MEGGLE

# CASE STUDY

# Overcome Challenges of Elastic Deformation with the Right Excipient

## - CASE STUDY WITH CAPTOPRIL

***Creator:*** *Guilherme Brandão & Gabrielli Vitória da Cunha* | ***Product(s):*** *FlowLac® 100, CombiLac®*

# 1. Executive Summary

In this study the difficulties in formulations with conventional Captopril were shown and it has been highlighted how these obstacles can be overcome by lactose-based excipients and also, how these excipients can improve the results of a problematic manufacturing process with an elastic deformable drug.

As mentioned, Captopril consists of a molecule with elastic deformation, it leads to problems like tablet capping during production, high friability and variation in tablet breaking force.

Therefore, at the end of the study, it was shown with the right choice of excipient it is possible to overcome these difficulties and to work in a very robust manufacturing process. Ttwo excipients were used to compare the performance of Captopril, normal spray-dried lactose FlowLac® 100 and a co-processed excipient, combining lactose monohydrate (70 %), MCC (20 %) and native corn starch (10 %), called CombiLac®. The formulation with CombiLac® was able to achieve excellent mechanical stability of the tablets, even at low compression forces. High tablet breaking force, no or only low friability and no capping tendency. The disintegration time was also excellent.

**This case study illustrates the robustness and quality that CombiLac® can promote for developments with difficult active ingredients and that it is a perfect fit to ease processes during up-scaling.**

## Content

## 2. Abstract

Developing a medicine in which the active ingredient has elastic deformation is always challenging, as elastic forces affect the compression capacity of the formulation, resulting in tablets with capping, low tablet breaking force and high friability. Finding an ideal formulation with excipients that can mask the effects of elastic deformation is part of obtaining a tablet with good tablet properties so that the manufacturing process has quality and robustness.
Among the active ingredients that have elastic deformation is Captopril, an antihypertensive, sold in solid pharmaceutical form. Conventional Captopril formulations are often unable to mask the effects of elastic deformation, which can cause significant implications during production and also on the effectiveness of the medicine.

## 3. Objective

This study aims to present the obstacles encountered in conventional Captopril formulations and highlight how lactose-based technological excipients can promote improvement and scaling more effective and robust.

## 4. Materials and Methods

Three formulations have been designed for these studies.

The blends were blended by a Turbula Mixer T2F (Willy A. Bachofen AG Maschinenfabrik), with a 2 L vessel, running at 42 rpm. Mixing time was 15 minutes for all the components and additional 3 minutes after adding the lubricant.
The tablets were produced by direct compression using a pilot scale rotary tableting machine Piccola–D (Riva SA – Argentina), controlled by the software "The Director®" (SMI – USA). Compression was performed using a gravimetric feeder. For the placebo tablets, a 7 mm circular, concave punch was used, stettings of machine were adjusted to obtain tablets of 130 mg.
The machine operated at 20 rpm and 50 rpm and compression force of 5 kN, 10 kN, 15 kN and 20 kN to verify the behavior of each formulation under different process parameters.

| EXCIPIENT | Functionality | F.1 | F.2 | F.3 |
|---|---|---|---|---|
| Captopril | API | 19.23 | 19.23 | 19.23 |
| FlowLac®100 | Diluent | 77.27 | 54.8 | - |
| CombiLac® | Diluent | - | - | 78.27 |
| Microcrystalline Cellulose | Diluent | - | 15.67 | - |
| Corn Starch | Disintergration/Lubricant | - | 7.8 | - |
| Crospovidone | Disintergration | 2.5 | 1.5 | 1.5 |
| Aerosil®200 Pharma | Moisture Protector | 0.5 | 0.5 | 0.5 |
| Magnesium Stearate | Lubricant | 0.5 | 0.5 | 0.5 |

*Table 1: Composition of investigated tablets in %*

**Formulation F.1 represents a conventional formulation with FlowLac® 100.**

**Formulation F.2 represents the physical admixture of CombiLac®, which has the same concentrations of lactose, microcrystalline cellulose and maize starch as present in CombiLac® using FlowLac® 100.**

**Formulation F.3 represents a formulation with a co-processed excipient of 70 % alpha-lactose, 20 % microcrystalline cellulose and 10 % corn starch, CombiLac®.**

The comparison between formulation F.2 and F.3 aims to present the differences in results between co-processing by spray-drying and a physical mixture.

### Tablet Weight / Weight Variation (USP <2091>)

20 tablets were individually weighed in an analytical scale and the average weight and the deviation coefficient were determined.

### Tablet Breaking Force (USP <1217>)

10 tablets were investigated employing an ERWEKA TBH 125 hardness tester.

### Tablet Disintegration (USP <701>)

6 tablets were investigated in terms of disintegration according to the USP method, using water at 37 °C and an ETHIK disintegration apparatus.

### Tablet Friability (USP <1216>)

20 tablets were dedusted and weighed (w1), submitted to an ETHIK friability test apparatus according to USP-NF at 25 rpm for 4 minutes. At the end, tablet weight was checked again after dedusting of the tablets (w2).

- Process with parameters / Experimental Set-up
- Preparation of the data acquisition/ data acquisition
- Documentation

# 5. Results and Discussion

## 5.1 Tablet Compression

During the manufacturing process, all formulations showed excellent flow, which allowed the powder to flow freely through the funnel and properly filling the dies.

However, due to the elastic deformation of the Captopril molecule, laminated tablets were seen when increasing the speed from 20 rpm to 50 rpm and the compression force from 10 kN to 15 kN in formulation F.1. The same was repeated in formulation F.2 when the compression force was increased by 15 kN and 20 kN at both speeds, something that in formulation F.3 only happened at 20 kN and 50 rpm.

The compression process showed that despite the excellent flow and compressibility properties of the excipients, a conventional formulation, such as F.1 and F.2, are not capable of dealing with the characteristics of elastic forces and for this reason, problems such as capping were seen.

## 5.2 Tablet Weight

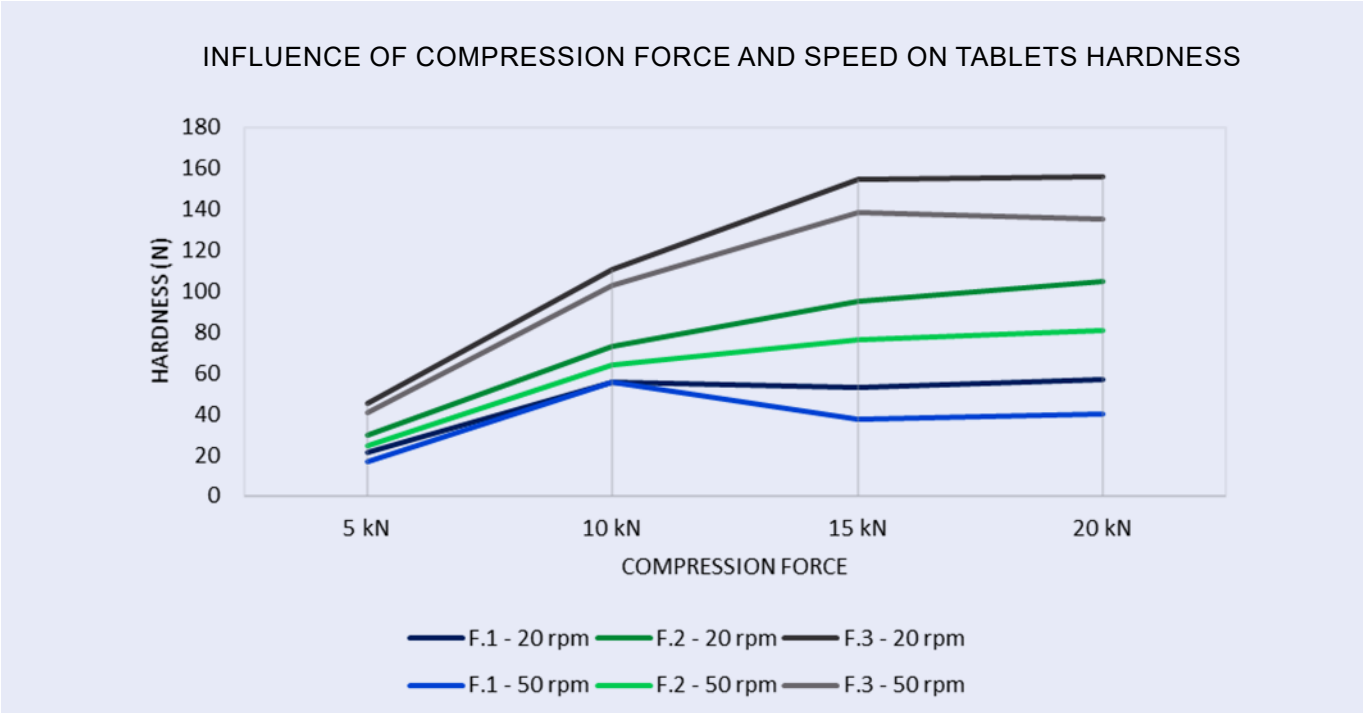
The weight of the tablets and the weight variation were investigated with the aim of verifying the ability of the excipients in the formulation to maintain homogeneity in different process parameters.

In all three formulations, excellent flow was observed from FlowLac® 100 and CombiLac®, which provided a low weight variation and in no test were tablets weighing outside the USP specification observed.

The smallest weight variation was seen in formulation F.3 (CombiLac®) of 1.1 %, followed by formulation F.1 (FlowLac® 100) of 1.7 % and 2.5 % of formulation F.2.

## 5.3 Tablet Breaking Force

The tablet hardness test results were illustrated in the graph below:




***Graph 1: Influence of compression force and speed on tablets breaking force.***

As seen in the graph, formulation F.1, which represents a conventional formulation, had the greatest influence of elastic deformation forces on the Captopril molecule, in addition to having lower tablet breaking force when compared to formulation F.2 and F.3, formulation F1 suffered a drop in tablet breaking force when reaching 10 kN compression force, with a drop of 5.54 % at 20 rpm and 32.37 % at 50 rpm and shortly thereafter, when we increased the compression force for 20 kN a 7 % increase in tablet breaking force was seen at both speeds.

On the other hand, the formulation with F.3, CombiLac®, despite there being a small drop in tablet breaking force when reaching 20 kN and 50 rpm of 2.3 %, was the formulation that had the highest tablet breaking force. When comparing the F.3 formulation, CombiLac® and the F.2 formulation, CombiLac® PAM (FlowLac® 100), the co-processed CombiLac® was able to provide a higher tablet breaking force of 34.9 % at 20 rpm and 40.7 % at 50 rpm compared to with the physical mixture.

## 5.4 Tablet Disintegration

All formulations present in this study contain Crospovidone, a super disintegrant. However, it is important to highlight that formulation F.1 has 3 % Crospovidone, while formulation F.2 and F.3 have only 1.5 %. The possibility of reducing the disintegrant concentration by half is due to the presence of starch, which helps in disintegration. The disintegration time for all three formulations was less than 4 minutes, even in formulations with 1.5 % Crospovidone.

As a result, all manufactured tablets maintained a very low disintegration time.

## 5.5 Tablet Friability

The results of the friability test are in the table below:

| FRIABILITY RESULTS (%) | | | | | | |
|---|---|---|---|---|---|---|
| **Speed** | **20 rpm** | | | **50 rpm** | | |
| Compression Force | F.1 | F.2 | F.3 | F.1 | F.2 | F.3 |
| 5 kN | 0.46 | 0.16 | 0 | 0.39 | 0.27 | 0 |
| 10 kN | 0.19 | 0.12 | 0 | 0.46 | 0.15 | 0 |
| 15 kN | 0.27 | 0.11 | 0 | 7.34 | 0.15 | 0 |
| 20 kN | 0.5 | 0.08 | 0 | 0.4 | 0.31 | 0 |

***Table 2: Influence of compression force and speed on tablets friability.***

In order to present the results of the friability test, it is possible to observe that the conventional formulation, F.1, had the highest friability, especially in tablets manufactured at 15kN and 50 rpm, a high friability was observed. The justification for this high wear is due to the formulation not being able to mask the effects of the elastic force of the Captopril molecule.
Meanwhile, formulation F.2 and F.3 showed reduced friability, with no friability seen in tablets from formulation F.3 regardless of the process parameter used.

## 6. Conclusions and Recommendations

According to the results obtained in this study, it was possible to identify that Captopril consists of a molecule with elastic deformation. This particular property of Captopril causes problems like tablet capping during production, high friability and variation in tablet breaking force.

Therefore, choosing the correct excipients to mask these effects was extremely important and necessary to guarantee a robust manufacturing process. At the end of the study, it was possible to confirm that conventional formulations have greater difficulty in maintaining adequate properties.

It was shown with the right choice of excipient it is possible to overcome these difficulties and to work in a very robust manufacturing process. In this case study two excipients were used to compare the performance of Captopril, normal spray-dried lactose FlowLac® 100 and a co-processed excipient, combining lactose monohydrate (70 %), MCC (20 %) and native corn starch (10 %). As a highlight, it can be shown that the formulation with CombiLac® was able to achieve excellent mechanical stability of the tablets, even at low compression forces. High tablet breaking force, no or only low friability and no capping tendency were seen. The disintegration time was also excellent.

**This case study illustrates the robustness and quality that CombiLac® can promote for developments with difficult active ingredients and that it is a perfect fit to ease processes during up-scaling.**

# Wherever you are – we are there for you.

## Do you have sales related questions?
## Our field sales representatives are available worldwide:


**Africa and Middle East**
T +20 100 1486 826
hani.calache@meggle.com

**Asian Regions**
T +65 9232 3378
siangmeng.chua@meggle.sg

**China**
T +86 21 3393 2457 308
yi.kang@meggle-china.com

**Japan**
T +81 3 3561 3491
yokomizo@meggle.co.jp

**Europe**
T +49 8071 73 118
info.excipients@meggle.com

**USA and Canada**
T +1 845 289 0264
customer.service@meggle.com

**Central and South American Regions**
T +55 11 2893 4831
carolina.almeida@meggle.com


## Do you need technical support?
## Our Experts in Excipients are there for you worldwide – please contact:


**Technical department**
T +49 8071 73 623

**Research and Development**
T +49 8071 73 812


## www.meggle-excipients.com


**MEGGLE GmbH & Co. KG - Business Unit Excipients**