# INTENSIFYING SOLUBILITY AND BIOAVAILABILITY OF ARTEETHER THROUGH MOLECULAR ENCAPSULATION BASED ORAL DRUG DELIVERY SYSTEM

**A**
**THESIS**
**SUBMITTED TO**

**MAHARAJA RANJIT SINGH PUNJAB TECHNICAL UNIVERSITY**

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**IN FULFILLMENT OF THE REQUIREMENTS**
**FOR THE DEGREE OF**

**DOCTOR IN PHILOSOPHY**

**IN**

**PHARMACY**

**By**

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**BATHINDA (PUNJAB)**

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# CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis, entitled "**Intensifying Solubility and Bioavailability of Arteether through Molecular Encapsulation based Oral Drug Delivery System"** in fulfillment of the requirements of the award of the degree of Doctor of Philosophy in **Faculty of Pharmacy** and submitted in **Maharaja Ranjit Singh Punjab Technical University, Bathinda** is an authentic record of my own work carried out during a period from Jan, 2018 to July, 2022 under the supervision of Dr. Ashish Baldi, Professor, Department of Pharmaceutical Sciences & Technology, Maharaja Ranjit Singh, Punjab Technical University, Bathinda, Punjab, India.

The matter embodied in this thesis has not been submitted by me for the award of any other degree of this or any other University/Institute.

**Ms. Neha**
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This is to certify that the above statement made by the candidate is correct to the best of our knowledge.

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The Ph.D. Viva-Voice examination of Ms. Neha, Research Scholar, has been held on _____.

**Signature of Supervisor** **Signature of External Examiner**

# DEDICATED

# TO

# MY FATHER-IN-LAW

## *Dr. Charanjit Singh Nabha*

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-Neha

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# LIST OF ABBREVIATIONS

| Abbreviation | Full Form |
|---|---|
| %F | Percentage Friability |
| %T | Percentage Transmittance |
| ∑ | Sum |
| µg/mL | Microgram Per Millilitre |
| 2D | 2-Dimensional |
| 3D | 3-Dimensional |
| A | Absorbance |
| ACN | Acetonitrile |
| ANOVA | Analysis of Variance |
| API | Active Pharmaceutical Ingredients |
| ART | α, β-Arteether |
| ART -SLNs | α, β-Arteether Loaded Solid Lipid Nanoparticles |
| ART-CD | α, β-Arteether-Cyclodextrin Complex |
| ATP | Analytical Target Profile |
| AUC | Area Under Curve |
| BBD | Box-Behnken Design |
| BCS | Biopharmaceutical Classification System |
| °C | Degree Celsius |
| CAA | Critical Analyte Attribute |
| CAP | Cellulose Acetate Phthalate |
| CAT | Cellulose Acetate Trimellitate |
| CCD | Central Composite Design |
| CD | Cyclodextrin |
| cm | Centimetres |
| CMA | Critical Material Attributes |
| $C_{max}$ | Maximum Concentration |
| CMPs | Critical Method Parameters |
| COVID | Corona Virus Disease |
| CCSEA | Committee for Control and Supervision of Experiments on Animals |
| CPP | Critical Process Parameters |

| | |
|---|---|
| CQ | Chloroquine |
| CQA | Critical Quality Attributes |
| CQR | Chloroquine Resistant |
| CRT | Chloroquine Resistant Transporter |
| DF | Degree of Freedom |
| DLS | Dynamic Light Scattering |
| DoE | Design of Experiment |
| DSC | Differential Scanning Calorimetry |
| EDR | Endpoint Detection and Response |
| EDTA | Ethylene Diamine Tetraacetic Acid |
| EE | Entrapment Efficiency |
| FbD | Formulation by Design |
| FD | Factorial Design |
| FDA | Food and Drug Administration |
| FESEM | Field Emission Scanning Electron Microscopy |
| FFD | Fractional Factorial Design |
| FMEA | Failure Mode and Effects Analysis |
| FPQC | Finished Product Quality Control |
| FT-IR | Fourier Transform Infrared Spectroscopy |
| F-value | Fit Value |
| GI | Gastro Intestinal |
| gm | Gram |
| GMP | Good Manufacturing Practices |
| h | Hour |
| H | Height |
| HP-F | High Powder Field |
| HPLC | High Performance Liquid Chromatography |
| HPMC | Hydroxy Propyl Methyl Cellulose |
| HPMCP | Hydroxy Propyl Methylcellulose Phthalate |
| HPMC-AS | Hydroxypropyl Methylcellulose Acetate Succinate |
| HP-β-CD | Hydroxy Propyl- β -Cyclodextrin |
| HR-TEM | High Resolution Transmission Electron Microscopy |

| | |
|---|---|
| *i.m.* | *Intra –muscular* |
| *i.v.* | *Intra-venous* |
| IAEC | Institutional Animal Ethics Committee |
| ICH | International Conference on Harmonization |
| IP | Indian Pharmacopoeia |
| IPA | Isopropyl Alcohol |
| IPQC | In Process Quality Control |
| IR | Infrared |
| KN | Kneading Technique |
| KV | Kilo Volt |
| LOD | Limit of Detection |
| LOQ | Limit of Quantification |
| Max | Maximum |
| MA-EA | Methacrylic Acid-co-Ethyl Acrylate |
| MCC | Microcrystalline Cellulose |
| MDR | Multi Drug Resistant |
| min | Minutes |
| µg | Microgram |
| mL | Millilitre |
| mL/min | Millilitre Per Minute |
| MLRA | Multiple Linear Regression Analysis |
| MRT | Mean Residence Time |
| M-β-CD | Methyl- β-Cyclodextrin |
| NIC | Nicotinamide |
| NLCs | Nanostructured Lipid Carriers |
| nm | Nano Meter |
| ODMT | Oro Dispersible Mini Tablets |
| OVAT | One Variable at A Time |
| PAT | Process Analytical Tools |
| PBPK | Physiological Based Pharmacokinetics |
| PBS | Phosphate Buffer Solution |
| PDE | Percentage Drug Entrapped |

| | |
|---|---|
| PDE | Partial Differential Equation |
| PDI | Polydispersibility Index |
| PEG | Poly Ethylene Glycol |
| PFCRT | *Plasmodium. falciparum* Chloroquine transporter gene |
| PFMDR1 | *Plasmodium. falciparum* Multi Drug Resistant 1 |
| PGH | Permeability -Glycoprotein Homologue |
| Poly (MA-EA) | Poly (Methacrylic Acid-Co-Ethyl Acrylate) |
| PS | Particle Size |
| P-value | Probability Value |
| PVAP | Polyvinyl Acetate Phthalate |
| PVP | Polyvinyl Pyrrolidone |
| PXRD | Powder X-ray diffraction |
| QbD | Quality by Design |
| QN | Quinine |
| QRM | Quality Risk Management |
| QTPP | Quality Target Product Profile |
| r | Radius |
| $R^2$ | Correlation Coefficient |
| RAM | Risk Assessment Matrix |
| RES | Reticulo Endothelial System |
| RH | Relative Humidity |
| rpm | Rotation Per Minute |
| RSD | Relative Standard Deviation |
| $R_t$ | Retention Time |
| S | Slope |
| SB | Sodium Benzoate |
| SC | Sodium Citrate |
| SD | Standard Deviation |
| SE | Standard Error |
| SEM | Scanning Electron Microscope |
| SLNs | Solid Lipid Nanoparticles |
| SMEDDS | Self-Microemulsion Drug Delivery System |

| | |
|---|---|
| SOP | Standard Operating Procedure |
| S-SMEDDS | Solidified Self-Microemulsion Drug Delivery System |
| TDC | Total Drug Content |
| TDW | Triple Distilled Water |
| TEM | Transmission Electron Microscopy |
| $T_{max}$ | Time for Drug to Reach Maximum Concentration |
| USP | United States Pharmacopoeia |
| UV-VIS | Ultra Violet-Visible |
| $V_d$ | Volume of Distribution |
| w/o/w | Water/Oil/Water |
| w/v | Weight/Volume |
| WHO | World Health Organization |
| XRD | X-Ray Diffraction Analysis |
| ZS | Zeta Sizer |
| $\Delta H$ | Enthalpy Change |
| $\rho_b$ | Bulk Density |
| $\rho_t$ | True Density |
| $\rho_{tap}$ | Tapped Density |
| ɵ | Angle of Repose |