

# **Cyclosporine Nanosuspensions: Optimised Size Characterisation & Oral Formulations**

## **Ciclosporin Nanosuspensionen: Optimierte Partikelgrößencharakterisierung & Orale Formulierungen**

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**Cornelia M. Keck**

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1. Gutachter: Prof. Dr. Rainer H. Müller

2. Gutachter: Prof. Dr. Alfred Fahr

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*For my mother and my brother*



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**Abstract:** A more reliable laser diffractometer analytical procedure was developed to assess with higher accuracy the size of nanocrystals, the prerequisite for a sound formulation development. The screening procedure for optimised nanosuspension formulations was distinctly improved and the mechanism, leading to artefacts in the previous procedures, could be identified. A next generation approach for drug nanocrystals was realised by the SmartCrystal<sup>®</sup> technology, by combining nanocrystal technology with the inhibition strategy for p-glycoprotein. On top, an even simpler approach was realised by the development of the stabiliser free Cycloperls. In this formulation cyclosporine is dissolved in an oil with inhibitory effect on p-glycoprotein (peppermint oil), the oily solution is simply absorbed into porous Aeroperls. In this thesis two alternative cyclosporine formulations were developed—SmartCrystals<sup>®</sup> and Cycloperls. The formulations are physically stable and should theoretically show an improved oral bioavailability, which should be proved in in vivo tests.

**Abstrakt:** In dieser Arbeit wurde die Partikelgrößencharakterisierung mittels Laserdiffraktometrie optimiert. Mit dieser optimierten Methodik ist es möglich, Partikelgrößen und Partikelgrößenverteilungen von Nanosuspensionen genauer und vor allem korrekt zu bestimmen. Nur mit Anwendung dieser hier etablierten Methode kann ein aussagekräftiges Ergebnis bei der Charakterisierung von Nanosuspensionen erzielt werden. Es konnte gezeigt werden, dass die herkömmliche Screening-Methode zur Identifizierung optimaler Stabilisatoren für Nanosuspensionen einige bisher nicht beachtete Fehlerquellen beinhaltet, die zu Artefakten führen können. Die Screening-Methode wurde dahingehend verbessert. Eine neue Generation von Nanokristallen wurde am Beispiel von Ciclosporin entwickelt, die SmartCrystal<sup>®</sup> Technologie. Diese Technologie beinhaltet die Vorteile einer Nanosuspension sowie die Fähigkeit, P-Glykoprotein zu hemmen. Eine weitere Formulierung mit Ciclosporin und zusätzlichen inhibitorischen Eigenschaften wurde mit den Cycloperls realisiert. Cycloperls bestehen nur aus Ciclosporin gelöst in Pfefferminzöl, absorbiert in Aeroperls 300. Sie enthalten keinen Emulgator. In dieser Arbeit konnten somit zwei alternative Ciclosporin-Formulierungen entwickelt werden – SmartCrystals<sup>®</sup> und Cycloperls – : zwei stabile Formulierungen, die theoretisch eine erhöhte orale Bioverfügbarkeit aufweisen, was nun in in vivo Studien getestet werden sollte.