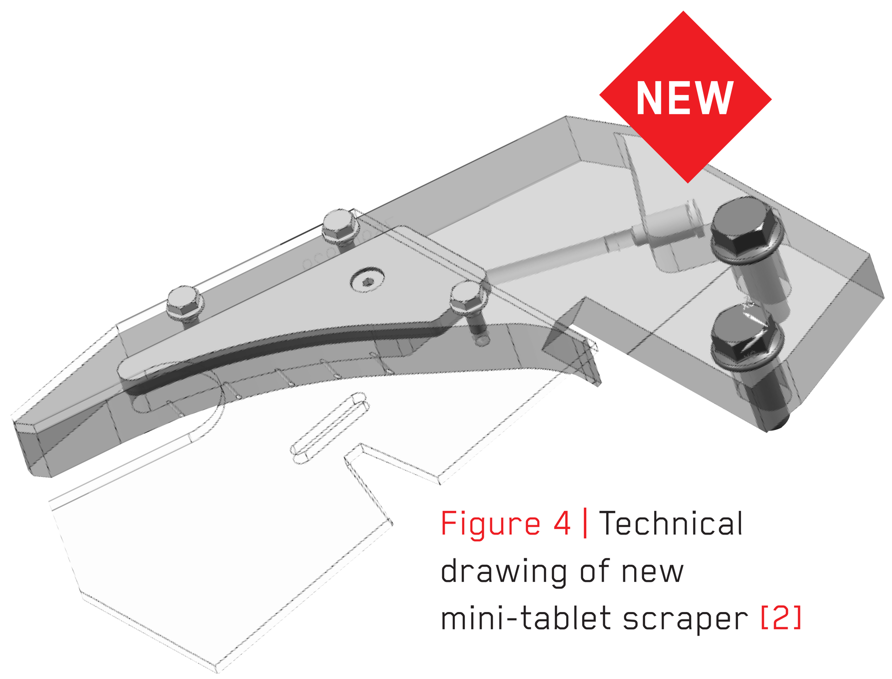


Figure 4 | Technical drawing of new mini-tablet scraper [2]

After the successful proof of concept, the tablet scraper was manufactured out of stainless steel, to comply with GMP-standard (see Figure 4). As shown in Table 2 no issues or defective tablets were observed since the optimized tablet scraper has been used.

BATCH HISTORY	
Batch	**Observation**
Initial Batch	Severe Issues, Broken Tablets, damaged multi-tip tooling
3 Technical Batches	Development & Testing of new tablet scraper
Clinical Batch 1 – 4	No issues observed anymore Mini-Tablets did not show any defects Batches were used for clinical testing

Table 2 | Mini-Tablet Batch History

IV CONCLUSION

After a successful technical optimization it was possible to completely overcome the previously noticed issues and enable a robust mini-tablet compression process. Several GMP batches were manufactured up to now without defective mini-tablets (see Table 2). However, it was also noticed that there is still potential for optimization in terms of downstream mini-tablet handling. Due to the small size standard equipment like e.g. discharge chutes, deduster and metal checker are in need to be assessed and modified.

References

[1] P. Lennartz, J.B. Mielck, Minitabletting: improving the compactability of paracetamol powder mixtures, International Journal of Pharmaceutics, Volume 173, Issues 1-2,1998, Pages 75-85, ISSN 0378-5173 [2] drawing provided by Korsch AG