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Formulation And Ex-Vivo Evaluation Of Mannose Conjugated Nanostructured Lipid Carriers (M-Nlcs) For HOP-62 Lung Carcinoma Cell Targeting

Mannose Conjugated Nanostructured Lipid Carriers (M-NLCs) for HOP-62 Lung Carcinoma Targeting

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Abstract: The present study focuses on the formulation and ex-vivo evaluation of mannose-conjugated nanostructured lipid carriers (M-NLCs) for targeted delivery of Paclitaxel to HOP-62 lung carcinoma cells. Paclitaxel-loaded NLCs (P-NLCs) were prepared using the solvent injection method, optimizing key formulation parameters to achieve nanosized particles with high drug entrapment. Characterization via SEM, TEM, and laser light scattering confirmed uniform morphology, particle size (~254 ± 2.3 nm), polydispersity index (0.319), and zeta potential. Mannose conjugation was achieved through Schiff's base formation, validated by FT-IR spectroscopy. Drug entrapment efficiency reached 79.4 ± 1.6%. Cytotoxicity was assessed using SRB assay across a concentration range of 0.05–0.5 µg/mL. M-NLCs demonstrated superior dose-dependent cell growth inhibition compared to P-NLCs and free Paclitaxel, attributed to receptor-mediated targeting. Statistically significant differences in IC50 values ($p < 0.05$) highlight the enhanced therapeutic potential of mannose-functionalized NLCs. These findings suggest that M-NLCs offer a promising strategy for targeted lung cancer therapy with improved efficacy and reduced systemic toxicity.

Index Terms**:** *Paclitaxel, NLCs, HOP-62, SRB, Lung Cancer*

I. INTRODUCTION

INTRODUCTION

Cancer is a growing worldwide concern and is a serious public health issue [1]. It is a disease that is both complex and vastly heterogeneous in nature characterized by progressive and uncontrolled cellular division. Cancer is considered to be the leading reason for death worldwide, causing 15 million new cases and 8.2 million deaths each year [2]. Cancer is considered a complex disease associated with some genetic mutations, deletions, epigenetic alterations and chromosomal translocations that are involved in cancer initiation, promotion, metastasis and drug resistance [3]. The rapidly expanding tumor vasculature often has a discontinuous endothelium, with gaps between the cells that may be several hundred nanometers large. Physiological barriers at the tumor level (i.e., poorly vascularized tumor regions, acidic environment, high interstitial pressure and low microvascular pressure) as well as at the cellular level (i.e., altered activity of specific enzyme, altered apoptosis regulation and transport-based mechanisms) and in the body (i.e., distribution, biotransformation and clearance of anticancer agent) must be overcome to deliver anticancer agents to tumor cells. Lung cancer is the leading cause of cancer death worldwide (20.6% of all cancer deaths),

and non-small cell lung cancer (NSCLC) accounts for 80% of cases of lung cancer [4]. Lung cancer is characterized by uncontrolled growth of cells in tissue/cells in lungs. Thereby, the cancer cells spread to nearby tissues or cells through metastasis, which is invasion of adjacent tissue and infiltration beyond the lungs [5]. The vast majority of primary lung cancers are carcinomas of the lung, derived from epithelial cells. Lung cancer is classified into small-cell lung cancer (13%) and non-small-cell lung cancer (NSCLC) (87%) according to the therapeutic purpose. Surgical resection is still the main treatment for early-stage NSCLC [6]. Unfortunately, the majority of lung cancers are diagnosed at an advanced stage [7]. For advanced NSCLC, chemotherapy is currently the standard first-line treatment. The symptoms associated with NSCLC includes cough, chest pain, shortness of breath, coughing up blood, wheezing, hoarseness, recurring infections such as bronchitis and pneumonia, weight loss, loss of appetite and unusual fatigue [8].

Cancer is the second most common cause of death in the developed world. Cancer occurs due to abnormal growth of cells and can invade into normal tissue or organ and spread to other parts of the body. Conventional modes of administration have limited utility
because anticancer drugs in such systems lack efficient selectivity towards melanoma cells. This not only precipitates toxicity, but also there is considerable loss of dose before reaching the desired site [9]. The site-specific delivery of drugs to the target sites has the potential to reduce the side effects and to increase pharmaceutical response. Nano-size carrier systems are extensively used as targeted drug delivery system for efficient management of several disorders and diseases. The various systems including liposomes,
solid lipid nanoparticles, functionalized nanoparticles, dendrimer, mixed micelles have been worked extensively for their targeting potential. Nanocarrier offers an opportunity in this direction [10].

Another strategy is the passive targeting that relies on the well-known enhanced permeation and retention (EPR) effect. The effect first described by Maeda and Bhadra takes advantage of poorly formed (leaky) vasculature of solid tumors that allows selective accumulation of polymer-drug conjugates/complexes ranging in size between 10 to 500 nm within tumors when compared to that of free drugs [11]. The polymeric molecules are retained following the accumulation due to their larger size whereas free drug molecules are easily eliminated from the cells. Nanocarrier has an advantage for this strategy as well because drugs can be physically encapsulated into the interior of nanometer sized nanocarrier thereby increasing the uptake of drugs into tumors [12]. In the present thesis work, it is proposed to design and develop Nanostructured Lipid carriers (NLCs) conjugated with mannose bearing Paclitaxel to target the drug directly to the tumor cells (Lung Cancer), to minimize its side effects and maximize drug utilization [13].

II. NEED OF THE STUDY

The formulation and ex-vivo evaluation of mannose-conjugated nanostructured lipid carriers (M-NLCs) for HOP-62 lung carcinoma cell targeting is a vital step toward improving the precision and efficacy of lung cancer treatment. Lung carcinoma remains one of the leading causes of cancer-related mortality, and conventional therapies often suffer from poor selectivity and systemic toxicity [14]. By leveraging the overexpression of mannose receptors on cancer cells and macrophages, mannose-functionalized NLCs offer a promising strategy for receptor-mediated drug delivery. Nanostructured lipid carriers provide enhanced drug loading, stability, and controlled release, while their nanoscale size facilitates deep tissue penetration [15]. The *ex-vivo* evaluation using HOP-62 cells allows for early assessment of cellular uptake, cytotoxicity, and targeting efficiency, helping optimize the formulation before in vivo studies. This approach not only enhances therapeutic outcomes but also minimizes off-target effects, paving the way for safer and more effective lung cancer therapies [16]. Mannose was selected as the ligand for the proposed system, which was appended to the nano-carrier carrying drug and hence the overall system was targeted to the desired site of action i.e., tumor and thus proving out to be a very effective strategy for the management of cancer. This system is proposed to enhance drug delivery to cancer cells and reduce the dose as well as toxicity related to the anticancer drug [17].

III. MATERIAL AND METHODS

Preparation of Nanostructured Lipid Carriers

The Nanostructured Lipid Carriers were prepared by Ethanol Injection Method (Stevens et al., 2004, Gupta et al., 2007a) with little modifications. Briefly, Soya PC, Tristearin, stearyl-amine and DSPE was dissolved in ethanol at a concentration of 10 mg/ml, then drug 10 mg was added and injected into stirred solution at 4000 rpm for 2 hrs. of aqueous phase contain 0.5% w/v of Poloxamer-188. Both aqueous phase and lipid solution were pre warmed to and kept at 70˚C during the mixing [18]. The preformed lipid suspension is then further sonicated for 5 min using a probe-sonicator to form NLCs. The nanostructured lipid carriers were then

concentrated by centrifugation at 5000 rpm for 10 minute and resuspended in phosphate buffer saline (pH 7.4) [19]

Preparation of Mannose Conjugated Nanostructured Lipid Carrier

Mannose (CDH, India) coating was done by ring opening reaction followed by reaction of aldehyde group of mannose in Sodium acetate buffer (pH 4.0). This leads to the formation of Schiff's base, which may then get reduced to secondary amine and remain in equilibrium with Schiff's base [20].

Characterization

Particle Size Determination

For the determination of average particle size and polydispersity index of the NLCs photon correlation spectroscopy using a Zeta-sizer (DTS Ver. 4.10, Malvern Instruments, England) was used. The formulations were diluted with 1:9 (%v/v) deionized water. The particle size distribution is represented by the average size and polydispersity of the Gaussian distribution function in logarithmic axis mode [21].

Surface Charge Measurement

The zeta potential of the nanoparticles was determined by laser Doppler anemometry using a Malvern Zeta-sizer also called Doppler Electrophoretic Light Scatter Analyzer. The instrument is a laser-based multiple angle particle electrophoresis analyzer. Using Doppler frequency shifts in the dynamic light scattering from particles, the instrument measures the electrophoretic mobility (or zeta potential) distribution together with the hydrodynamic size of particles (size range 10 to 30 μm) in liquid suspensions by photon correlation spectroscopy measurements [22].

Particle Morphology

Transmission electron microscope (TEM) was used as a visualizing aid for studying the particle morphology. The sample (10μL) was placed on the grid and allowed to stand at room temperature for 90 sec. Excess fluid was removed by touching the edge with filter paper. The samples were examined under a transmission electron microscope (Philips Morgagni 268, Eindhoven, Netherlands) at an acceleration voltage of 100 kV, and photomicrographs were taken at suitable magnification [23].

Estimation of Drug Entrapment

Drug entrapment of the anticancer drug paclitaxel in NLCs was determined by using Sephadex mini column. To prepare Sephadex mini column, firstly 1 gm of Sephadex G-50 was allowed to swell in 0.9% NaCl aqueous solution for 8 hrs. and then the hydrated gel was filled in the barrel of 2 ml disposable syringe plugged with filter pad. The barrel was centrifuged at 2000 rpm for 2 minutes to remove excess of saline solution to form the Sephadex separating column. To separate free drug from NLCs formulation 0.2 ml of NLCs dispersion was applied drop wise on the top of the Sephadex column and then centrifuged at 2000 rpm for 2 min. to expel and remove void volume containing NLCs in to the centrifuged tubes. This eluted NLCs dispersion was collected and lysed by disrupting with 5% Triton-X100 and then the amount of entrapped drug was analyzed using spectrophotometric method. The amount of drug entrapped in mannose conjugated NLCs was determined employing similar procedure as reported for paclitaxel loaded solid lipid nanoparticles [24].

***In-vitro* drug release**

The *In-vitro* drug release of entrapped paclitaxel from NLCs formulation was determined using dialysis tube. The NLCs formulation was first separated from free drug by passing through Sephadex column and then centrifugation. Separated NLCs formulation (5ml) was taken in to the dialysis tube (molecular weight cut off 12,000 Da, Hi Media, India) and placed in a beaker containing 50 ml of PBS (pH 7.4) [25]. The beaker was placed over a magnetic stirrer and the temperature was maintained at 37±2˚C throughout the procedure. Samples were withdrawn at definite time intervals and replaced with same volume of phosphate buffer. It was then spectrophotometrically analyzed for drug content by measuring absorbance at 237.0 nm against blank [26].

***In-vitro* cell line studies**

The purpose of a targeted drug delivery system is to deliver the drug at the desired site. The developed NLCs formulations were evaluated for their toxicity, storage conditions, leakage and drug release and were found to be stable enough with desired drug release profile, for further evaluation in-vitro cell line study [27]. However, developed formulations were designed to target drugs to tumor. In the present section in-vitro assessment of the formulations was performed to ascertain cytotoxicity and cellular uptake against cancer cell line (HOP-62). However, prior to in-vivo studies, the formulations should be evaluated for their efficacy through ex-vivo by checking for various interactions [28]. Hence the ex-vivo studies were taken up prior to direct in-vivo efficacy studies in animals and were performed in a view to explore the target ability of the prepared formulation against human adenocarcinoma cell line HOP-62. Cell line studies were performed in a view to explore the target ability of the prepared formulations against cancer cell lines. HOP-62, a human adenocarcinoma cell line, was selected for the study as it over expresses mannose receptors. Two different studies cell inhibition cytotoxicity assay [29] and cell uptake assay were performed to assess the target ability of the formulations. Choosing a cell viability or cytotoxicity assay from amongst the many different options available can be a challenging task. Picking the best assay format to suit particular needs requires an understanding of what each assay is measuring as an endpoint, of how the measurement correlates with cell viability, and of what the limitation of the assay chemistries are. Specific project goals or the drug target that is being investigated often dictates the species of origin and cell types used in cytotoxicity studies. Regardless of the model system chosen, establishing a consistent and reproducible procedure for setting up assay plates is important. The number of cells per well and the equilibration period prior to the assay may affect cellular physiology [30]. Maintenance and handling of stock culture at each step of manufacturing process should be standardized and validated for consistency. Assay responsive to test compounds can be influenced by many subtle factors including culture medium surface-to-volume ratio, gas exchange, evaporation of liquids and edge effects. Human Adenocarcinoma cell (HOP-62) was selected for the analysis as it has been investigated several times in number of studies and this was the reason for selection of HOP-62 cell line for the present studies [31].

IV. RESULTS AND DISCUSSION

The P-NLCs with drug loaded were prepared by solvent injection method, which involves the solvent across the solvent-lipid phase into the aqueous phase by rapid diffusion. All weighed ingredients such as Tristearin, DSPE, Soya PC, stearyl-amine and drug were dissolved in ethanol, it maintained an elevated temperature of 70°C. Then this solution was injected into an aqueous solution maintained at the similar temperature (70˚C) and kept for 2 hrs. under continuous stirring formed the lipid suspension, then suspension was sonicated, and Nanostructured Lipid Carrier was prepared. To optimized the prepared formulation for various parameters like lipid/ lecithin, drug-lipid ratio, surfactant ratio, stirring time, stirring speed and sonication time to obtain nanosized NLCs with maximum drug entrapment. P-NLCs formulation was characterized on the basis of surface morphology, particle size, polydispersity index and zeta potential. Surface morphology of the particles was studied by SEM and TEM analysis [32]. Particle size, polydispersity index and zeta potential studies were carried out by Laser Light Scattering technique (Malvern Instrument U.K). Paclitaxel loaded Nanostructured Lipid Carrier was confirmed by IR spectroscopy as it is showing peaks i.e. C=O stretching at 1737.6 cm^{-1} and strong O-H stretching of alcohol at 3509.8 cm^{-1}. Drug entrapment was determined using Sephadex G50 column. Keeping all optimization parameters under consideration, entrapment was found to be optimum in the selected formulation. Mannose conjugation was carried out by coupling amine group present on the surface of NLCs. Broad intense O-H stretch and C-O stretch of mannose around 3509.8 cm^{-1} and 1073.3 cm^{-1} respectively and N-H deformation of secondary amine at 3245.7 cm^{-1} confirmed the Schiff's base formation (Fig. 1) and some amine formation in the linkage between aldehyde of mannose and amine termination groups of NLCs [33]. The average particle size of the M- NLCs was found to be 254±2.3 nm with a PDI of 0.319. The drug entrapment efficiency of M-NLCs was measured to be 79.4±1.6%.

Cancer Cell Inhibition assay

To evaluate the cytotoxic efficacy of Paclitaxel and its nano-formulations, P-NLCs and M-NLCs, a standard SRB assay was performed across a concentration range of 0.05–0.5 µg/ml. The percentage of cell growth inhibition was measured and analyzed to determine the dose-dependent response of each formulation. All three formulations exhibited a progressive increase in cell growth inhibition with rising concentrations, indicating a clear dose-dependent cytotoxic effect. M-NLCs consistently demonstrated the highest inhibition at each concentration, followed by P-NLCs and free Paclitaxel. Higher percent cell growth inhibition was observed with formulation M-NLCs as compared to P-NLCs and Paclitaxel [34]. M-NLCs displayed highest

percent cell growth inhibition among Paclitaxel based formulations (P-NLCs). The difference between IC_{50} values of P-NLCs and FC-NLCs were found to be statistically significant ($p<0.05$).

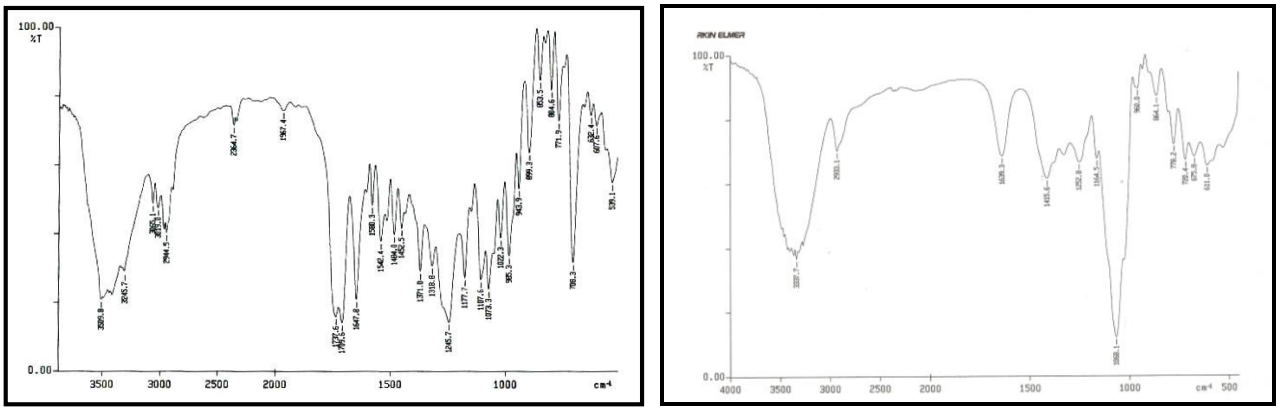

Fig. 1: (a) FT-IR of M-NLCs (b) Mannose

Table 1: *In-vitro* cytotoxicity of Paclitaxel and NLCs formulations on HOP-62 cell line

Concentration (µg/ml)	Percent Cell Growth Inhibition (µg/mL, SRB Assay)		
	Paclitaxel	P-NLCs	M-NLCs
10	44.4	41.6	36.0
20	42.0	40.3	34.9
40	39.8	37.4	31.8
80	36.6	33.2	28.2

Values represent mean ± SD (n=3); P-NLCs: Paclitaxel loaded nanostructured lipid carrier; M-NLCs- Mannose conjugated paclitaxel loaded nanostructured lipid carrier

The observations clearly indicated that the M-NLCs exhibited higher cell inhibition compared to plain NLCs. At 80 µg/mL concentration P-NLCs showed 33.2% percent cell growth inhibition while this percentage was 28.2 in case of M-NLCs, at similar concentration. While at same concentration paclitaxel has shown 36.6% percent cell growth inhibition (Table 1).

Cancer Cell Inhibition Assay

HOP-62 cells were treated with six equivalent doses ranging from 10 to 80 µg/mL. The result of the cell inhibition assay exhibited significant differences with paclitaxel and NLCs formulations. M-NLCs exhibited highest percent cell growth inhibition compared to P-NLCs formulations as well as drug itself. However, all the formulations showed dose-dependent inhibition of HOP-62 carcinoma cells. Higher uptake in case of the M-NLCs was possibly due to the receptor specific targeting of NLCs due to surface conjugation with folic acid. The difference between IC_{50} values of P-NLCs and M-NLCs were found to be statistically significant ($p<0.05$). The observations clearly indicated that the M-NLCs exhibited higher cell inhibition compared to P-NLCs. At 0.5µg/ml concentration M-NLCs has showed 28.2 percent cytotoxicity while 33.2% and 36.6% in case of P-NLCs and Paclitaxel respectively, at 80 µg/ml concentration. These findings underscore the therapeutic potential of nanostructured lipid carriers, particularly when functionalized with targeting ligands such as folic acid. The observed reduction in effective dose not only enhances anticancer efficacy but may also mitigate systemic toxicity, a critical consideration in chemotherapeutic regimens.

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