

Accelerating drug product development by utilizing the benefits of the Virtual Pharma Assistant ZoomLab®

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Introduction

In modern formulation development, formulators need to respect a framework of guiding rules. Next to regulatory demands, inherent commercial aspects, like time-to-market, are of major relevance. One essential key for a fast development of a high-quality drug product is a structured approach. Following the Quality by Design (QbD) guidelines and utilizing benefits of virtual pharma assistants (VPAs) are the tools a formulator must employ to address these modern requirements.

In this study, ZoomLab® [1] was employed to support the formulation of enalapril maleate with the doses of 5, 10, and 40 mg, in a direct compression approach. Both, prediction accuracy of the ZoomLab® algorithm, as well as the suitability of the formulation recommendations were evaluated.

Materials and methods

ZoomLab® is a web-based VPA [1], of which the following apps were assessed in this study:

- Developability Classification
- Dissolution Profile of Active Ingredient
- Content Uniformity Check
- Formulation Wizard
- Processability of Active Ingredient
- Tableability of Active Ingredient
- Incompatibility Check
- Processability of Powder Blend
- Tableability of Powder Blend

Active and excipients

Beside enalapril maleate (Midas Pharma), a co-processed excipient based on lactose monohydrate, macrogol poly(vinyl alcohol) grafted copolymer (Kollicoat® IR), crospovidone, and sodium stearyl fumarate (Kollitab® DC 87 L, BASF), and sodium stearyl

fumarate (PRUV®, JRS) were used (Table 1). In a subsequent formulation optimization, sodium hydrogen carbonate (Merck) and iron oxide yellow and red (both Rockwood Pigments) were added as additional ingredients (Table 2).

Table 1. Prototype formulations.

Ingredient	Content (different dose)		
	5.00 mg	10.00 mg	40.00 mg
Enalapril maleate	5.00 mg	10.00 mg	40.00 mg
Enalapril (equivalent)	3.82 mg	7.64 mg	30.57 mg
Kollitab® DC 87 L	95.00 mg	140.00 mg	220.00 mg

Table 2. Optimized prototype formulations.

Ingredient	Content (different dose)		
	5.00 mg	10.00 mg	40.00 mg
Enalapril maleate	5.00 mg	10.00 mg	40.00 mg
Enalapril (equivalent)	3.82 mg	7.64 mg	30.57 mg
Kollitab® DC 87 L	155.32 mg	150.88 mg	252.10 mg
Sodium hydrogen carbonate	2.56 mg	5.12 mg	20.47 mg
Iron oxide yellow	3.44 mg	-	-
Iron oxide red	-	-	9.53 mg
Sodium stearyl fumarate	1.68 mg	-	4.90 mg

Equipment

The tableting trials were conducted on a compaction simulator (STYL'One Evolution, KORSCH/Medelpharm) using round-shaped, flat-faced punches with a diameter of 7 mm (5 and 10 mg dose) and 10 mm (40 mg dose) respectively.

Equipment in accordance with compendial methods (USP, Ph.Eur.) was used for powder and tablet characterization.

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Results and discussion

Assessment of enalapril maleate

Based on the chemical nature of enalapril maleate and its physico-chemical properties, ZoomLab® was capable to predict the active ingredient's developability classification (Figure 1). Enalapril maleate was characterized as class III component, describing an active ingredient of sufficiently soluble, yet poor permeability [2]. However, enalapril is a prodrug, which is hydrolyzed by carboxylesterases to the active ACE-inhibitor enalaprilat [3]. For that reason, the development of a direct compressible tableting formulation remained reasonable.

ZoomLab® could also predict the probability of passing the content uniformity test for the final tablets, employing the same set of particle size information. Considering a p-value of 0.99, a high probability could be expected (Figure 2).

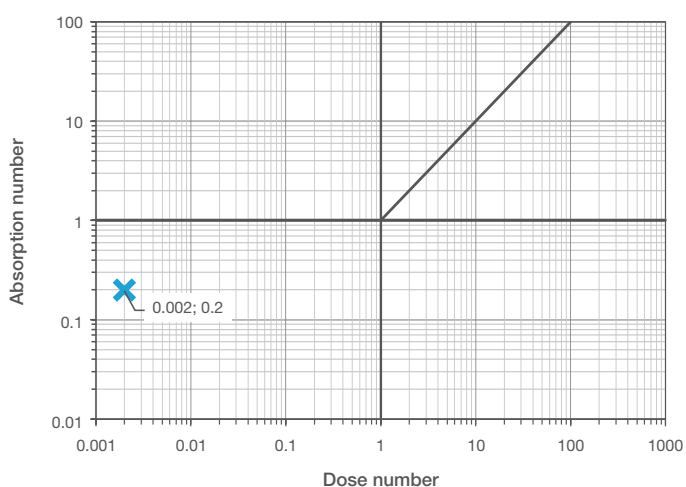


Figure 1. Developability classification chart of enalapril maleate.

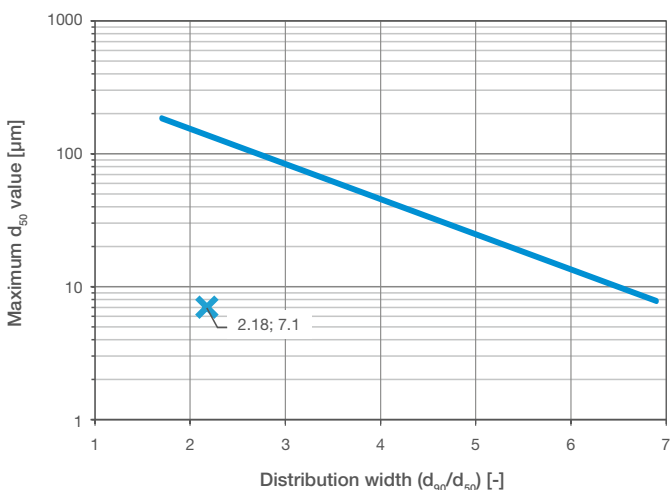


Figure 2. Content uniformity prediction ($p=0.99$) based on the PSD of enalapril maleate according to a modified version of the Yalkowsky-Bolton equation [2].

Characterization of enalapril maleate

To enable ZoomLab® the calculation of a suitable formulation, information on active ingredient's particle size, density, flowability, and tableability were required. In addition to the compendial methods for characterizing powders, five tablets of the pure

enalapril maleate powder had to be compressed at five different compression force levels. The results were used to calculate the compressibility and compactability of enalapril maleate, an essential part of the assessment. The summary of the characterization is visualized in a radar-chart, in which the individual results are normalized on a 0 to 10 scale (Figure 3).

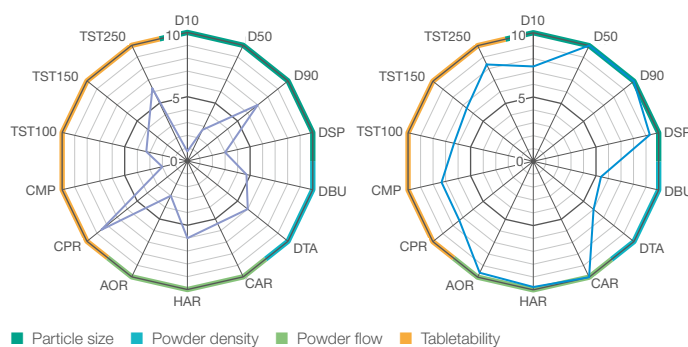


Figure 3. Radar-chart of enalapril maleate.

Figure 4. Radar-chart of Kollitab® DC 87 L.

Using the results plotted in the radar-chart (Figure 3) and the information on the chemical nature of enalapril maleate, ZoomLab® recommended the use of Kollitab® DC 87 L to gain a direct compressible tableting blend. The performance of this all-in-one co-processed excipient matched perfectly with the performance deficits of enalapril maleate (Figure 4); no incompatibilities were predicted.

In addition to the formulation concept, ZoomLab® predicted the performance of the formulation in direct compression.

Prototype formulation

All three prototype formulations were rather simple combining the all-in-one component Kollitab® DC 87 L with a different dose of enalapril maleate. However, the formulation components (e.g., lactose, crospovidone) match the ingredients contained in marketed formulations, suggesting that the incompatibility check ran successfully in the background.

The three blends were compressed at five different compression forces and the results were compared with the ZoomLab® prediction (Figure 5). The solid black lines indicate ideal minimum values for tablet strength and maximum compression pressures, the dashed black lines indicate preferred values [4].

ZoomLab®'s prediction for the 5 and 10 mg dose formulation was precise whereas some deviation was seen for the 40 mg dose. Typically, the predictive performance of ZoomLab® is very high and in the present case, two formulations were predicted correctly. This indicated that there had to be a conceptual problem with the 40 mg formulation.

The deficit of the 40 mg dose formulation became obvious when evaluating the formulation components regarding their specific share of the surface area (Figure 6). As a rule of thumb, about 25% of the surface area of a tableting blend must be represented by the lubricant sodium stearyl fumarate to allow for a sufficiently low ejection stress. As about 50% of the surface area of Kollitab® DC 87 L is covered with lubricant, this rule was fulfilled for the 5 mg and the 10 mg dose. The lubricant load for the 40 mg dose was too low, resulting in ejection stress values of 5.0

to 9.7 MPa (depending on compression pressure). These values were far above the accepted threshold of 3 MPa [4]. As a result, a pre-lamination stage was obtained which lowered tablet strength.

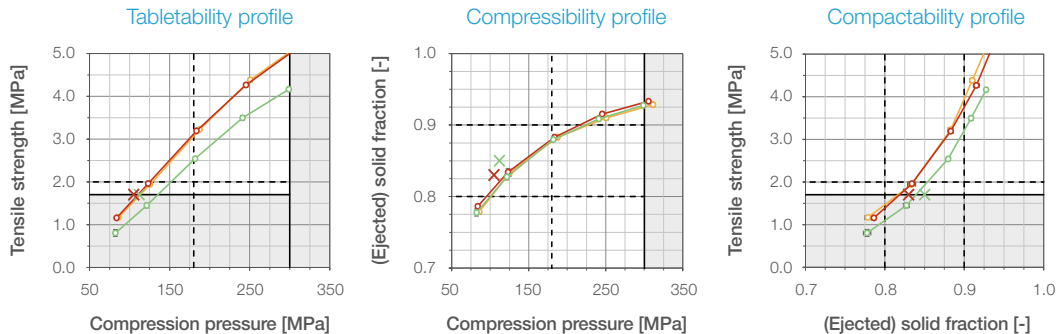


Figure 5. Tabletability, compressibility, and compactability profile of the three formulations: 5 mg dose (orange), 10 mg (red), and 40 mg (green). The respectively colored crosses indicate the ZoomLab® prediction for tablets with a tensile strength of 1.7 MPa.

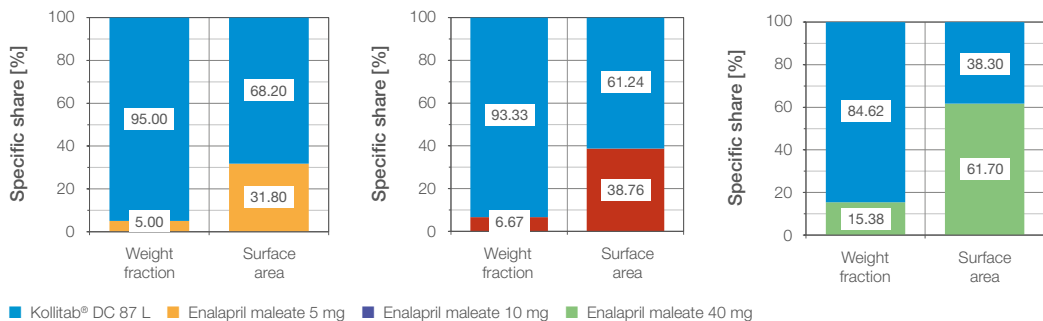


Figure 6. Specific share of weight fraction and surface area of the two formulations components enalapril maleate and Kollitab® DC 87 L in the different formulations.

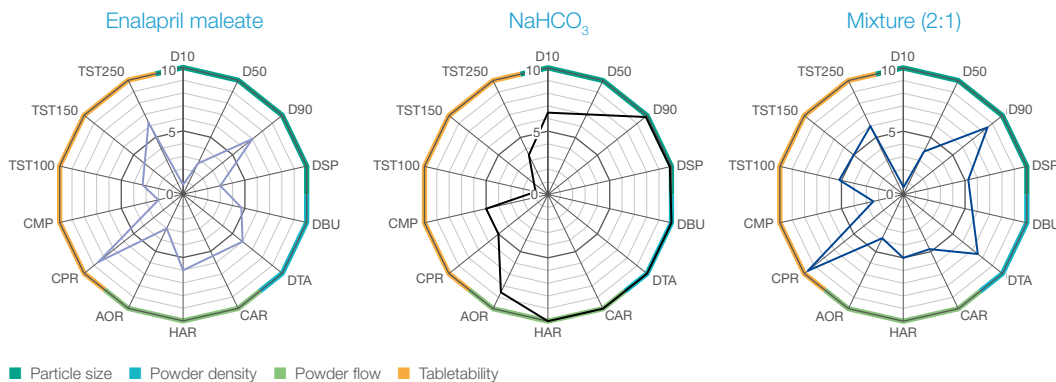


Figure 7. Radar-chart of the enalapril maleate, sodium hydrogen carbonate, and the 2:1 blend of the two components.

Optimization of prototype formulation

Generally, the optimization step is intended to implement minor modifications. Even though the prototype formulation is built on a sound scientific base, minor adaptations might be required regarding disintegration time or ejection stress (like in the case of the 40 mg dose formulation). However, enalapril maleate presents an additional challenge: even though it is very stable as crystalline solid, it might become unstable when mixed with excipients (depending on humidity and micro-environmental pH) [5]. Therefore, the addition of an alkaline component such as NaHCO_3 is recommended to maintain a basic pH-value. Though, the salt required for the stabilization of the active ingredient also causes a chemical reaction, resulting in the formation of the enalapril sodium salt and carbon dioxide (next to other side products) [6]. As of this carbon dioxide formation, enalapril tablets cannot be coated. To differentiate the different dose products, colorants are added to the tableting blend to color the whole matrix.

These aspects made the optimization step more complex compared to other case studies. Next to additional quantities of lubricant, a colorant and NaHCO_3 had to be introduced to the formulation (Table 2).

The addition of NaHCO_3 to the formulation is like the combination of two active ingredients. ZoomLab® is not capable to combine the tableting characteristics of two individually characterized actives, to determine the overall tableting characteristics. As workaround, a blend of the components (in the respective ratio) must be characterized. In the present case study, the tableting characteristics of the blend were dominated by enalapril maleate (Figure 7). Therefore, it can be assumed that the optimization can be based on the original prototype formulation.

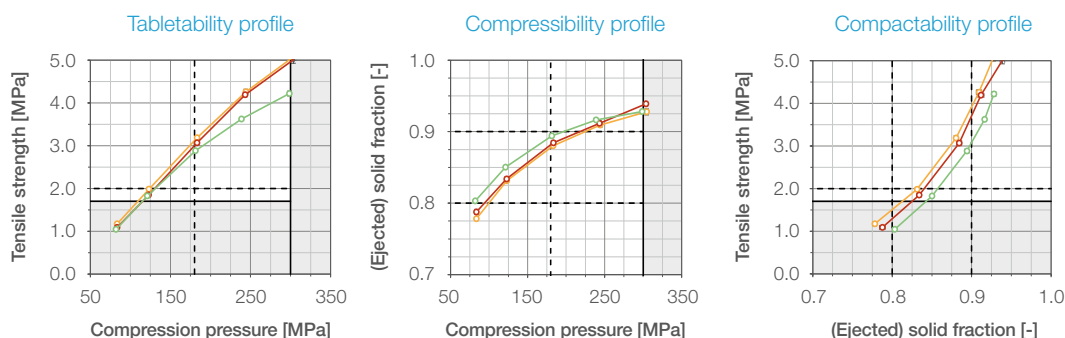


Figure 8. Tabletability, compressibility, and compactability profile of the three optimized formulations: 5 mg dose (orange), 10 mg (red), and 40 mg (green).

As expected, the overall tableting performance of the 5 and 10 mg dose hardly differed from the prototype formulation. With additional amounts of lubricant added to the 40 mg formulation, its performance improved, and matched the one of the two low dose products (Figure 8).

Conclusion

ZoomLab® provides a service formulators require today. It offers valuable information even before first experiments are conducted.

Based on a simple characterization, a prototype formulation based on the specific needs of the active ingredient and the target product profile is suggested. The ability to predict the processing characteristics of the prototype formulation is high. Minor adaptations (e.g., adjusting ejection stress) can be implemented in an optimization step.

In sum, the use of ZoomLab® reduces formulation efforts to a minimum. After the API characterization, two tableting steps were required to develop three formulations representing a 5, 10, and 40 mg enalapril maleate dose. Less than two working days and less than 50 g of enalapril maleate were required for this case study.

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