Introduction
During the development of medicines for pediatric patients challenges occur such as the need for multiple dose strengths, palatability requirements and acceptability of excipients for pediatric use. Dispersible tablets combine the advantage of improved palatability of liquid dosage forms with the stability and dosing accuracy of solid dosage forms. According to Ph. Eur. dispersible tablets need to disintegrate within 3 min. Compendial disintegration testing at 37°C with the help of agitation does not seem to be appropriate for this administration form and therefore an alternative characterization method for dispersible tablets needs to be established.

The aim of this study was
- to evaluate suitable methods for disintegration characterization,
- to determine the influence of different formulation components on the resulting properties of dispersible tablets, focusing on disintegration behavior.

Materials and Methods

Materials
The materials used in this study and their suppliers are listed in Table 1.

Preparation of tablets
A modular approach in early formulation development offers the opportunity to easily adjust variable formulation components to quickly adapting new dose strength requirements. Therefore, the developed dispersible tablet formulations consisted of 50% granules and 50% extragranular components, which can be varied easily. Granules were obtained by fluid-bed granulation (Midili-Glatt, Glatt GmbH) and, after blending with extragranular components, were compressed to small dispersible tablets with 7 mm diameter and 150 mg weight containing 2.5 mg Cetiuril Hydrochloride (Korsch XL-100, Korsch AG). The composition of the tablets is shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Composition of dispersible tablets [%]</th>
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<tbody>
<tr>
<td><strong>Tablet Level</strong></td>
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<td>------------------</td>
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<tr>
<td>Granules (220 µm)</td>
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<tr>
<td>Superdisintegrant</td>
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<tr>
<td>Viscosity enhancer</td>
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<td>Solid function</td>
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Experimental design
To determine the influence of two different superdisintegrants and viscosity enhancers on the disintegration time of the resulting dispersible tablets, a half factorial design of experiment (DoE) was set up using MODDE software (Umetrics, Sweden) (Table 2).

<table>
<thead>
<tr>
<th>Table 2: Factors and responses of DoE</th>
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<tr>
<td><strong>Quantitative factors</strong></td>
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<tr>
<td>Type of superdisintegrant</td>
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<tr>
<td>Level of viscosity enhancer</td>
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<tr>
<td>Type of viscosity enhancer</td>
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<td>Solid function</td>
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Disintegration testing
A method described by Dor et al. [1] and el-Arini et al. [2] using a Texture Analyzer (TA) was adapted for the determination of the disintegration time of small dispersible tablets. A scheme of the TA method is shown in Figure 1. Instead of attaching the tablet flat to the TA probe head, as described in the literature, the tablet was attached on its edge, in order to increase the available surface for water uptake. Additional to the TA method, another disintegration testing method was employed using a Tensiometer, based on Stirnimann et al. [3]. Briefly, a tablet was placed in a glass tube limited by a cross made of wire. The tube was then immersed in a beaker filled with tap water and the weight change due to water uptake and subsequent disintegration was recorded by the Tensiometer.

Results and Discussion

Disintegration testing
The Texture Analyzer method enabled
- discrimination of different disintegration behaviors,
- determination of the endpoint of disintegration,
- determination of disintegration time.
Comparing the disintegration time determined in a beaker filled with 5 ml tap water by physical resistance to spatula with the disintegration time measured with the TA exhibited good correlation.

The Tensiometer method could be used for
- discrimination of different water uptake behaviors, but
- not for determination of the endpoint and therefore disintegration time.
Due to floating and sticking of the dispersed particles to the glass tube, only a small weight loss was detected by the Tensiometer during the measurement.

Design of Experiment – Disintegration time
A PCA model (R² = 0.68, Q² = 0.76) for the disintegration time was derived. The coefficient plot and 4D Response contour plot are shown in Figure 3. The level of viscosity enhancer exhibited the strongest influence on the disintegration time; by increasing it, the disintegration time is prolonged. The use of xanthan gum and croscarmellose sodium is associated with prolonged disintegration times. The use of carrageenan and crospovidone are associated with shorter disintegration times. The disintegration time is increased by increase of solid fraction and level of viscosity enhancers. The level of superdisintegrant and the interaction term between solid fraction and level of viscosity enhancer were found to be insignificant.

Conclusion
This study shows that
- disintegration testing methods, especially the TA method were successfully adapted for the disintegration characterization of dispersible tablets.
- dispersible tablets revealing different properties were successfully manufactured by extragranular components variation only, using low viscosity enhancer levels and low solid fraction levels dispersible tablets with short disintegration times were derived.
- it is of central importance to find a good balance between viscosity of the suspension (mouth feel, aspiration, sedimentation) and short disintegration times (prolonged when using high amounts of viscosity enhancer).

References