BOVINE MILK EXOSOMES FOR THE TREATMENT OF MELANOMA

Thesis submitted in partial fulfillment for the Award of Degree

Doctor of Philosophy

By

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Place: Varanasi **Dulla Naveen Kumar**

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List of Abbreviations

Abbreviations	Description
2FI	Two-factor interaction model
ABC	ATP-binding cassette
ABCD	Asymmetry, border irregularity, color variation, and large diameter
AFM	Atomic force microscope
Akt	Ak strain transforming kinase
ALP	Alkaline phosphatase
ANOVA	Analysis of variance
AP-1	Activated protein-1
AT	Artemisinin
AUC	Area under the curve
b.wt	Body weight
BBB	Blood-brain barrier
BCC	Basal-cell carcinoma
BM	Branching myocytes
BRAF	Serine/threonine-protein kinase B-Rapidly Accelerated Fibrosarcoma
C.V.	Co-efficient of variation
CCD	Central composite design
CDER	Center for Drug Evaluation and Research
CDK4	Cyclin-dependent kinase 4
CDKN1A	Cyclin-dependent kinase inhibitor 1A
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CLSM	Confocal laser scanning microscopy
CM	Cutaneous melanoma

C_{max}	Maximum plasma concentration
COX-2	Cyclooxygenase 2
CPCSEA	Committee for the Purpose of Control and Supervision of Experiments on Animals
CQA	Critical quality attributes
CREB	Cyclic AMP response element-binding protein
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
CU-6	Cumarin-6
DAD	Diode array detector
DHA	Dihydroartemsinin
DM	Desmoplastic melanoma
DMBA	Dimethylbenz[a]anthracene
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	DimethylSulphoxide
dNTPs	Deoxynucleoside triphosphate
DTIC	Dacarbazine
ECL	Enhanced Chemiluminescence
EE	Encapsulation efficiency
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ERK1/2	Extracellular signal-regulated kinases 1 and 2
ESCRT	Endosomal sorting complexes required for the transport
EVs	Extracellular vesicles
Exo	Exosomes
Exo-C-6	Exosomes loaded coumarin-6
Exo-DHA	Dihydroartemisinin loaded exosomes
Exo-HES	Hesperidin loaded exosomes

FbD	Formulation by design
FBS	Fetal bovine serum
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
F_{rel}	Relative bioavailability
GCO	Global Cancer Observatory
GEM	Genetically engineered models
GGT	γ-glutamyl transpeptidase
GHS	Globally Harmonised System
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GSH	Glutathione
GTP	Guanosine triphosphate
HEK 293	Human embryonic kidney 293 cells
HES	Hesperidin
HIF-1α	Hypoxia-inducible factor-1α
HPLC	High-performance liquid chromatography
HRAS	Harvey rat sarcoma viral oncogene homolog
HRSEM	High-resolution scanning electron microscopy
HRTEM	High-resolution transmission electron microscopy
i.p.	Intra peritonial
iNOS	Inducible nitric oxide synthase
IAEC	Institutional Animal Ethics Committee
ICH	International Conference on Harmonization
IFN	Interferon
IL	Interleukin

ILVs	Intraluminal vesicles
K_0	Zero order rate constant
K_1	1^{st} order rate constant
KDR/FIK-1	Kinase insert domain receptor/fetal liver kinase 1
K_{el}	Elimination rate constant
LD_{50}	Lethal Dose 50
LOD	Lower limit of detection
LOQ	Lower limit of quantification
LMM	Lentigo maligna melanoma
LOD	Limit of detection
LOQ	Limit of quantification
MAPK	Mitogen-activated protein kinase
MCWO	Molecular weight cutoff
MEK	Mitogen-activated protein kinase kinase
MEK1/2	MAP kinase extracellular signal regulated kinases 1 and 2
MHC	Major histocompatibility complex
MMP	Mitochondrial membrane potential
MMPs	Matrix metalloproteinases
MRT	Mean residence time
MVBs	Multivesicular bodies
NCCS	National Centre for Cell Science
NCEs	New chemical entities
NCI	National Cancer Institute
NF-κβ	Nuclear factor kappa β
NK	Natural killers
NRAS	Neuroblastoma RAS viral oncogene homolog

OECD	Organization for Economic Co-operation and Development
p.o.	Per oral
PBS	Phosphate-buffered saline
PCNA	Proliferating cell nuclear antigen
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
p-DMAB	p-dimethylaminobenzaldehyde
PDTXs	Patient-derived tumor xenografts
P-gp	P-glycoprotein
PI3K	Phosphatidylinositol-3-kinase
PIP2	Phosphatidylinositol- 4, 5-biphosphate
PIP3	Phosphatidylinositol-3, 4, 5-triphosphate
PK	Pharmacokinetic
PKCα	Protein kinase C alpha
PLGA	Poly(lactic-co-glycolic acid)
QbD	Quality by design
QC	Quality control
Raf	Rapidly accelerated fibrosarcoma
Ras	Rat sarcoma virus
RDW	Red cell distribution width
RET	Receptor tyrosine kinase
RES	Reticuloendothelial system
ROS	Reactive oxygen species
RSD	Relative standard deviation
Rt	Retention time
RTK	Receptor tyrosine kinase

SCC	Squamous cell carcinoma
SCID	Severe combined immune-deficient
SD	Standard deviation
SEC	Size exclusion chromatography
SPM	Scanning probe microscopy
$t_{1/2}$	Elimination half-life
TCR	T-cell receptor
TDDS	Transdermal drug delivery system
TGF	Transforming growth factor
TGI	Tumor growth inhibition
TIMP	Tissue Inhibitor of Metalloprotease
TLC	Total leucocyte count
T_{max}	Time to reach maximum concentration
TMF	5,7,4′trimethoxyflavone
TNF	Tumor necrosis factor
TRBCs	Total red blood cell counts
TV	Tumor volume
UV	Ultraviolet
VDT	Volume doubling time
VEGF	Vascular endothelial growth factor
VPS4	Vacuolar protein sorting associate protein 4
WBC	White blood cells
XRD	X-ray diffraction

List of Symbols

Symbols	Description
%	Percentage
°	Degree
α	Alpha
μ	Micro
β	Beta
γ	Gamma
μg	Microgram
mm	Milli meter
cm	Centi meter
>	Greater than
<	Less than
↑	Increase
↓	Decrease
°C	Degree Celsius
T_g	Glass transition temperature
MW	Molecular weight
®	Registered trademark
TM	Trademark
μL	Micro liter
mAU	Milli-absorbance unit
ppm	Parts per million
v	Volume
nm	Nano meter

λ_{max}	Absorption maxima
bp	Base pair
kH	Kilohertz
W	Watt
min	Minute
#	Mesh size
rpm	Rotation per minute
θ	Theta
g	Gram
mg	Milli gram
cm	Centi meter
w	Weight
s	Second
h	Hour
ζ	Zeta potential
mV	Milli volt
mg/dL	Milligram/deciliter
U/L	Unit/liter
g/dL	Gram/deciliter
fL	Femtoliters
pg	Picogram