



# **Nanoparticle Carriers for Targeted Pulmonary Drug Delivery**

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# **Nanoparticle Carriers for Targeted Pulmonary Drug Delivery**

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## **ABSTRACT**

The pulmonary route for drug delivery offers multiple advantages over other routes of drug administration owing to its large surface area, high vascularization and thin blood-alveolar barrier. Drug delivery by this route is convenient to patients, less painful (non-invasive) and can be employed for local and systemic delivery of active pharmaceutical ingredients (APIs). The use of dry powder inhalers (DPI) enables the delivery of APIs to the lung with favorable properties. To do that, powder should possess critical quality attributes pertinent to size, flowability and ability to reach the lower parts of the respiratory system. Nano aggregate formulations are suitable technology that enables the development of successful DPIs. Therefore, the aim of this project is to employ Nano technology to develop iron oxide containing nanoparticles using model API- dactinomycin. Iron oxide nanoparticles will serve as a carrier for directing the API to the targeted site of action within the lung. The development and optimization of iron oxide nanoparticles was carried out employing Quality by Design (QbD) methodology. Nanoparticles were built up from iron oxide that was chemically prepared using bottom up method. Two polymers were investigated (chitosan and sodium alginate). The quantitative method for the analysis of dactinomycin by HPLC was validated according ICH guidelines. That was followed by screening studies for iron oxide nanoparticles development. The produced dactinomycin containing nanoparticles was characterized for mass median aerodynamic diameter (MMAD), fine particle fraction (FPF), burst effect, iron

oxide FPF and the emitted dose in the initial screening studies to investigate the most suitable input and process parameters to take to an optimization study by employing QbD principles through Design of Experiment. Results revealed the superiority of the nanoparticle aggregates containing DPIs in delivering high emitted dose, high FPF and targeted MMAD. Design space in QbD analysis showed that when using a concentration of API between 4% to 5% w/w accompanying with polymer concentration ranging from 0.5% to 0.8% w/w using sodium alginate or concentration of API is between 2.7% to 4% w/w accompanying with polymer concentration ranging from 1.2% to 2% using sodium alginate will get the desired outcome. Similarly, favorable critical quality attributes (CQA) results were attained with chitosan as a polymer, when API concentration was between 4.5% to 5% w/w and polymer concentration ranging from 0.5% to 0.8% w/w. Therefore, the outcome of this research project could be a starting point for further work to optimize and assess DPI for delivering other drugs employing iron oxide- polymer nano aggregates.

## Dedication

I dedicate this thesis to **my lovely mother**. Because she is the one who made me the person I am, she is and will be always my role model.

I also dedicate this thesis to my super hero **my father**, this accomplishment would not have been possible without his encouragement.

To all **my family** members, **my brother** and **my sisters** who have been a constant source of support and encouragement also to the **soul** that has always been by my side thank you.

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## List of Abbreviations

ANOVA	Analysis of variance
CPP	Critical process parameter
CQA	Critical quality attributes
DoE	Design of experiment
ED	Emitted dose
FPF	Fine particle fraction
FDA	Food drug administration
FTIR	Fourier-transform infrared spectroscopy
FPF-Theo	Fine particle fraction theoretical
ICH	International Conference of Harmonization
IFPF	Iron oxide fine particle fraction
IONP	Iron oxide nanoparticles
NGI	Next generation impactor
PLS	Partial least squares method
PDD	pulmonary drug delivery
pMDIs	pressurized metered dose inhalers
QbD	Quality by Design
QbT	Quality by Testing
R <sup>2</sup>	Regression coefficient
RSD	Relative standard deviation
SPION	Super paramagnetic iron oxide
TGA	Thermogravimetric analysis or thermal gravimetric analysis
USP	United State Pharmacopeia
UV\Vis	Ultraviolet-visible Spectroscopy
VIP	Variable important plot
XRD	X-Ray Diffraction