Annexure- III

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Synergistic co-loading of vincristine improved chemotherapeutic potential of pegylated liposomal doxorubicin against triple negative breast cancer and non-small cell lung cancer

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Abstract

The current work aims to explore the biological characteristics of vincristine synergistic co-loading into pegylated liposomal doxorubicin in non-indicated modalities of non-small cell lung cancer (NSCLC) and triple negative breast cancer (TNBC). The combinatorial liposome prepared by active co-loading of the drugs against modified ammonium ion gradient exhibited 95% encapsulation of both drugs. The cellular uptake studies using confocal microscopy and flow cytometry showed significantly increased uptake of dual drug formulation as against liposomal doxorubicin. The co-loaded liposome formulation had significantly increased cell cycle arrest in G_2/M phase with subsequent apoptosis and reduced cell viability in both tumor cell lines than doxorubicin liposome. This carrier exhibited similar acute toxicity, pharmacokinetic and tissue distribution profiles with significant increase in tumor regression as compared to liposomal doxorubicin. These results indicate that co-encapsulation of vincristine into clinically used pegylated liposomal doxorubicin significantly improved *in-vitro* and *in-vivo* therapeutic efficacy against NSCLC and TNBC.

Key words: Breast cancer; Doxorubicin; Liposome; Lung cancer; Vincristine

Cancer is characterized by heterogenous proliferation of cells having intrinsic potential to metastasize to major organs. Triple negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC) are aggressive forms of breast and lung cancer whose treatment efficiency is often affected by the metastasis associated with them.[1,2] Additionally, TNBC has been clinically observed to metastasize to secondary NSCLC.[3] The treatment of such cancers includes multiagent-mechanistic treatment approach

Abbreviations: AFM, atomic force microscopy; ANOVA, analysis of variance; *CF*, 5,6-carboxyfluorescein; CPCSEA, Committee for the Purpose of Control and Supervision of Experiments on Animals; cryo-TEM, cryogenic transmission electron microscopy; DOX, doxorubicin hydrochloride; FACS, fluorescence-activated cell sorting; FBS, fetal bovine serum; FESEM, field emission scanning electron microscopy; HPLC, high performance liquid chromatography; IAEC, Institutional Animal Ethics Committee; IC_{50}, inhibitory concentration (50%); MRT, mean residence time; MTD, maximum tolerated dose; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; NCCS, National Centre for Cell Science,; NSCLC, non-small cell lung cancer; QELS, quasi-elastic light scattering; SPIL, Sun Pharmaceutical Industries Limited; SUV, small unilamellar vesicles; %T/C, percentile ratio of test with control; TNBC, triple negative breast cancer; VCR, vincristine sulfate.

Conflict of interest: The authors Saikat Ghosh, Kuntal Maiti, Shubhadeep Banerjee and Subhas Bhowmick are associated with Sun Pharmaceutical Industries Limited. However, all authors and the organization report no conflict of interest. Further, no financial assistance and research grant funding were received for this study.

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Research Article

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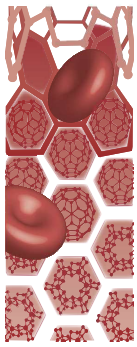

Optimization and efficacy study of synergistic vincristine coloaded liposomal doxorubicin against breast and lung cancer

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Aim: To improve the efficacy of poly-ethylene glycol (PEG)ylated liposomes coloaded with doxorubicin and vincristine against triple-negative breast cancer (TNBC) and non-small-cell lung cancer (NSCLC). **Methods:** The combinatorial index of the drugs was established using the Chou-Talalay method in MDA-MB-231 and A549 cell lines. The most effective ratio was co-encapsulated in factorial design optimized nanoliposomes which were characterized for similarity to clinical standard and evaluated *in-vitro* and *in-vivo* for therapeutic efficacy. **Results & conclusion:** The formulation exhibited more than 95% co-encapsulation, a size of 95.74 ± 2.65 nm and zeta potential of -9.17 ± 1.19 mV while having no significant differences in physicochemical and biochemical characteristics as compared with the clinical standard. Efficacy evaluation studies showed significantly improved cytotoxicity and tumor regression compared with liposomal doxorubicin indicating improvement in efficacy against TNBC and NSCLC.

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Keywords: Chou-Talalay method • combination • doxorubicin • factorial design • liposome • non-small-cell lung cancer • PEGylated • synergism • triple-negative breast cancer • vincristine

Cancer may be defined as the abnormal, uncontrolled growth of cells with the inherent ability to spread to other tissues of the human body, facilitated majorly through the components of the hematic system. One of the current treatment options for cancer involves the use of a cocktail of chemotherapeutic drugs, this allows multiple agents to act through multiple mechanistic pathways on tumor cells [1].

Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer which is more difficult to treat than the hormone sensitive forms of breast cancer and often necessitates the use of combination chemotherapy [2]. Similarly, the adenocarcinoma form of non-small-cell lung cancer (NSCLC) is among the most aggressive forms of lung cancer and requires combination therapy for effective treatment [3]. Two aspects critical for the efficacy of such combination therapies include synergism between the drugs and the use of a suitable carrier system that can ferry the synergistic drug load to the tumor site [4].

The drug doxorubicin in solution dosage form has been widely used in combination therapy of various cancers including NSCLC and TNBC [5]. However, treatment efficacy of the chemotherapeutic agent in these two cancers has been limited due to drug resistance and toxicity [6,7]. Poly-ethylene glycol (PEG)ylated liposomal doxorubicin (Doxil™) as a clinical standard with naive chemotherapeutic agents has been previously tested against the aforementioned cancers but with limited success [8]. Reports suggest that microtubule destabilizing agents have significant tumor cell killing properties in both TNBC and NSCLC. These cell cycle specific mitotic agents have been found to potentiate the action of non-cell cycle specific anthracyclines [9,10]. Combining the drugs doxorubicin hydrochloride (DOX) and vincristine sulphate (VCR) allows action on multiple targets during different

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Review article

Triple negative breast cancer and non-small cell lung cancer: Clinical challenges and nano-formulation approaches

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ABSTRACT

Triple negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC) are amongst the most aggressive forms of solid tumors. TNBC is highlighted by absence of genetic components of progesterone receptor, HER2/neu and estrogen receptor in breast cancer. NSCLC is characterized by integration of malignant carcinoma into respiratory system. Both cancers are associated with poor median and overall survival rates with low progression free survival with high incidences of relapse. These cancers are characterized by tumor heterogeneity, genetic mutations, generation of cancer-stem cells, immune-resistance and chemoresistance. Further, these neoplasms have been reported for tumor cross-talk into second primary cancers for each other. Current chemotherapeutic regimens include usage of multiple agents in tandem to affect tumor cells through multiple mechanisms with various such combinations being clinically tested. However, lack of controlled delivery and effective tempor-ospatial presence of chemotherapeutics has resulted in suboptimal therapeutic response. Consequently, passive targeted albumin bound paclitaxel and PEGylated liposomal doxorubicin have been clinically used and tested with newer drugs for improved therapeutic efficacy in these cancers. Active targeting of nanocarriers against surface overexpressed proteins in both neoplasms have been explored. However, use of single agent nano-particulate formulations against both cancers have failed to elicit desired outcomes. This review aims to identify clinical unmet need in these cancers while establishing a correlation with tested nano-formulation approaches and issues with preclinical to clinical translation. Lipid and polymer-based drug-drug and drug-gene combinatorial nanocarriers delivering multiple chemotherapeutics simultaneously to desired site of action have been detailed. Finally, emerging opportunities such as pharmacological targets (immune check point and epigentic modulators) as well as gene-based modulation (siRNA/CRISPR/Cas9) and the nano-formulation challenges for effective treatment of both cancers have been explored.

1. Introduction

Cancer as a broad cluster of disorders may be defined as the abnormal uncontrolled growth of the cells with inherent ability to spread to other tissues of the human body facilitated majorly through the components of haematic systems. Amongst all cancers affecting the human system, American Cancer Society (ACS) estimates indicate lung cancer and breast cancer to be amongst the most plausible causes of newer cases and deaths for the year 2020 [1]. The basal subtype of breast cancer, Triple negative breast cancer (TNBC) is characterized by the lack of expression of hormonal receptors (estrogen receptor and progesterone receptor) and tyrosine-protein receptor kinase human epidermal growth factor (HER2). This aggressive form is often associated with poor prognosis and lack of effective therapeutic treatments

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Review article

Combinatorial nanocarriers against drug resistance in hematological cancers: Opportunities and emerging strategies

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ABSTRACT

Hematological cancers are a group of malignancies affecting human hematopoietic and lymphoid tissues. Although the patients respond to treatment regimen during initial phases, the hematoma tumor heterogeneity results in the presence of some minimal disease residue thereby exhibiting remission, relapses or refractoriness in disease conditions leading to poor overall survival period. The current therapeutic standard practices involve blending of conventional agents with novel targeting agents or immune-therapeutics in a cocktail to effectively reap the benefits of drugs acting through multiple signaling pathways. Considerable evaluation of the risk benefit ratio on part of clinicians is necessitated to select the best optimum therapy considering the high incidences of drug resistance. This drug resistance may be attributed to faulty upregulation or mutation of multiple drug resistance regulating genes, increased tumor cell immune system cross talk, increased expression of drug efflux pump inducers and inhibition of apoptosis among others. Conventional single drug nanotherapeutics as modulators of drug resistance have already clinically exhibited their potential by passively delivering the active cargo to desired targets in hematological neoplasms. However, with the ever-growing clinical failures of such therapies, the landscape of hematological cancer treatment has seen a plethora of changes in the last few years. The two towering changes in the treatment has been the approval of combinatorial drug nanocarrier Vyxeos™ and chimeric antigen receptor T cell (CAR-T) therapy Kymriah™ as well as Yescarta™. The approval of CAR-T therapy not only resulted in a paradigm shift in the avenues of blood cancer treatment towards personalized approaches but also saddled it with questions of economic viability and effectiveness in the entire spectrum of such neoplasms. Under such conditions, combinatorial drug nanocarriers encompassing synergistic ratios of clinically effective drug combinations affording temporal and spatial control present an exciting approach to overcome these drug resistance modalities. This platform provides increased chances of therapeutic in-vitro in-vivo correlation along with minimization of drug resistance and associated disease relapse conditions. The present review intends to present the current preclinical and clinical advances in combinatorial nanocarrier mediated management of drug resistance in hematological cancers.

1. Introduction

Cancer as a group of diseases may be defined as uncontrolled abnormal proliferation of cells with increasing propensity of infiltration into the various tissues of human body facilitated by hemato-lymphatic circulatory systems (1). Depending on the etiology and affected areas of these malignancies, it is further classified as carcinoma, sarcoma, leukemia, lymphoma, brain tumors or simply as solid tumors and hematological or liquid tumors (2). Hematoma or liquid tumors are cancers associated with hemato-immune system comprising leukemias, lymphomas and myelomas. While leukemia originates from blood-forming tissues such as the bone marrow, lymphoma and multiple myeloma emanates from the cells of the immune system (3,4). According to the 2017 estimates of US Leukemia and Lymphoma society, hematological malignancies accounted for 9–10% of the newly diagnosed cancers in 2016–17, while these cancers accounted for estimated 10% of total cancer deaths. Although the initial five year survival rate varies between 38 and 85%, the multidrug resistance and high incidence of

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Surface engineered liposomal delivery of therapeutics across the blood brain barrier: recent advances, challenges and opportunities

Saikat Ghosh, Rohan Lalani, Vivek Patel, Subhas Bhowmick & Ambikanandan Misra

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CHAPTER

TARGETING APPROACHES USING POLYMERIC NANOCARRIERS 14

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14.1 INTRODUCTION TO POLYMERS AND TARGETING

14.1.1 CURRENT STATE OF THERAPEUTIC REGIMENS

Rapid advancement in medical sciences targeting the advent of human disorders has shifted the drug discovery orientation toward identification of potent targeted drug candidates. Such target-specific approaches involve the identification of the molecular targets overexpressed in the particular disease along with in-depth understanding of the disease etiology, which is being intended for the treatment. Despite extensive research coupled with innovative discovery, translation of the identified potential drug candidates from preclinical to clinical set up is affected primarily through poor bioavailability, lack of target-based efficacy, and drug delivery approaches. Small molecules often suffer from low solubility, poor stability, short circulation time, and nonspecific toxicity limiting their therapeutic efficacy. In addition, the pharmacokinetic profile of the drug candidates makes them more unsuitable for their cospatial and temporal presence at desired loci of action with the presence of suboptimal concentrations insufficient to elicit a therapeutic response. Thus as compared to the usage of naked drug, drug delivery approaches that can deliver the drugs surpassing the various barriers encountered by the drugs in the various diseases are the need of the hour.

Drug delivery approaches through various submicron-sized carriers aim at drug repurposing using biodegradable and biocompatible materials that alter the pharmacodynamic as well as pharmacokinetic profile of each active molecule to tune it to particular needs of disease system. Among such materials that have clinically been proven to be carriers of the drugs, lipids and polymers have proven to be therapeutically efficient. Clinically effective therapies against various diseases include Abraxane (albumin-bound paclitaxel nanoparticle), Doxil (liposomal doxorubicin hydrochloride injection), Ambisome (liposomal amphotericin B), Lupron (Leuprolide depot), and Sandostatin (octreotide acetate depot) exhibit formulations based on carrier systems that have changed the

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Approaches in Barriers, Modifications, Route of Administrations, and Formulations of Therapeutic Agents for Brain Delivery

11

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ORIGINAL ARTICLE

Co-delivery of cisplatin and siRNA through hybrid nanocarrier platform for masking resistance to chemotherapy in lung cancer

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Accepted: 12 October 2020

Abstract

The resistance of cancer cells to chemotherapy has presented a formidable challenge. The current research aims at evaluating whether silencing of the cisplatin efflux promoter gene ABCC3 using siRNA co-loaded with the drug in a nanocarrier improves its efficacy in non-small cell lung cancer (NSCLC). Hybrid nanocarriers (HNCs) comprising lipids and poly(lactic acid-polyethylene glycol) di-block copolymer (PEG-PLA) were prepared for achieving the simultaneous delivery of cisplatin caprylate and ABCC3-siRNA to the cancer cells. PEGylation of the formulated HNCs was carried out using post-insertion technique for imparting long circulation characteristics to the carrier. The optimized formulation exhibited an entrapment efficiency of 71.9 ± 2.2% and 95.83 ± 0.39% for cisplatin caprylate and siRNA respectively. Further, the HNC was found to have hydrodynamic diameter of 153.2 ± 1.76 nm and + 25.39 ± 0.49 mV zeta potential. Morphological evaluation using cryo transmission electron microscopy confirmed the presence of lipid bilayer surrounding the polymeric core in HNCs. The *in vitro* cellular uptake studies showed improved uptake, while cell viability studies of the co-loaded formulation in A549 cell-line indicated significantly improved cytotoxic potential when compared with drug solution and drug-loaded HNCs; cell cycle analysis indicated increased percentage of cell arrest in G2-M phase compared with drug-loaded HNCs. Further, the gene knock-down study showed that silencing of ABCC3 mRNA might be improved *in vitro* efficacy of the formulation. The optimized cisplatin and ABCC3 siRNA co-loaded formulation presented significantly increased half-life and tumour regression in A549 xenograft model in BALB/c nude mice. In conclusion, siRNA co-loaded formulation presented reduced drug resistance and increased efficacy, which might be promising for the current cisplatin-based treatments in NSCLC.

Keywords Cisplatin · Lung cancer · Nanocarrier · Resistance · Simultaneous · siRNA

Abbreviations

HNCs	Hybrid nanocarriers
CCL-HNCs	Cisplatin caprylate-loaded HNCs
CCL-p-HNCs	PEGylated CCL-HNCs
rCCL-p-HNCs	SiRNA complexed CCL-p-HNCs
ncr	FITC-labelled negative control siRNA (FITC-NC-siRNA)
ncrL2K	FITC-labelled negative control siRNA complexed with lipofectamine 2000
ncrCCL-p-HNCs	FITC-labelled negative control siRNA complexed CCL-p-HNCs

Introduction

Lung cancer has been the leading cause for cancer death, making up 25% of all cancer related deaths. The treatment regimen for metastatic forms of non-small cell lung cancer (NSCLC) includes intravenous administration of chemotherapeutic agents in combination with either another chemotherapeutic agent or radiation [1, 2]. However, delivery of these agents is nonselective and has led to toxicity to unintended organs. Additionally, the efficacy of these treatments has been reduced due to emergence of drug resistance. Drug resistance has been associated with decreased effectiveness

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Review Article

Theme: Lipid-Based Drug Delivery Strategies for Oral Drug Delivery
Guest Editor: Sanyog Jain

Lipid-Based Oral Formulation Strategies for Lipophilic Drugs

Vivek Patel,[1] Rohan Lalani,[1] Denish Bardoliwala,[1] Saikat Ghosh,[1] and Ambikanandan Misra[1,2]

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Abstract. Partition coefficient (log *P*) is a key physicochemical characteristic of lipophilic drugs which plays a significant role in formulation development for oral administration. Lipid-based formulation strategies can increase lymphatic transport of these drugs and can enhance bioavailability many folds. The number of lipophilic drugs in pharmacopoeias and under discovery are continuously increasing and making the job of the formulation scientist difficult to develop suitable formulation of these drugs due to potent nature and water insolubility of these drugs. Recently, many natural and synthetic lipids are appearing in the market which are helpful in the development of lipid-based formulations of these types of drugs having enhanced solubility and bioavailability. One such reason for this enhanced bioavailability is the accessibility of the lymphatic transport as well as avoidance of first-pass effect. This review discusses the impact of lipophilicity in enhancing the intestinal lymphatic drug transport thereby reducing first-pass metabolism. The most appropriate strategy for developing a lipid-based formulation depending upon the degree of lipophilicity has been critically discussed and provides information on how to develop optimum formulation. Various formulation strategies are discussed in-depth by classifying lipid-based oral drug delivery systems with case studies of few marketed formulations with challenges and opportunities for the future of the formulations.

KEY WORDS: oral lipid delivery; lymphatic system; lipophilicity; formulation; lipid system; triglycerides.

INTRODUCTION

The need for a preferred delivery of therapeutics *via* the oral routes arises from the fact that this route is patient friendly and the easiest one for self-administration. However, the delivery of therapeutics orally is constantly challenged by the physicochemical properties of drug molecules that display poor solubility, extreme first-pass metabolism, and instability in the gastrointestinal tract (GIT). Also, the chances of dose dumping and inter- and intrasubject variability challenge their quaint success (1). Of the new molecules discovered or being invented through drug discovery and screening pathways that have therapeutic effect, most of them are potent and are lipophilic in nature (2,3). This hydrophobic nature limits the dissolution and absorption of the drug and limits the bioavailability for achieving therapeutic benefits by the oral route. Research in improving the solubility for drug molecules has been addressed by using many techniques such as physical modifications (micronization/nanonization, nanocrystal, solid dispersion), chemical modifications (salt formation or prodrug formation), solubilization (use of wetting agents, co-solvents or pH adjustment), carrier system approach (complexation, microemulsion, liposomes), *etc.* Such techniques have paved the way for increasing the oral product portfolio for lipophilic molecules (4,5).

In the past decade, much of the attention is gained in the research related to the use of lipids and lipophilic excipients in delivery by the oral route (6,7). This is based on the empirical findings of their advantageous effects on the absorption profile of lipophiles following concurrent administration with lipids and postprandial changes in physicochemical and physiological state in the GIT (8,9). This approach has also been extended to include hydrophilic drugs for tweaking the solubilization effect in the GIT for achieving pharmaceutical benefits (10–13).

Lipids play a diverse role in the cellular and developmental functions of the body as well as a physiological role in the functioning of cells. They are ubiquitously present in the entire body and form a part of normal diet in human population (14). Lipids have also been known to play a diverse role in the absorption of medications from the GIT. As it is known, in most of the cases, there are wide alterations in postprandial

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Therapeutic Delivery

Nanocarriers in effective pulmonary delivery of siRNA: current approaches and challenges

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Research on siRNA is increasing due to its wide applicability as a therapeutic agent in irreversible medical conditions. siRNA inhibits expression of the specific gene after its delivery from formulation to cytosol region of a cell. RNAi (RNA interference) is a mechanism by which siRNA is silencing gene expression for a particular disease. Numerous studies revealed that naked siRNA delivery is not preferred due to instability and poor pharmacokinetic performance. Nanocarrier-based delivery of siRNA has the advantage to overcome physiological barriers and protect the integrity of siRNA from degradation by RNAase. Various diseases like lung cancer, cystic fibrosis, asthma, etc, can be treated effectively by local lung delivery. The selective targeted therapeutic action in diseased organ and least off targeted cytotoxicity are the key benefits of pulmonary delivery. The current review highlights recent developments in pulmonary delivery of siRNA with novel nanosized formulation approach with the proven *in vitro*/*in vivo* applications.

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Keywords: hybrid formulations • inorganic nanocarriers • lipid-based formulations • polymer-based formulation • pulmonary delivery • siRNA

Introduction to pulmonary delivery of siRNA

This review presents a critical analysis of available literature for pulmonary administration of siRNA. Analysis on such a topic is important to compare feasibility of different routes for administration, different formulations and formulation parameters for better targeting. This review aims to play an important role in defining safe and effective pulmonary delivery of siRNA and provides cumulative data for future research. RNAi interference is a biological mechanism by which a small dsRNA directs the degradation of complementary mRNA and executes sequence-specific inhibition of a particular gene [1]. Many diseases are targeted by post-transcriptional silencing specific gene expression inhibition. These mechanisms were discovered and published officially in *Nature* in 1998, but it gained momentum when Andrew Fire and Craig Mello received the Nobel prize in physiology or medicine in 2006 [2]. They investigated the RNAi phenomenon during their experiments of gene expression regulation in the nematode worm *Caenorhabditis elegans*. They discovered that dsRNA has the capacity to silence a particular gene whose code is similar to that of the injected RNA molecule and it is a catalytic process which can also be inherited. DsRNA binds to a protein complex, dicer, which cleaves it into smaller fragments. After that, the RNA-induced silencing complex (RISC) binds to the dicer and one strand of RNA is eliminated. The other is still bound to RISC serving as a probe to identify mRNA molecules. RISC is linked to the mRNA strand by a base pairing, thereby cleaving and destroying the mRNA strand and directs specific protein synthesis inhibition [1].

The simple synthesis of siRNA makes RNAi technology fast and an efficient tool. This is because there is no requirement of cellular expression system, upstream and downstream protein purification related steps and sequences can be designed from sense and antisense strand analysis of target-related specific knockdown of the gene of interest [3]. The delivery of siRNA is an easy and efficient process compared with shRNA plasmid or pDNA delivery. This is because the site of action for siRNA is cytosol, whereas shRNA plasmids and pDNA have to enter the nucleus for its action [4]. The intravitreal delivery of VEGF targeted siRNA in age-related macular degeneration (AMD) gained success and entered the first clinical trial of RNAi technology in 2004 [5]. Nucleic acids like DNA and antisense oligonucleotides have been used as therapeutics for a long time, but nuclease induced degradation

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Research Article

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Therapeutic Delivery

Development of a dry powder for inhalation of nanoparticles codelivering cisplatin and *ABCC3* siRNA in lung cancer

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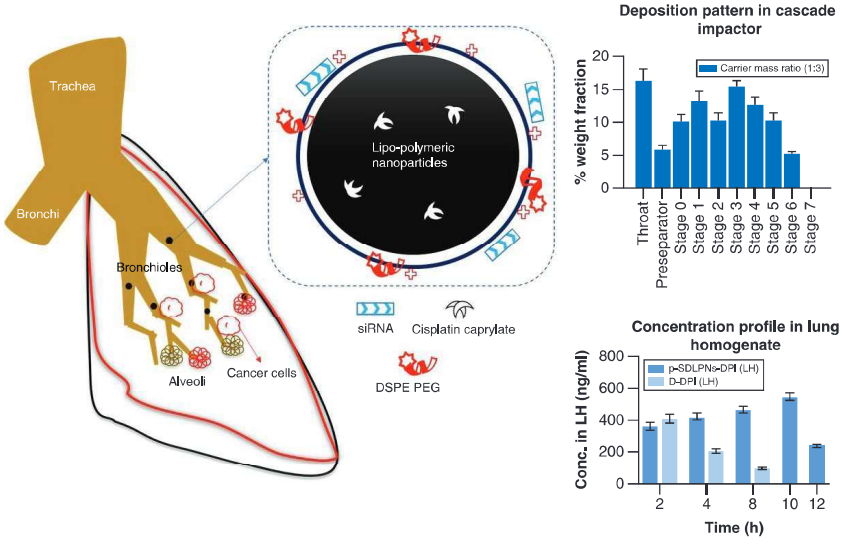
Background: The current study sought to formulate a dry powder inhalant (DPI) for pulmonary delivery of lipopolymeric nanoparticles (LPNs) consisting of cisplatin and siRNA for multidrug-resistant lung cancer. siRNA against ABCC3 gene was used to silence drug efflux promoter. **Results & discussion:** The formulation was optimized through the quality by design system by nanoparticle size and cisplatin entrapment. The lipid concentration, polymer concentration and lipid molar ratio were selected as variables. The DPI was characterized by *in vitro* deposition study using the Anderson cascade impactor. DPI formulation showed improved pulmonary pharmacokinetic parameters of cisplatin with higher residence time in lungs. **Conclusion:** Local delivery of siRNA and cisplatin to the lung tissue resulted into an enhanced therapeutic effectiveness in combating drug resistance.

Graphical abstract:



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Keywords: chemosensitization • cisplatin • Cryo-TEM • DPI • gene knockdown • lung cancer • MTT assay • PEG-PLA • RT-PCR • siRNA

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Review

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Therapeutic Delivery

Formulation and clinical perspectives of inhalation-based nanocarrier delivery: a new archetype in lung cancer treatment

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Despite tremendous research in targeted delivery and specific molecular inhibitors (gene delivery), cytotoxic drug delivery through inhalation has been seen as a core part in the treatment of the lung cancer. Inhalation delivery provides a high dose of the drug directly to the lungs without affecting other body organs, increasing the therapeutic ratio. This article reviews the research performed over the last several decades regarding inhalation delivery of various cancer therapeutics for the treatment of lung cancer. Nevertheless, pulmonary administration of nanocarrier-based cancer therapeutics for lung cancer therapy is still in its infancy and faces greater than expected challenges. This article focuses on the current inhalable nanocarrier-based drugs for lung cancer treatment.

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Keywords: dry powder inhalation • formulation perspectives • inhalation delivery • lung cancer • nanocarriers

The American Cancer Society estimates for lung cancer in the USA indicate an alarming number of new cases (228,820) with 135,720 deaths occurring in 2020 [1]. Lung cancer has been reported to be responsible for approximately 25% of cancer-related deaths, and the possibility of delayed detection combined with minimal survival rates may be responsible for its extraordinary fatality rate. Non-small-cell lung cancer (NSCLC) and small cell lung cancer are the major forms of this carcinoma and are based in components of the respiratory system and neuroendocrine system/neurofilaments, respectively [2]. Both forms of lung carcinoma have been reported to be aggressive, with increased potential for lymphatic system-based metastasis and variable chemotherapeutic response, leading to a low median survival time of 5.8 months for small cell lung cancer and 8.0 months for NSCLC [3].

Conventional chemotherapeutic options in lung cancer include the use of platins, taxanes, anthracyclines and antimetabolites. Immunotherapy involves agents blocking the downstream functions of CTLA4, PD-1 and PDL-1 [4]. Consequently, fixed-dose combinations of carboplatin and paclitaxel or cisplatin and gemcitabine are first-line therapies in the treatment of nonadvanced, metastatic and advanced stages of lung cancer. Although such fixed-dose combination therapies provide better control and an improved therapeutic index against heterogeneous tumor load, these therapies have often been associated with unintended toxicities, even leading to death [5]. Additionally, these regimens include the use of systemic delivery of highly lipophilic agents, which requires the use of increased drug doses along with surfactant solubilization approaches for delivery of therapeutics to the intended sites of action [6].

Nontargeted, naive systemic delivery often leads to adverse effects in the normal tissues along with an inefficient drug load for therapeutic outcomes [7]. Consequently, current therapeutic regimens offer low overall survival rates along with a poor quality of life. Passively targeted, clinically tested nanotherapeutics (Doxil™, Onivyde™ and Lipoplatin™) (USA) have shown limited efficacy, whereas Abraxane™ (Bristol-Myers Squibb, USA), which is indicated for locally advanced lung cancer, demonstrates mixed results. Although biological ligand-based, active targeting nanoparticle approaches (peptides, polysaccharides, proteins, aptamers) present suitable alternatives for modulating the issue of localization to lung tumor tissues, these approaches may lead to localization at other

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