Evaluating different manufacturing options to formulate loperamide HCl as orally disintegrating tablet

Thorsten Agnese[1], Thorsten Cech[1]

[1]Application Lab Pharma Ingredients & Services Europe, BASF SE, Ludwigshafen, Germany
Corresponding author: thorsten.cech@basf.com

150 years

BASF
We create chemistry

INTRODUCTION

Orally disintegrating tablets (ODTs) have become a popular dosage form [1]. Even though formulators have ready-to-use aids on hand, allowing quick and simple drug formulation [2], some formulations can raise the need for customised formulation development.

Generally, ODTs are fast disintegrating dosage forms which should offer a pleasant mouth sensation. In previous studies it could be shown that lactose based granules (agglomerated with maize starch) in combination with crospovidone super fine led to ODTs offering excellent performances [3, 4].

MATERIALS AND METHODS

Loperamide HCl (Selectchemie) was formulated as ODT. The active pharmaceutical ingredient (Figure 1) was either added as external (ext.) component to the tabletting blend or was processed during the high shear granulation process (int.).

Lactose fine powder (GranuLac® 230, Meggle Pharma) was used as filling agent. As disintegrant cross-linked poly(vinyl pyrrolidone) super fine (crospovidone, Kollidon® CL-SF, BASF) was either added ext. [4] or int. to the formulation. The agglomeration process was conducted using native maize starch (C*PharmGel™, Cargill) paste as binder [3]. Eventually, magnesium stearate was introduced as lubricant to the tabletting blend. The detailed formulation is listed below (Table 1).

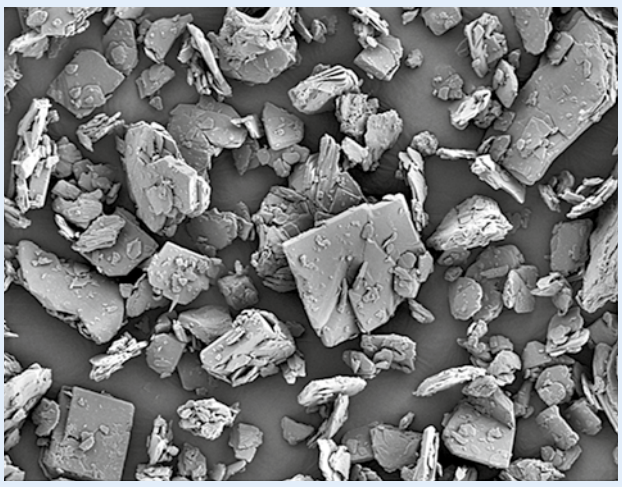

Figure 1. Scanning electron microscopy (SEM) image of loperamide HCl (SE, 5 kV).

Table 1. Tabletting formulation, including processing details

Component	Concentration	Variations
Loperamide HCl	2.00%	int./ext.
Lactose (fine powder)	87.75%	int.
Crospovidone (super fine powder)	10.00%	int./ext.
Native maize starch	1.75%	int.
Magnesium stearate	0.50%	ext.

Wet Granulation

The wet granulation processes were conducted in a high shear mixer (Diosna P 1/6) applying an impeller speed of 200 rpm and a chopper speed of 2,000 rpm. The binder was added as aqueous solution within 120 s, followed by a granulation time of 180 s. The wetted agglomerates were passed through an oscillating sieving machine (w=1.6 mm, AR400, ERWEKA), dried on a tray (ambient conditions), and finally passed through a sieve (w=0.8 mm).

Tabletting

The compression was done using a single punch press XP 1 (Korsch) equipped with flat faced, faceted punches with a diameter of 6.0 mm. Compression forces of about 1 to 7 kN were applied at a tabletting speed of 20 tablets per minute. The tablets were characterised (n=20) using a multi-tester (HT100, Sotax). The disintegration time (n=6) was determined in an automated disintegration tester (ERWEKA ZT 74) using demineralised water (37°C ±1 K).

RESULTS AND DISCUSSION

In general, tensile strength and friability are important characteristics of a tablet. However, both features are markedly influenced by the disintegrant used whereas chemical nature is (from a processing point of view) of less importance compared to the more critical aspects: particle shape and size. As regards ODT application, texture of the disintegrated tablet exposed to the tongue is worth noting: The smaller the insoluble particles present in the tabletting formulation, the more convenient the mouth sensation after tablet's disintegration. Therefore, particle size of the disintegrant is of utmost importance. In this regard, super fine crospovidone comes in useful. Due to its small particles even in a wetted state, this disintegrant is to be preferred for ODT formulations [4].

In the present loperamide HCl ODT formulation, the small particle size of super fine crospovidone was also found to be very beneficial in regard to the strength of the tablets. While applying compression forces as low as 3 kN, tensile strength values of 1.25 N/mm² were achieved, which was set internally as minimum limit (Figure 2). The value was regarded as being sufficient enough to allow bulk transportation and packaging of the tablets even in multiple dose containers.

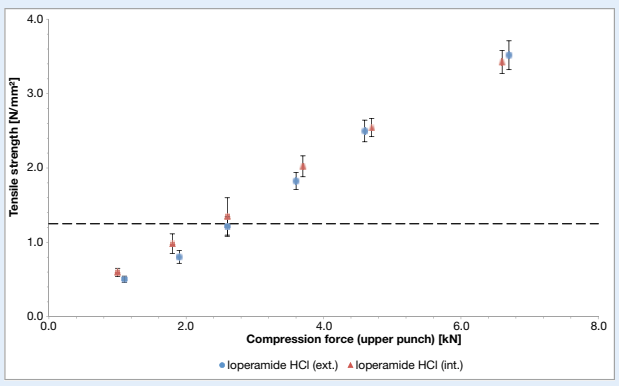

Figure 2. Tensile strength of the two ODT formulations as function of compression force (mean values (n=20), ±SD).

Interestingly, even though very high tensile strength values (>3.5 N/mm²) could be achieved at compression forces of about 7 kN, the disintegration characteristics hardly changed (Figure 3). Independent of their crushing strength, all tablets disintegrated within less than 20 s.

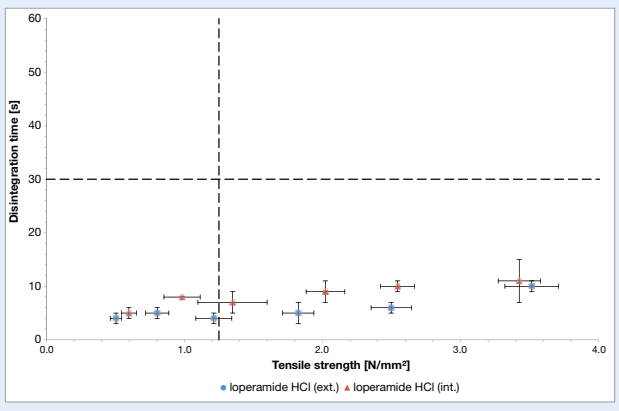

Figure 3. Disintegration time of the two ODT formulations as function of tensile strength (mean value (n=6), ±SD).

Tablets of both formulations being compressed at 3 kN were put upon stability to investigate potential changes of their features over time. However, no distinct changes could be found within 12 months (6 months at 40°C/75% r.h.) storage time (Figure 4, 5).

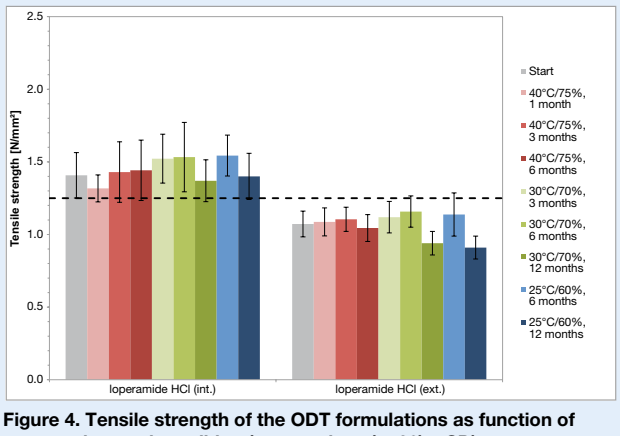

Figure 4. Tensile strength of the ODT formulations as function of storage time and condition (mean values (n=20), ±SD).

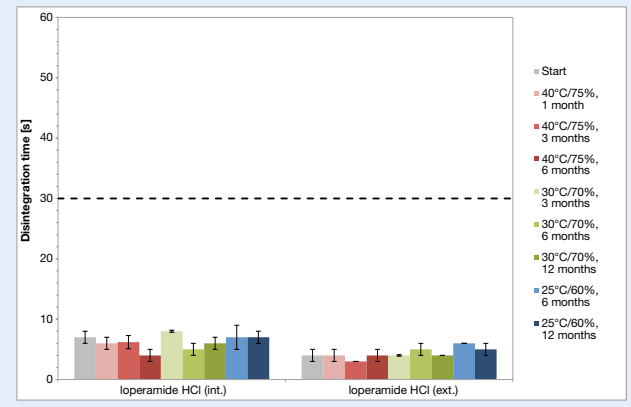

Figure 5. Disintegration time of the ODT formulations as function of storage time and condition (mean value (n=6), ±SD).

Generally, the processing procedure (ext. or int.) did not affect the physical characteristics of the ODTs. Therefore, the developer is free to choose an appropriate procedure in each particular case:

CONCLUSION

The processing procedure didn't affect the physical characteristics of the loperamide HCl ODTs.

Both ODT formulations were stable during the stability testing. No distinct change in tensile strength or disintegration characteristics could be observed.

Even though starch paste had disadvantages in regard to its application, it offered benefits regarding the agglomerates formed (e.g. strength of the agglomerates).

The use of super fine crospovidone provided three advantages: firstly, a superior mouth sensation, secondly, high tensile strength, and thirdly, very fast disintegration, independent of compression force applied.

REFERENCES

[1] Bohnacker, R.; Streil, F.; Schweizer, S.; Müller, I.; Determination of the disintegration time of mouth melt tablets with texture analyser method; Pharm. Ind. 67 (3), 327–35 (2005).

[2] Kruse, S.; Gebert, S.; Kolter, K.; et. al; Development of orally disintegrating tablets based on a new excipient, 2007 AAPS Annual Meeting and Exposition; November 11–15, 2007; San Diego (CA), USA

[3] Agnese, Th.; Cech, Th.; Mistry, M.; Evaluating various wet binders to gain lactose based agglomerates applicable for orally disintegrating tablet formulations; 1st European Conference on Pharmaceutics: Drug Delivery; April 13–14, 2015; Reims, France

[4] Agnese, Th.; Bang, F.; Cech, Th.; Mistry, M.; Evaluating various disintegrants regarding their performance in orally disintegrating tablet formulations; 1st European Conference on Pharmaceutics: Drug Delivery; April 13–14, 2015; Reims, France

PRESENTED AT:

1st European Conference on Pharmaceutics,
April 13–14, 2015; Reims, France
Pharma Ingredients & Services | G-ENP/ET449