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

A Thesis

submitted

by

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(Roll No: D11019)

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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.) Research Guide

Date: **Dr. Prem Felix Siril**

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Table of Contents

Chapter 3 Ultrafine carbamazepine nanoparticles with enhanced water solubility and rate of dissolution

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

Ɵ……... Theta

OLEDs……... Organic light emitting diodes

PBS…….. Phosphate buffer saline

PDI……... Polydispersity index

PEGs…….. Polyethyelene glycols

PGSS…… Particles from gas saturated solution/suspension

PLA-PEG…… Polylactic acid-polyethyelene glycol

PTA……. Phosphotungstic acid

PVA…….. Poly vinylalcohol

PVP…….. Polyvinylpyrolidone

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

SCCO2…….. Supercritical corbondioxide

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.