Optimization of parameters for scaled-down dissolution method for controlled release pellets

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ABSTRACT SUMMARY
The rate and extent of samples analyzed by classical dissolution testing is limited, therefore there is a need to develop alternative high-throughput methods. In our scaled-down dissolution method several parameters (amount of pellets, temperature, shaking intensity) have been evaluated by design of experiments (DoE) to achieve the best correlation to the classical method. In our case greater amount of pellets, low temperature, and low shaking intensity were necessary to achieve good correlation. These results have shown that careful optimization through DoE is highly recommended.

INTRODUCTION
As stated in the United States Pharmacopeia (USP) and the European Pharmacopeia (EP), in vitro dissolution testing is often imperative in evaluating pharmacokinetic performance and may be used as surrogate to assess the in vivo drug release and eventual absorption or bioequivalence. One way to identify factors that are critical for drug dissolution is to screen a variety of possible dissolution variables and optimize those that are identified as having some effect. Established statistical methods such as design of experiments (DoE) are suitable methodological approaches for the purpose of optimization and standardization of pharmaceutical operations.1–4

In this study we have utilized DoE to address the specific parameters that could lead to a better correlation between the classical and the scaled-down dissolution method and maximizing the precision of the scaled-down dissolution method in order to provide a tool for testing the quality of the final dosage for and its performance. For this purpose, ketoprofen controlled release pellets were used.

EXPERIMENTAL METHODS
Tested samples were ketoprofen controlled release pellets (200 mg), manufactured at Lek Pharmaceuticals d.d. (high-shear wet granulation, extrusion-spheronization, coating and drying in fluid bed system). Samples with different amount of coating (60%: 060P, 80%: 080P, 100%: 100P and 120%: 120P) or 100% coating at prolonged curing time (5h: 005C; 23h: 023C were prepared.

Classical dissolution testing was performed at 37 °C in USP XXII dissolution apparatus, type 1 (pellets remained within the basket). The release medium was 900 mL 0.05 M phosphate buffer, pH 6.8, stirring rate was 100 rpm. Samples were collected at 2, 4, 6 and 8 h, filtered (hydrophilic PVDF, 0.22 µm) and analyzed (absorbance measurement at 254 nm).

The scaled-down dissolution was performed using a Freedom EVO robotic platform (Tecan, Switzerland), equipped with an 8-tip liquid-handling arm, robotic arm and incubator/shake, using EVOware Standard software. The pellets were added to 6-well microplates with 9 mL of the same release medium. The plates were then transferred to the incubator/shaker. The samples were automatically collected at predetermined time points (as above), filtered (hydrophilic PVDF, 0.22 µm filter plate) and analyzed (absorbance measurement at 254 nm).

By using a D-optimal experimental design (MODDE 9.0, Umetrics, Sweden), the following factors were considered as independent variables: a) amount of pellets (10, 17.5 and 25% of the capsule filling mass), b) temperature (22, 37, 50 ºC) and c) shaking intensity (0, 6, 8 Hz). All the variables were quantitative. The responses studied were the correlation of the scaled-down dissolution method with the classical method (R²), the slope of the correlation curve (k), and the standard deviation between the methods (SD). Prior to
modeling the responses were pre-processed using a suitable transformation.

RESULTS AND DISCUSSION
The initial scaled-down dissolution experiment was performed with 10% of capsule filling mass at 37°C and shaking intensity of 6 Hz (Figure 1). The SD for correlation between both methods was 9.6%. Therefore we decided to optimize the experimental conditions to improve the correlation between both methods.

Figure 1. Comparison between classical and scaled-down dissolution method in the initial experiment.

The experimental design levels for the (17 trial) DoE are summarized in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T (°C)</td>
<td>22, 37, 50</td>
</tr>
<tr>
<td>Shaking intensity (Hz)</td>
<td>0, 6, 8</td>
</tr>
<tr>
<td>Capsule filling mass (%)</td>
<td>10, 17.5, 25</td>
</tr>
</tbody>
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Table 1: Studied parameter levels for optimized correlation between the scaled-down and classical dissolution.

The accuracy of the obtained statistical regression models was assessed by inspecting the multiple regression coefficients $R^2$ and $Q^2$ which were above 0.75 in all cases. The estimated effects of the independent variables on the predefined method correlation quality measures ($R^2$, $k$, SD) are shown in Figure 2.

According to the DoE results we have obtained the following optimized experimental conditions: $T = 37$ °C, shaking intensity = 0 Hz, capsule filling mass = 25%. The optimized SD of the correlation between both methods was 1.8%, significantly lower than the SD of the initial trial. The beneficial effect of higher amount of pellets is expected due to greater sample representativeness; however the increased correlation at low temperature and low shaking intensity was not.

CONCLUSION
The results have revealed that low T (°C), no shaking and high amount of pellets were parameters that resulted in the best correlation between both dissolution methods for ketoprofen controlled release pellets. We conclude that careful optimization through DoE is recommended for the development of accurate scaled-down dissolution methods for other products as well.

REFERENCES