UNIVERSITI PUTRA MALAYSIA

HISTOLOGICAL AND SAFETY EVALUATION OF COCKLE SHELL-DERIVED CaCO3 NANOPARTICLE LOADED WITH DOXORUBICIN IN DOGS

DANMAIGORO ABUBAKAR

FPV 2018 21

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By

DANMAIGORO ABUBAKAR

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

August 2018

DEDICATION

This thesis is dedicated to my late Dad, Alh. M. A Danmaigoro, for his words of motivation and reinforcement in search of excellence, May your soul rest in peace Ameen. To my Mum Fatima M. Danmaigoro for her patient, guidance and moral supports.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

HISTOLOGICAL AND SAFETY EVALUATION OF COCKLE SHELL-DERIVED $CaCO_3$ NANOPARTICLE LOADED WITH DOXORUBICIN IN DOGS

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Chairman : Professor Md. Zuki bin Abu Bakar @ Zakaria, PhD
Faculty : Veterinary Medicine

Detrimental tissue effects are associated with chemotherapeutics, despite research progress in cancer treatments. Difficulties are still encountered with tumour targeting due to cancer structural complexity. Doxorubicin (DOX) is a potent anticancer lacking cell specificity leading to reduction in its efficacy. Meanwhile, increase therapeutic targeting to tumour has been shown to have promising therapeutic effect using nanomedicine. Encapsulation of anticancer within bio-nanomaterial aids in their delivery to cancer tissues, thus, ameliorates off-targeted effects of drugs, which has necessitated the importance of exploring the potency of cockle shell-derived calcium carbonate nanoparticle (CS-$CaCO_3$NP) for DOX delivery safely. Homogenous CS-$CaCO_3$NP with sufficient physicochemical properties which exhibits promising potential as targeting nanocarrier is desired for chemotherapy. Stimuli-responsive nanocarriers have received great attention in drug delivery towards aiding better selectivity and specificity of drugs in the plasma circulation. DOX is associated with cardio-hepato-renal toxicity effects which hampered its clinical application. CS-$CaCO_3$NP is a biodegradable carrier with considerable potential for DOX targeted delivery. Thus, the aim of this study was to evaluate the safety of CS-$CaCO_3$NP-DOX in dogs. The homogeneity of CS-$CaCO_3$NP was obtained through a top-down approach with the help of a roller mill. The CS-$CaCO_3$NP and CS-$CaCO_3$NP-DOX were characterized for physicochemical properties using Transmission Electron Microscopy, Field Emission Electron Microscopy, Zeta Sizer, X-ray Diffraction, Fourier Transformed infrared, and Brunauer-Emmett-Teller techniques. A dissolution non-Fickian control based release kinetics using dialysis bag was employed to evaluate the release pattern. A bioanalytical methods were developed on High Liquid Pressure Chromatography for pharmacokinetic studies in six dogs, which were equally divided and given free DOX and CS-$CaCO_3$NP-DOX for study, a total of 15 healthy dogs were randomized into 5 groups. The Dogs were subjected to slow intravenous

infusion up to 5 doses at every 3 weeks interval with (i) normal saline, (ii) DOX 30 mg/m^2, and the experimental groups; CS-$CaCO_3$NP-DOX at (iii) high dose, 50 mg/m^2, (iv) clinical dose, 30 mg/m^2 and (v) low dose, 20 mg/m^2. Physical and clinical examination, radiography, electrocardiography, blood profile, cardiac injury biomarkers, histopathology and ultrastructure were employed to evaluate the toxicity and safety while blood profile, tumour biomarker, tumour size and survival rate were used to evaluate the dogs. A homogenous, spherical, porous pH-responsive CS-$CaCO_3$NP was obtained with a mean diameter and zeta potential of 24.9 ± 4.07 nm and -26.1 mV respectively. While a mean diameter and zeta potential of CS-$CaCO_3$NP-DOX were 39.4 ± 3.04 nm -34.7 mV, respectively. The energy dispersion X-ray analysis revealed a high proportion of calcium with a spectrum peak on FTIR spectra suggesting no alteration upon incorporation of DOX into CS-$CaCO_3$NP with a higher loading capacity and encapsulation efficiency were recorded. An excellent bioanalytical method with high extraction yield and linearity of 89.87% and 0.997 was discovered. The kinetic release profile in neutral buffer medium had 13.7% of DOX released from CS-$CaCO_3$NP after 96 hours, with about 25% concentration release in weak acid medium, while 52.6% of DOX were release from free-DOX in neutral buffer medium. CS-$CaCO_3$NP-DOX increased half-life and area under the curve, with lower clearance rate as compared to free DOX. The cumulative dose of 150 mg/m^2 of free-DOX over 15 weeks revealed significant ($p<0.05$) changes in clinical, haematological profile, serum biochemical alteration, elevations in the cardiac injury markers and histopathologic changes on tissues as compared to dogs given an equivalent cumulative dose of CS-$CaCO_3$NP-DOX. In addition, dogs given CS-$CaCO_3$NP-DOX at cumulative dose below 150 mg/m^2 did not show any significance ($p>0.05$) changes as when compared to those given normal saline**.** This study also revealed no significant changes in systemic toxicity effects in dogs and thus, confirmed the safety of the repeated dose administration CS-$CaCO_3$NP-DOX (30 mg/m^2), which improves the quality of life and efficacy in dogs with non-resectable tumours when given 4-5 doses of CS-$CaCO_3$NP-DOX 30 mg/m^2. This finding offers great hope to reduce toxicity in dogs with cancer that might undergoes long-term regiment with DOX. These properties underscore the potential of CS-$CaCO_3$NP in the delivery of DOX as new intelligent composite, giving it a high potential in the delivery of the anticancer in the management of dog with cancers.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENILAIAN HISTOLOGI DAN KESERASIAN PARTIKEL NANO $CaCO_3$ DARI KULIT KERANG DIMUATKAN DENGAN DOXORUBICIN DALAM ANJING

Oleh

DANMAIGORO ABUBAKAR

Ogos 2018

Pengerusi : Profesor Md Zuki bin Abu Bakar @ Zakaria, PhD
Fakulti : Perubatan Veterinar

Disebalik kemajuan penyelidikan dalam rawatan kanser, kesan tisu yang memudaratkan masih dikaitkan dengan rawatan kemoterapi. Kesukaran masih dihadapi dengan rawatan sasaran tumor disebabkan oleh struktur kanser yang rumit. Doxorubicin (DOX) adalah antikanser yang kuat namun kekurangan spesifikasi sel membawa kepada pengurangan keberkesanannya. Sementara itu, peningkatan sasaran terapeutik ke tumor menggunakan perubatan nano telah terbukti mempunyai kesan terapeutik. Memuatkan antikanser kedalam bio-bahan nano membantu dalam penyampaian antikanser ke tisu kanser, dengan itu, meningkatkan kesan sasaran dadah antikanser. Ini menjadikan kepentingan meneroka potensi kalsium karbonat nanopartikel berasal dari kulit kerang (CS-$CaCO_3$NP) untuk penghantaran DOX dengan selamat adalah perlu. CS-$CaCO_3$NP yang seragam dengan ciri-ciri fizikokimia yang mencukupi mempamerkan potensi cerah sebagai pembawa nano disasarkan yang diperlukan untuk kemoterapi. Pembawa nano responsif-rangsangan telah mendapat perhatian yang besar dalam penghantaran ubat bagi membantu pemilihan dan pengkhususan ubat dengan lebih baik dalam edaran plasma. DOX dikaitkan dengan kesan ketoksikan kardio-hepato-ginjal yang menghalang aplikasi klinikal. CS-$CaCO_3$NP adalah pembawa yang boleh terurai secara biologi didalam badan yang mempunyai potensi yang besar untuk penghantaran DOX disasarkan. Oleh itu, tujuan kajian ini adalah untuk menilai keserasian CS-$CaCO_3$NP-DOX pada anjing. CS-$CaCO_3$NP yang sekata telah diperolehi melalui pendekatan atas-bawah dengan bantuan alat pemusing. CS-$CaCO_3$NP dan CS-$CaCO_3$NP-DOX telah dicirikan untuk ciri-ciri fizikokimia menggunakan Mikroskop Imbasan Elektron, Mikroskopi Elektron Pelepasan Medan, Medan Pelepasan Mikroskopi Elektron, Zeta Sizer, Difraksi sinar-X, Inframerah Fourier Bertukar, dan teknik Brunauer-Emmett-Teller. Pembubaran kinetik pelepasan non-Fickian yang menggunakan beg dialisis digunakan untuk menilai corak pembebasan. Kaedah bioanalitik telah dibangunkan pada Kromatografi

Tekanan Cecair Tinggi untuk kajian farmakokinetik dalam enam ekor anjing, dengan tiga ekor setiap kumpulan dan masing-masing diberikan DOX dan CS-$CaCO_3$NP-DOX. Sebanyak 15 ekor anjing yang sihat telah dibahagikan secara rawak kepada 5 kumpulan. Kesemua anjing tersebut diberi infusi intravena secara perlahan sebanyak 5 dos pada setiap selang 3 minggu dengan (i) saline normal, (ii) DOX 30 mg/m^2, dan kumpulan eksperimen; CS-$CaCO_3$NP-DOX pada (iii) dos tinggi, 50 mg/m^2, (iv) dos klinikal, 30 mg/m^2 dan (v) dos yang rendah, 20 mg/m^2. Pemeriksaan fizikal dan klinikal, radiografi, elektrokardiografi, profil darah, biomarker kecederaan jantung, histopatologi dan ultrastruktur digunakan untuk menilai ketoksikan dan keserasian, manakala profil darah, biomarker tumor, saiz tumor dan kadar kelangsungan hidup serta RECIST v1.1 digunakan untuk menilai anjing. CS-$CaCO_3$NP pH-responsif berliang, sfera dan seragam telah diperolehi dengan diameter purata dan potensi zeta masing-masing adalah 24.9 ± 4.07 nm dan -26.1 mV. Manakala purata diameter dan potensi zeta bagi CS-$CaCO_3$NP-DOX masing-masing adalah 39.4 ± 3.04 nm -34.7 mV. Analisis sinaran penyebaran tenaga mendedahkan kadar kalsium yang tinggi dengan puncak pada spektrum FTIR menunjukkan tiada perubahan apabila dimasukkan DOX kedalam CS-$CaCO_3$NP dengan kapasiti muatan yang lebih tinggi dan kecekapan enkapsulasi dicatatkan. Kaedah bioanalitik yang sangat baik dengan hasil pengeluaran yang tinggi dan linieriti, masing-masing 89.87% dan 0.997 telah ditemui. Profil pembebasan kinetik dalam medium penyangga neutral mempunyai 13.7% DOX yang dibebaskan dari CS-$CaCO_3$NP selepas 96 jam, dengan kira-kira 25% kepekatan dibebaskan dalam medium asid lemah, manakala 52.6% DOX dibebaskan dari DOX dalam medium penimbal neutral. CS-$CaCO_3$NP-DOX meningkat separuh hayat dan kawasan di bawah lengkung, dengan kadar pembebasan yang lebih rendah berbanding dengan DOX percuma. Dos kumulatif 150 mg/m^2 bagi DOX lebih daripada 15 minggu menunjukkan perubahan ($p < 0.05$) yang signifikan dalam profil klinikal, haematologi, perubahan biokimia serum, ketinggian dalam penanda kecederaan jantung dan perubahan histopatologi pada tisu berbanding dengan anjing yang diberikan dos kumulatif setara CS-$CaCO_3$NP-DOX. Di samping itu, anjing yang diberi CS-$CaCO_3$NP-DOX pada dos kumulatif di bawah 150 mg/m^2 tidak menunjukkan apa-apa perubahan ($p > 0.05$) dibandingkan dengan yang diberi normal saline. Kajian ini juga menunjukkan tiada perubahan ketara dalam kesan ketoksikan sistemik dalam anjing dan oleh itu, mengesahkan keserasian pemberian dos berulang CS-$CaCO_3$NP-DOX (30 mg/m^2), yang meningkatkan kualiti hidup dan keberkesanan pada anjing yang tidak dapat dibuang tumor apabila diberikan 4-5 dos CS-$CaCO_3$NP-DOX 30 mg/m^2. Penemuan ini menawarkan harapan yang tinggi untuk mengurangkan ketoksikan dalam anjing dengan kanser yang memerlukan rawatan jangka panjang dengan DOX. Ciri-ciri ini membuktikan bahawa CS-$CaCO_3$NP berpotensi untuk membawa DOX sebagai komposit pintar baharu yang bermanfaat serta berpotensi cemerlang sebagai pembawa antikanser untuk merawat anjing yang menghidapi kanser.

ACKNOWLEDGEMENTS

I begin by thanking Almighty Allah for His blessings of wisdom and life to witness the completion of this programme despite the challenges. I pray for Allah's continuous guidance, Amin.

The termination of every journey that started with a step, finally advanced into a great mission. The gravity of the words does not in any way down thrown the effort and support I received from anyone not mention or mention herein. I am sincerely grateful to my mentor, my promoter, Prof. Dr Md. Zuki Abu Bakar, Prof. Madya Dr Gayathri Thevi Selvarajah, Prof. Madya Mohd Hezmee Mohd Noor and Prof. Dr Rozi Mahmud for their mentorship and guidance. I am most grateful to the prototype grant (PRGS) and Usmanu Danfodiyo University, Sokoto for their financial support and fellowship awards.

I would like to acknowledge the support of Prof. Dr Zuki Nano's team, UDUS scholars UPM, Encik Hilman, Encik Maniam, UVH UPM staff, and Nigerian community in UPM for the joyful living environment during the study period. To all my research fellows, too numerous to mention, I sincerely appreciate your friendship. I also noted deeply and acknowledge my entire family for their support and understanding, praying for guidance and strength during the course of this programme. Special thanks to my Wife, Rahmat and the kids Abba and Daddy for all we have gone through during the period together; your patience and understanding all the period I was away from them. I Thank God Almighty Allah who sees me through during my entire life.

I certify that a Thesis Examination Committee has met on 17 August 2018 to conduct the final examination of Danmaigoro Abubakar on his thesis entitled "Histological and Safety Evaluation of Cockle Shell-Derived $CaCO_3$ Nanoparticle Loaded with Doxorubicin in Dogs" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

Arifah bt Abdul Kadir, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Hazilawati binti Hamzah, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Internal Examiner)

Md Sabri bin Mohd Yusoff, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Internal Examiner)

Anudep Rungsipipat, PhD
Professor
Chulalongkorn University
Thailand
(External Examiner)

RUSLI HAJI ABDULLAH, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 27 September 2018

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Md Zuki Abu Bakar @Zakaria, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Gayathri Thevi Selvajarah, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Mohd Hezmee Mohd Noor, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Rozi Mahmud, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
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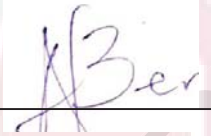
Signature:  Date: _____

Name and Matric No: Danmaigoro, Abubakar, GS44949

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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Signature: _____
Name of Chairman of Supervisory Committee: Professor Dr. Md Zuki Abu Bakar @Zakaria

Signature: _____
Name of Member of Supervisory Committee: Associate Professor Dr. Gayathri Thevi Selvajarah

Signature: _____
Name of Member of Supervisory Committee: Associate Professor Dr. Mohd Hezmee Mohd Noor

Signature: _____
Name of Member of Supervisory Committee: Professor Dr. Rozi Mahmud

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%	Percentage
µm	Micrometer
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AO	Acridine Orange
BET	Brunner Emmett and Teller
BS-12	Dodecyl dimethyl betaine
BW	Body weight
Ca	Calcium
$CaCO_3$	Calcium carbonate
Cl	Chloride
Cmax	Concentration maximum
CR	Complete response
CRE	Creatinine
COSA	Canine osteosarcoma cell
CS-$CaCO_3$NP	Cockle shell derived calcium carbonate nanoparticle
CS-$CaCO_3$NP-DOX	Cockle shell derived calcium carbonate nanoparticle loaded with Doxorubicin
DOX	Doxorubicin
DW	Distilled water
ECG	Electrocardiography
EDTA	Ethylenediaminetetraacetic acid
EDX	Energy Diffraction x-ray

ELISA	Enzyme-linked immunosorbent assay
FDA	Food development agent
FESEM	Field emission scanning electron microscopy
FITR	Fourier transform infrared spectroscopy
FPV	Faculti Perubatan Veterinar
g	Gram
H & E	Haematoxylin and Eosin
HCL	Hydrochloric acid
HPH	High Pressure Homogenizer
HPLC	High performance liquid chromatography
HRTEM	High resolution transmission electron microscopy
IACUC	International Animal Care Use Committee
K	Potassium
kDA	Kilo Dalton
Kg	Kilogram
LD	Lactases dehydrate
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
mg	Milligram
Min	Minute
mL	Millilitre
MPV	Mean Platelets Volume
MTD	Maximum tolerable dose
mV	Millivolts

Na	Sodium
nm	Nanometer
NO	Nitric oxide
^{o}C	Degree celcius
OD	Optical density
OECD	Organisation economic committee development
OS	Osteosarcoma
PBS	Phosphate buffer saline
PDI	Polydispersity index
PEG	Polyethylene glycol
pH	Potential of Hydrogen
PI	Propidium Iodide
PLT	Platelet
RBC	Red blood cell
RDW	Red Cell Distribution Width
RNA	Ribonucleic acid
SB-12	*N*-dodecyl-*N, N*-dimethyl-3-ammonio-1-propanesulfonate
SD	Standard deviation
$T_{1/2}$	Half life
TEM	Transmission electron microscopy
UPM	Universiti Putra Malaysia
UV/VIS	Ultraviolet visible
VCOG	Veterinary Cooperative Oncology Group
WBC	White blood count

WHO	World health organization
Wk	Week
XRD	X-ray dispersity
Zp	Zeta potential

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Current advance in nanotechnology led to increase interest in the use of nanoparticles in medicine in resolving challenges related to chemotherapy by combining therapeutic agents and bio-nanomaterial for therapeutic application (Seleci et al., 2016). Tumour is an aggressive, progressive and invasive fatal disease as a result of oncogenic cell activation at specific point mutation with few management preferences, and its global incidence and mortality rate is increasing due to improper delivery of drugs of interest to the targeted neoplastic cells (Selvarajah and Kirpensteijn, 2016; Lengyel, 2010). Chemotherapy is the major cancer treatment methods, which has toxic effects and unsatisfactory treatment effects which have led physician to dose reduction, multiple or combine therapy and treatment delay, resulting in decrease in survival rate (Hossain et al., 2013; Rudnick-Glick et al., 2014; Yin et al., 2013). This necessitated the importance of identifying potential drugs formulations and to explore more effective therapeutic strategies for the cancer treatment.

The emergence of nanotechnology has made significant impact on clinical therapeutics in the last decades, with advances in biocompatible nanoscale drug carriers such as assembled polymers and liposome nanoparticle has enabled safer delivery of anticancers (Khanbabaie and Jahanshahi, 2012; Sun et al., 2015; Wu et al., 2015). In fact, a wide spectrum of nanocarrier has been extensively investigated to address the emerging need in pre-clinical and clinical stage.

Nanoparticles are designed to reach their targets site safely and dislodging its therapeutic agents at the site of the pathology, thereby increasing the drug bioavailability at the targeted tumour sites (Barua and Mitragotri, 2014; Hossain et al., 2013). Since, targeting the cells of interest is important in minimise cytotoxicity damage to healthy proliferating cells (Florea and Büsselberg, 2011; Smith, 1994; Varbiro, 2014). Although, both synthetic and natural polymers have been used for drug delivery, with polymers like poly (ε-caprolactone) and poly (glycolic acid) being the most widely used (Barua and Mitragotri, 2014).

However, the use of inorganic biomaterial is currently more useful in the development of drug delivery nanocarrier for anticancer due to their stability and biocompatibility (Isa et al., 2016). Cockle shell-derived $CaCO_3$ nanoparticle is biogenic, biocompatible, biodegradable, and osteoconductive sounding more promising in the delivery of anticancer drug and hormone with little or toxic effects to healthy cells (Jaji et al., 2017; Kamba et al., 2013). Currently biodegradable nanocarrier are most needed since they can be degraded without releasing any harmful product (Mozafari, 2006). Cockle shell-derived $CaCO_3$ aragonite nanoparticle (CS-$CaCO_3$ NP) is unstable and the size,

shape and surface chemistry depends on the synthesis method employed (Jaji et al., 2017). CS-$CaCO_3$NP has shown promising properties as a good drug delivering agent with great drug loading capability and controlled release of doxorubicin into cancer cells line as well as an antiosteoporotic agent when loaded with hormone respectively (Kamba et al., 2013a; Jaji et al., 2017). Moreover, calcium from the decomposed CS-$CaCO_3$NP is essential in bone development, nerve, muscles, blood, enzymes activation and cell proliferation (Pu et al., 2016). Doxorubicin (DOX) is a chemotherapeutic agent that acts effectively against various types of cancers, however, releases oxygen free radicals which affect myocardiocytes and haematopioetic precussor cells leading to organ failure (Hossain et al., 2013).

1.2 Statements of the Problem

Conventional chemotherapy in cancer management results in off-target effects causing damage to healthy rapidly mitotic cells. Presently the delivery of DOX to solid tumour is a major problem due to lack of specific targeting, selectivity and tumour structural complexity leading to inadequacy and mild cell drug interaction (Desai, 2012; Tang et al., 2007). Several chemotherapeutic drugs for cancer are used in conjugation with $CaCO_3$ nanoparticle in *in vitro* studies and have shown encouraging abilities to circumvent the shortcomings with their free drug counterparts by increasing the concentration of the therapeutic drug at the tumour bio site (Kamba et al., 2013; Ueno et al., 2005).

Some studies on nanomedicine have proven effective with the used of cockle shell-derived $CaCO_3$NP loaded with doxorubicin (CS-$CaCO_3$ NP-DOX) in the treatment of some specific tumour cell lines, *in vitro* and *in vivo* studies in small laboratory experimental animals (Kamba et al., 2014 and Fu et al., 2017). However, CS-$CaCO_3$ synthesized using Fu et al. (2017) method offer many advantages as drug carrier system, Although, associated with particle agglomeration and size heterogeneity, with other limitations yet to be resolved in term of kinetic release mechanism, pharmacokinetics, toxicity, safety and therapeutic potential in dogs. So, there is a need for synthesis method modification to achieved homogenous monodisperse $CaCO_3$NP. Until now, the toxicity and therapeutic potential of CS-$CaCO_3$NP-DOX in the treatment of spontaneous tumour has not yet been applied clinically.

1.3 Significance of the Study

Targeted nano-therapies have shown improved therapeutic efficient on neoplastic cell line through accumulative and sustain release of drugs. To avoid the toxicity of DOX on healthy mitotic cells, CS-$CaCO_3$NP-DOX was formulated using nanotechnology approach for treating the spontaneous solid non re-sectable tumours in dogs. Based on the data review on studies made on $CaCO_3$NP from Cockleshell, CS-$CaCO_3$NP-DOX could be used in managing dogs with tumour to increased quality of life and survival rate.

In addition, adequate dose of DOX required for effective drug-tumour cell interaction is achievable when nanotechnology approach is employed. However, there is a need to synthesis homogenous carrier and to evaluate the pharmacokinetics, repeated dose toxicity effect, safety and its therapeutic potential in dogs. This could go a long way in resolving the challenging effect of chemotherapy. Finally, the outcome of this work is expected improved method of cancer treatment in dogs suffering from tumour of different degrees.

1.4 Hypothesis

This study generally, hypothesed that spherical homogenous monodispersed CS-$CaCO_3$NP-DOX alters the pharmacokinetics of DOX, safely delivered DOX and could improve increase the efficiency of DOX in dogs.

1.5 General Objectives

This study is aimed at evaluating the histological effects and safety of Cockle shell-derived $CaCO_3$ nanoparticle loaded with doxorubicin on dog.

1.5.1 Specific Objectives

i. To synthesis and characterise CS-$CaCO_3$NP for DOX delivery.
ii. To evaluate the *in vitro* kinetics release mechanism, developed and validate bioanalytical method for detection and quantification of CS-$CaCO_3$NP-DOX and determine the pharmacokinetics of free and DOX-loaded CS-$CaCO_3$ nanoparticles in dogs.
iii. To evaluate the histological and safety of free and DOX-loaded CS-$CaCO_3$NP on tissues in healthy dogs.
v. To determine the therapeutic potential of the DOX-loaded CS-$CaCO_3$NP on dogs bearing spontaneous tumour.
vi. To evaluate the histological changes of tumor tissue and selected organs post treatment.

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