

**A novel evaporation assisted solvent antisolvent interaction
method for the nanocrystallization of organic compounds**

A Thesis

submitted

by

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(Roll No: D11019)

for the award of the degree of

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Affectionately

Dedicated

To

Almighty God

My Parents

&

My

Loving Family

Declaration by the Research Scholar

This is to certify that the thesis entitled “**A novel evaporation assisted solvent antisolvent interaction method for the nanocrystalization of organic compounds**”, submitted by me to the Indian Institute of Technology Mandi for the award of the degree of Doctor of Philosophy is a bonafide record of research work carried out by me under the supervision of Dr. Prem Felix Siril. The contents of this thesis, in full or in parts, have not been submitted to any other Institute or University for the award of any degree or diploma.

In keeping with the general practice of reporting scientific observation, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

I.I.T. Mandi (H.P.)

Date:

Signature of Research Scholar

Raj Kumar

Thesis Certificate

This is to certify that the thesis entitled “**A novel evaporation assisted solvent antisolvent interaction method for the nanocrystallization of organic compounds**”, submitted by Mr. Raj Kumar to the Indian Institute of Technology Mandi for the award of the degree of Doctor of Philosophy is a bonafide record of research work carried out by him under my supervision. The contents of this thesis, in full or in parts, have not been submitted to any other Institute or University for the award of any degree or diploma.

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I.I.T. Mandi (H.P.)

Date:

Research Guide

Dr. Prem Felix Siril

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Abbreviations

%DL.....	Percentage drug loading
%EE.....	Percentage encapsulation efficiency
AC.....	Acetone
ADR.....	Adriamycin
AFM.....	Atomic force microscopy
APIs.....	Active pharmaceutical ingredients
ASES.....	Aerosol solvent extraction system
BCS.....	Biopharmaceutical classification system
ACN.....	Acetonitrile
CBZ.....	Carbamazepine
CH.....	Cyclohexane
d/nm.....	Diameter in nanometer
DL.....	Drug loading
DLS.....	Dynamic light scattering
DMF.....	Dimethyl formamide
DMSO.....	Dimethyl sulfoxide
DSC.....	Differential scanning calorimetry
EA.....	Ethyl acetate
EASAI.....	Evaporation assisted solvent antisolvent interaction
EE.....	Encapsulation efficiency
EN.....	Ethanol
EPAS.....	Evaporation precipitation into aqueous solution

FDA.....	Food and drug administration
FESEM.....	Field emission scanning electron microscopy
FF.....	Fenofibrate
FTIR.....	Fourier transform infrared
GAS.....	Gas antisolvent
GBM.....	Glioblastomamultiforme
GF.....	Griseofulvin
GI.....	Growth inhibition
HEMs.....	High energetic materials
HMX.....	Octohydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine
HPH.....	High pressure homogenization
HPMC.....	Hydroxypropyl methylcellulose
HRTEM.....	High resolution transmission electron microscopy
IBP.....	Ibuprofen
IR.....	Infrared
JCPDS.....	Joint commission for powder diffraction standards
KP.....	Ketoprofen
LAS.....	Liquid antisolvent
LDL.....	Low density lipoprotein
mg.....	Milligram
ml.....	Milliliter
mM.....	Millimolar
MN.....	Methanol

MW.....	Molecular weight
NAP.....	Naproxen
NIBS.....	Non-invasive backscatter optics
nm.....	Nanometer
NMP.....	N-methyl pyrrolidone
NPs.....	Nanoparticles
NSAIDs.....	Non-steroidal anti-inflammatory drugs
Θ	Theta
OLEDs.....	Organic light emitting diodes
PBS.....	Phosphate buffer saline
PDI.....	Polydispersity index
PEGs.....	Polyethylene glycols
PGSS.....	Particles from gas saturated solution/suspension
PLA-PEG.....	Polylactic acid-polyethylene glycol
PTA.....	Phosphotungstic acid
PVA.....	Poly vinylalcohol
PVP.....	Polyvinylpyrrolidone
PXRD.....	Powder x-ray diffraction
RDX.....	1,3,5-trinitroperhydro-1,3,5-triazine
RESS.....	Rapid expansion of supercritical solution
RESS-SC.....	Rapid expansion of supercritical solution with solid co-solvent
RPM.....	Revolutions per minute
Ru.....	Ruthinium

SAA.....	Supercritical fluid assisted atomization
SCCO ₂	Supercritical carbon dioxide
SCF.....	Supercritical fluid
SDS.....	Sodium dodecylsulfate
SEDS.....	Solution enhanced dispersion of supercritical fluids
SMEDDS.....	Self emulsifying drug delivery system
T.....	Temperature
TATB.....	1,3,5-triamino-2,4,6-trinitrobenzene
TCA.....	Trichloroacetic acid
TEM.....	Transmission electron microscopy
TGA-DSC.....	Thermal gravimetric analysis coupled with differential scanning calorimetry
TGI.....	Total growth inhibition
TNT.....	2-Methyl-1,3,5-trinitrobenzene
UV.....	Ultraviolet
Vis.....	Visible
VLDL.....	Very low density lipoprotein
w/v.....	Weight to volume ratio
w/w.....	Weight to weight ratio
WBM.....	Wet ball milling
XRD.....	X-ray diffraction
Z-Average.....	Average of particles size
α.....	Alpha
β.....	Beta

γ	Gaama
δ	Delta
ζ	Zetapotential
λ	Wavelength
μ	Micro
μm	Micrometer

Abstract

The dramatic change in properties of materials with particle size reduction into nanometer length scales led to the advancement of nanoscience and development of nanotechnology. A plethora of methods were developed to prepare nanoparticles of inorganic materials such as metals, metal oxides and semiconductors with efficient control of their size and shape. However, there are only a few methods available for the preparation of nanoparticles of simple organic compounds. Nanosizing of simple organic compounds such as lipids, dyes, high energetic compounds and pharmaceutical drugs leads to enhancement in some of their desirable properties. Hence, there is a need to develop novel methods for the preparation of simple organic compounds. Development of a novel evaporation assisted solvent antisolvent interaction (EASAI) method is detailed in the present thesis. A number of experimental parameters that affects the particle size such as nature of solvent, solvent to antisolvent ratio, concentration, temperature of antisolvent and presence of stabilizers have been optimized during this study. The applicability of this method has been established by successfully preparing nanoparticles of some high energetic compounds and a number of pharmaceutical drugs with average particle size well below 100 nm. The objective of nanosizing is to enhance the energetic performance while reducing the sensitivity of high energetic compounds. Whereas, particle size reduction leads to substantial increase in solubility and bioavailability of poorly water soluble pharmaceutical drugs. Infact, poor water solubility of pharmaceutical drugs is a major challenge for pharmaceutical companies as nearly 40 % potential drug targets suffers from poor water solubility.

Nanoparticles of military explosives such as RDX and HMX were prepared with the desired crystal morphology. Interestingly, it was found that both the particle size as well as the shape of these high energetic compounds can be controlled by using the EASAI method by choosing an appropriate solvent. Similarly, nanoparticles of Carbamazepine which is an anti-epileptic drug were prepared and this has resulted in enhanced solubility and rate of dissolution. It was also found that we can control the particle size of drug nanoparticles by using water soluble and biocompatible polymers as stabilizers, even with high concentration of the drug. Food and drug administration (FDA) approved polymers such as polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA) and hydroxyl propyl methyl cellulose (HPMC) can be used to control the particle size of drugs effectively using EASAI method. Thus, polymer stabilized nanoparticles of Griseofulvin, a potential drug for anticancer therapy and fenofibrate, a widely used hypolipidemic drug having average particle size below 30 nm could be prepared. Interestingly, anti-leukemia activity of the non-steroidal anticancer drugs such as ibuprofen, ketoprofen and naproxen were found to be enhanced by the nanosizing. Naproxen nanoparticles that are stabilized using PVP showed two times higher anti-leukemia activity compared to Doxorubicin.

Thus, a novel EASAI method has been developed for the preparation of nanoparticles of simple organic compounds during the present study and a patent has been filed on this invention. The method can be used to lower the sensitivity of energetic compounds and thus alleviate consequences that are associated with accidental explosions during transportation and storage. At the same time solubility, rate of dissolution and bioavailability of poorly water soluble drugs can be enhanced by nanoformulation using EASAI method. While this can result in more effective

therapy of approved drugs it can also lead to the repositioning of them for novel applications and thus save a lot of time and cost associated with drug development.