NOVEL APPROACHES FOR NIOSOMAL DRUG DELIVERY IN CANCER CHEMOTHERAPY

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1. INTRODUCTION

Today the challenge to drug delivery scientists is to work and investigate to deliver the drug using promising drug carriers including biodegradable polymers. The systems that are capable of releasing the therapeutic agents by well defined kinetics are available at present. But in many cases these don't yet represent the ultimate therapy to needs of recipient. Hence attention should also be focused to fabricate controlled, modulated drug delivery system that are capable of receiving the physiological feedback information and adjusting the drug output and system that are capable of precisely targeting the specific tissue or cells.

Novel drug delivery provides either sustained drug action at a predetermined rate or by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

Niosomes as Nanocarrier Systems

Niosomes are non ionic surfactant vesicles which can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in vesicular membrane made of lipid materials. Niosomes are either unilamellar or multilamellar vesicles that have a better stability than liposomes.

Advantages of Niosomes: -

1. Reduction of toxicity and occurrence of adverse reactions.
2. Better drug utilization and controlled rate of drug release.
3. Specific site of drug release & enhancement of therapeutic effectiveness of drug.
4. Nontoxic and biodegradable.
5. Greater patient convenience and /or better patient compliance.

TYPES OF NIOSOMES

The niosomes have been classified as a function of the number of bilayer or as a function of size. The various type of niosomes are follows.

According to the nature of lamellarity

* Multilamellar vesicles (MLV) 1-5 μm in size.
* Large unilamellar vesicles (LUV) 0.1 – 1 μm in size
* Small unilamellar vesicles (SUV) 25 – 500 nm in size.

APPLICATIONS OF NIOSOMES

Niosomal drug delivery is potentially applicable to many pharmacological agent for their action against diseases. Some of its therapeutic applications as follow.

- **Targeting of bioactive agents**

a. To Reticulo endothelial system

The vesicles are preferentially taken up by the cells of reticulo endothelial system. The up take of niosomes by the cells is also by circulating serum factors known as opsonins. It is used in treatment of animal tumors in liver, spleen and in parasitic infestation of the liver.

b. To organ other than reticulo endothelial system

Immunoglobulins bind readily to the lipid surface which offering a sites specific targeting of drug carrier. Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants which can be useful for targeting carrier system to particular cells.

- **Neoplasia**

Doxorubicin, the antracycline antibiotic with broad spectrum antitumor activity drug as niosomal formulation to mice bearing S-180 tumour increased their life span and decreased the rate of proliferation of sarcoma. Doxorubicin Niosomes showed rapid distribution of drug and attainment of equilibrium in liver and heart tissue after intravenous injection with slow phase plasma drug clearance.

- **Leishmaniasis**

Leishmaniasis is a parasitic disease which invades cells of liver and spleen. The commonly used drugs are antimonials which related to arsenic and at high concentration cause damage to heart, liver and kidney. Encapsulation of such drug in niosomes which target the drug to effected organ, reduce the toxicity and dose needed to treat the infections.

- **Delivery of peptide drugs**

Oral delivery of 9-Desglycinamide, 8-Arginine Vasopressin entrapped in niosomes in an in-vitro intestinal loop model and reported stability of peptide increased significantly.

- **Immunological application of niosomes**

Niosomes have been used for studying the nature of immune response produced by antigens.

- **Niosomes as carrier for hemoglobin**

Niosomes can be used as a carrier for hemoglobin.

- **Transdermal delivery of drugs by niosomes**

Encapsulation of drug in niosomes can prolong the drug action, enhance penetration in to target tissue and reduce the toxicity.

- **Other applications**

a. Niosomes as sustained release dosage form:-

The sustained release action of niosomes could be applied to drugs with low therapeutic index and low water solubility, so that it can be maintained in the circulation through encapsulation.

b. Niosomes for localized drug action

Localization of drug action result in enhancement of efficacy or potency of the drug and reduces systemic toxic effects.

Niosomes and their role in cancer chemotherapy: -

Cancer (medical term: malignant neoplasm) is a class of diseases in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood). The branch of medicine concerned with the study, diagnosis, treatment, and prevention of cancer is oncology.

Cancer may affect people at all ages, even fetuses, but the risk for most varieties increases with age. Cancer causes about 13% of all human deaths. Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents. Other cancer-promoting genetic abnormalities may be randomly acquired through errors in DNA replication, or are inherited, and thus present in all cells from birth. The heritability of cancers is usually affected by complex interactions between carcinogens and the host's genome. New aspects of the genetics of cancer pathogenesis, such as DNA methylation and microRNAs are increasingly recognized as important.

Niosomal drug delivery system perhaps an useful strategy towards targeted drug delivery in cancer chemotherapy. The potential for niosomes in cancer drug delivery is infinite with novel applications constantly being explored. Niosomes play a very significant role in cancer drug delivery. In the past, cancer patients were using various anticancer drug formulations, but they were less successful and had major side effects. Niosomes have attracted the attention of scientists.

Chemotherapy

The term "chemotherapy" usually refers to cytotoxic drugs which affect rapidly dividing cells in general, in contrast with targeted therapy. Chemotherapy drugs interfere with cell division in various possible ways, e.g. with the duplication of DNA or the separation of newly formed chromosomes. Most forms of chemotherapy target all rapidly dividing cells and The treatment of some leukaemias and lymphomas requires the use of high-dose chemotherapy, and total body irradiation (TBI).

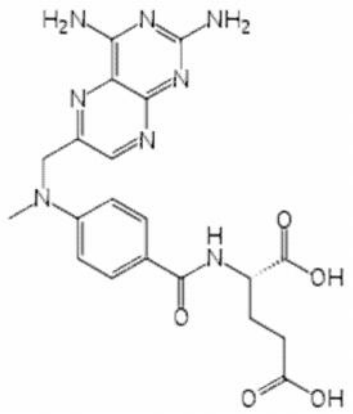
The chemotherapy of cancer is complex and should be confined to specialists in oncology. Cytotoxic drugs have both anti cancer activity and the potential for damage to normal tissue.Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms. All chemotherapy drugs cause side effects and a balance has to be struck between likely benefit and acceptable toxicity.

In the present study Methotrexate, Tamoxifen and Cisplatin were selected to formulate into niosomes to achieve new formulation for management of cancer.

Methotrexate:

Methotrexate is used for the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole and also for the treatment of severe psoriasis and severe, active, classical or definite rheumatoid arthritis.

Chemical structure



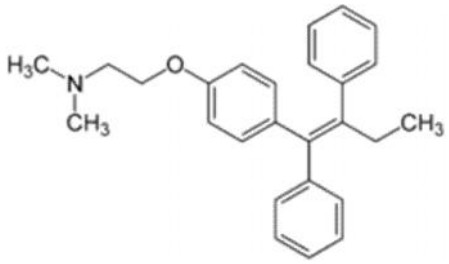
4amino-4-deoxy 10-methyl pteroyl L-glutamic acid

- Antimetabolities are incorporated into newnuclear material or combine irreversibility with vital cellular enzymes, preventing normal cellular division.
- Methotrexate inhibits the enzyme dihydro folate reductase, essential for the synthesis of purines and pyrimidines.
- Methotrexate is used as maintenance therapy for childhood acute lymphoblastic leukemia. Other uses include choriocarcinoma, non-hodgkin's lymphoma and anumber of solid tumors.
- Methotrexte causes myelosuppression, mucositis and rarely pneumonitis. It is contraindicated in significant renal impairment because it is excreted primarily by the kidney. It is also contraindicated in patients with severe hepatic impairment.

Tamoxifen:

Tamoxifen is an antagonist of the estrogen receptor in breast tissue via its active metabolite, hydroxytamoxifen.

Chemical structure



(*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethyl-ethanalamine

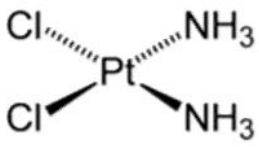
- One of the most severe side effects of Tamoxifen administration is reported to be its proliferative effect on the endometrium. Other side effects include liver cancer , increased blood clotting and ocular side effects such as retinopathy and corneal and opacities. These effects were reported to be dose dependent suggesting the use of lower doses with colloidal delivery to be the key approach for the formulation of tamoxifen for long term chemoprevention of breast cancer.this approach was based on achieving required amount of drug at tumor site for a certain period of time and minimizing side effects on other organs of the body.

- Tamoxifen was employed in this research because of its position in the first line of antiestrogen drugs used in treatment of patients in all stages of estrogen receptor positive breast cancer. The long term need of Tamoxifen and its undesirable side effects encourage the trials to develop sustained release dosage form, also possibly to increase its concentration at tumor site.

Cisplatin:

Cisplatin is a chemotherapy drug. It is used to treat various types of cancers, including sarcomas, some carcinomas (e.g. small cell lung cancer, and ovarian cancer), lymphomas, and germ cell tumors. It was the first member of a class of platinum-containing anti-cancer drugs, which now also includes carboplatin and oxaliplatin. These platinum complexes react *in vivo*, binding to and causing crosslinking of DNA, which ultimately triggers apoptosis (programmed cell death).

Chemical structure



{2(*SP*-4-2)-diamminedichloridoplatinum}

- Platinum anticancer drugs are administered by intravenous injection and with in one day 65-98% of the platinum in the blood plasma is protein bound. The binding of Cisplatin to proteins reduces the urinary excretion of platinum and causes the deposition of platinum in tissues.
- In addition, the binding of Cisplatin to proteins and enzymes is believed to be the cause of many of the severe side effects exhibited by the drug, especially ototoxicity and nephrotoxicity.
- Cisplatin has additional drawbacks, such as low solubility in aqueous solution, severe toxicity (nephrotoxicity, myelo suppression, CNS impairment) and side effects such as nausea and vomiting.

2. Aim of the work

In order to fulfill the need of a long term treatment with anti cancer drugs in conventional dosage forms, where most of them suffer from the drawbacks of frequent administration and inadequate plasma concentration, it is desirable to have sustained-release drug delivery systems to improve the overall therapeutic benefit and to achieve an ideal therapy regime. By sustained delivery, it is possible to achieve effective plasma concentration without significant fluctuation, to avoid sub-therapeutic and toxic plasma concentrations, to facilitate release of the medication in a controlled manner to obtain a continuous delivery, to achieve an effective therapy with low dosage of the drug, to reduce the frequency of medication and thus to improve patient adherence.

Current attempts to overcome these limitations include the development of novel drug delivery systems that can improve the efficacy of existing anti cancer drugs. Colloidal drug carriers (niosomes) are easily phagocytosed by macrophages. Therefore, they can facilitate the uptake of drugs by these cells and may enable a considerably improvement of cancer chemotherapy.

Niosomes formed from self-assembly of hydrated synthetic nonionic surfactant monomers capable of entrapping variety of drugs. The size of these vesicles is in the nanometer range. This size range offers the decisive advantage of this class of pharmaceutical dosage forms as it allows drug targeting which often is not possible with free drug.

The main limitations on the therapeutic effectiveness of Anti cancer drugs are its dose-dependent hematological toxicity, bone marrow depression Nephrotoxicity Neurotoxicity, osteoporosis, ototoxicity. After oral administration it is rapidly

absorbed from the gastrointestinal tract. This necessitates frequent administration of large doses since it is crucial to maintain the systemic drug concentration within the therapeutic level throughout the treatment course. The challenges associated with Anti cancer drug therapy have driven the impetus to explore nonionic surfactant vesicles (niosomes) delivery systems with the Anti cancer drug to target cancer cells.

The best formulation is to be selected on the basis of evaluation of entrapment and *invitro* dissolution studies.

Hence in this work an attempt was made

- To formulate and optimize niosomal formulation.
- To facilitate sustained release of Methotrexate, Tamoxifen and Cisplatin by niosomal delivery system.
- To study the stability of Methotrexate, Tamoxifen and Cisplatin niosome vesicles at room temperature and accelerated temperature.
- To passively target the drug to macrophages with minimal dose to achieve the objectives of Novel drug delivery systems.

The scope of the present work

To provide an ideal drug delivery system for sustained release of anticancer drugs maintaining the therapeutic plasma concentration for a required period of time.

To provide the niosomal drug delivery system, (i) for the patient compliance, (ii) effectiveness of anticancer therapy and (iii) reduction of adverse effect. This is achieved by maintaining the plasma drug concentration at the level with in therapeutic range for the required period of time.

Hence it is absolute necessity to develop effective drug delivery systems to target the site, with minimum dose for reducing undesired side effects.

3. PLAN OF WORK

- Calibration of standard curve for Methotrexate, Tamoxifen and Cisplatin.
- Formulation of Methotrexate, Tamoxifen and Cisplatin niosomes by thin film hydration technique
- Optimization of process related variables by trial and error method. The variables were optimized with respect to entrapment efficiency.
- Characterization Physicochemical properties of niosomes
    - Zeta potential, Polydispersity index
    - Entrapment efficacy
- Studies of
    - *In vitro* drug release
    - Kinetics of drug release
- Evaluation of anticancer activity
- Stability studies for optimized niosomes formulation

4. Materials and Methods

Materials:

Drugs:

Methotrexate,

Tamoxifen

Cisplatin

Surfactants used:

Span 20, Span 40, Span 60, Span 80,

Tween 20, Tween 40, Tween 60, Tween 80 and Brij 35.

Others:

Cholesterol and Dicetyl phosphate

All the Solvents and Chemicals used were of AR or GR grade.

Solvents :

- Diethyl ether
- Acetone
- Chloroform
- Methanol

5. Formulation and Evaluation of niosomes

Preformulation study for Niosomes

One of the requirements for the selection of suitable excipient or carrier for pharmaceutical formulations is its compatibility. Therefore in the present work, pure surfactant, cholesterol,pure drug and their physical mixtures were scanned from 4000 to 400cm^{-1} in FTIR and spectra were recorded.

Formulation of Methotrexate, Tamoxifen and Cisplatin niosomes:

Niosomes were prepared by thin film hydration technique. Accurately weighed quantity of cholesterol and surfactant were dissolved in solvent in a 100ml round bottom flask. The weighed quantity of drug, dicetyl phosphate was added to the solvent mixture. The solvent mixture was removed from liquid phase by flash evaporation at 60°C to obtain a thin film on the wall of the flask at a rotation speed of 150 rpm. The complete removal of residual solvent can be ensured by applying vacuum. The dry lipid film was hydrated with hydrating medium 6ml phosphate buffer saline of pH7.4 at a temperature of 60°C for a period of 2hrs until the formation of niosomes. All the batches were subjected to sonication process for 2 min using probe sonicator.

EVALUATION OF NIOSOMES

a). Optical Microscopy

A drop of niosomal suspension was placed on the microscopic glass slide. Photographs of sonicated and nonsonicated formulations were taken at 45x magnification using the digital camera attached to the eye piece of the microscope. Shape and lamellar nature of the vesicles was confirmed with the photographs.

b). Percentage Encapsulation of drug

Vesicles containing drugs were separated from unencapsulated drug by dialysis. Niosomal preparation of 0.5ml was taken after dialysis. To this 0.5ml of 10% Triton X-100 was added and incubated for 1 hour. The triton X-100 was added to lyse the vesicles in order to release the encapsulated drug. Then it was diluted with phosphate buffer saline solution (pH7.4) and filtered through whatmann filter paper. The filtrate was measured spectrophotometrically using phosphate buffer and triton X-100 mixture as blank.

$$\text{Percentage drug loading (PDL)} = \frac{\text{Entrapped drug (mg)}}{\text{Total Drug added (mg)}}$$

c). Particle size and Zeta Potential

Vesicles properties such as particle size and Zeta potential were determined by Malvern Zeta size analyser.

d). *In vitro* release study for Niosomal formulations and analysis by UV method.

In vitro release was studied using a dialysis bag (Himedia dialysis membrane, 12,000-14,000 molecular weight cut-off) as a donor compartment. Niosomal preparation was taken in a dialysis membrane of 5 cm length and suitably suspended

in a beaker containing 50 ml of diffusion medium (Phosphate buffer saline pH 7.4). The medium was maintained at a temperature of 37±0.5ºC. It was stirred by means of magnetic stirrer at a constant speed. Sample of 1ml (diffusion medium) was withdrawn at every 1 hour for 24 hours and replaced the diffusion medium. The samples were measured spectrophotometrically.

e). Drug release kinetics

In order to understand the mechanism and kinetics of drug release from niosomal formulations the results of the *in vitro* drug release study were fitted with various kinetic equations like zero order(% release Vs t), first order (log% release Vs t), Higuchi model (M_t/ M_∞ Vs $t_{1/2}$).

In order to define a model which would represent a better fit for the formulation, drug release data was further analysed by Korsmeyer- Peppas models. In peppas equation, $m_t / m_\infty = kt^n$, where m_t is the amount of drug released at time t and m_∞ is the amount released at the amount released at time t, K is the kinetic constant an n is the diffusional exponent, a measure of the primary mechanism of drug release. R^2 values were calculated for the given curves obtained by regression analysis of the above plots.

f). Evaluation of anti-cancer activity of Methotrexate, Tamoxifen and Cisplatin Niosomes Formulation

Treatment Protocol

Swiss Albino mice are divided in to four group of six each. All the animals in three groups are injected with DLA cells (1 x 10^6 cells per mouse) intraperitoneally, and the remaining one group is normal control group.

Group 1 served as the normal control.

Group 2 served as the tumor control. Group 1 and 2 receives normal diet and water.

Group 3 served as the treatment control, was treated with marketed drugs.

Group 4 served as the treatment control, was treated with optimized Niosomes

Treatment

After the 24 hrs of inoculation, drug is given once daily for 14 days.

After the last dose, the blood was withdrawn from each mouse by retro orbital puncture and then animals were sacrificed by euthanesia method and the following parameters were checked.

1) **Cancer cell count**

The fluid (0.1ml) from the peritoneal cavity of each mouse was withdrawn by sterile syringe and diluted with 0.8 ml of ice cold Normal saline or sterile Phosphate Buffer Solution and 0.1 ml of tryphan blue (0.1 mg/ml) and total numbers of the living cells were counted using haemocytometer.

$$\text{Cell count} = \frac{\text{No of cells Dilution}}{\text{Area} \times \text{Thickness of liquid film}}$$

2. Haematological parameters
    a. WBC count
    b. RBC count
    c. Hb content
    d. Platelet count
    e. Packed cell volume

2. Serum enzyme and lipid profile
    a. Cholesterol
    b. Triglycerides
    c. AST, ALP, ALT.
3. Derived parameter
    a. Body weight
    b. Life Span (%)
    c. Cancer Cell Count

g). Physical stability of Methotrexate, Tamoxifen and Cisplatin niosomes

Physical stability studies were carried out to determine the leaching of drug from niosomes (in a liquid form) during storage. The Methotrexate, Tamoxifen and Cisplatin niosomal formulations were sealed in 20mL glass vials and stored at refrigerator temperature (2–4◦C), Room Temperature and 45°C/65 %RH for a period of 3months. Samples from each batch were withdrawn at definite time intervals, the residual amount of the drug in the vesicles was determined after separation from unentrapped drug.

The samples were analyzed for the parameters such as colour, turbidity, pH, leakage and vesicle size.

Colour

The change in colour of the formulations was visually analyzed by keeping the sample at the dark background.

Invitro drug release studies

Physical stability studies were carried out to investigate the leaching of drug from niosomes (in a liquid form) during storage. The Methotrexate, Tamoxifen and Cisplatin niosomal formulations, composed of surfactant with cholesterol, were sealed in 20mL glass vials and stored at refrigerator temperature (2–4◦C), Room Temperature and 45°C/65 %RH for a period of 3months. Samples from each batch were withdrawn at definite time intervals, the residual amount of the drug in the vesicles was determined after separation from unentrapped drug.

Percentage Encapsulation of drug

Vesicles containing drug were separated from unencapsulated drug by dialysis. Niosomal preparation of 0.5ml was taken after dialysis. To this 0.5ml of 10% triton X-100 was added and incubated for 1 hour. The triton X-100 was added to lyse the vesicles in order to release the encapsulated drug. Then it was diluted with phosphate buffer saline solution (pH7.4) and filtered through whatmann filter paper. The filtrate was measured spectrophotometrically using phosphate buffer and triton X-100 mixture as blank.

6. Observations and Inferences

In the present study, Methotrexate, Tamoxifen and Cisplatin were encapsulated in niosomes by Thin film Hydration Technique. The film formed can be removed using Phosphate buffer saline as hydrating medium. The size of the vesicles was reduced by sonicating the niosomal preparation using probe sonicator.

The size of niosomes, Percentage of drug entrapment, release of Methotrexate, Tamoxifen and Cisplatin from the niosomes in Phosphate buffer solution and stability of niosomal preparation at various temperatures evaluated.

An effective niosomal targeted delivery system should incorporate high drug loading with stable encapsulation and should possess good physical and chemical stability during storage.

Niosomes must be stabilised by the addition of the charged molecule to the bilayers such as dicetylphosphate. Dicetylphosphate was added at a concentration of 15mM per batch to prevent the aggregation of Niosomes.

Zeta potential

Zeta potential values -29.3 for the formulations depending on the addition of the negatively charged Dicetyl phosphate. The value is sufficiently high for electrostatic stabilization. This shows that niosomes can be suspended in water well and this is important for their storage and administration. Polydispersity index an estimate of the width of the distribution, indicates the size heterogenicity.

The effect of optimized formulation of methotrexate, Tamoxifen and Cisplatin, niosomes on the survival of tumor-bearing mice was evaluated. There was increase in life span of tumor bearing mice treated with niosomal formulations.

Haematological parameters of tumor bearing mice on day 14 showed significant improvement when compared with the tumor group control. Regarding Ehrlich ascites carcinoma (EAC) there was reduction in the tumor volume of mice treated with optimized formulation of methotrexate, Tamoxifen and Cisplatin niosomes ($P < 0.01$).

The reliable criteria for judging the effectiveness of any cytotoxic drug are prolongation of lifespan and decrease the elevated levels of WBC. The result of the present study shows a significant enhancement of mean survival time and improvement in haematological parameters.

IR spectroscopic studies confirm the absence of any drug-polymer interactions. The entrapment efficiency and cumulative percentage of invitro drug release of formulation of methotrexate, Tamoxifen and Cisplatin niosomes were found.

7.Summary and conclusions

In the present study anti cancer drugs viz, Methotrexate, Tamoxifen and Cisplatin were selected to formulate into niosomes to achieve controlled drug delivery to increase cytotoxic activity. To formulate niosomes to achieve effective management of cancer.

The preformulation studies were performed by using FTIR. The spectra of crude drugs and their physical mixtures were examined. The study revealed the absence of significant interactions between drug and additives.

Niosomes of Methotrexate, Tamoxifen and Cisplatin were prepared successfully by using thin film hydration technique. Relationships between surfactant type and characterization parameters of niosomes were established. In the present study, the findings revealed that the process variables critically affect the formulation of niosomes with regards to drug entrapment and need to be carefully controlled. The process optimized parameters like speed of rotation 150rpm and 2hour hydration time. The results of this study showed that cholesterol content and the type of surfactant altered the entrapment efficiency and drug release.

Entrapment efficiency and in vitro studies showed that optimized formulations might be more beneficial for drug delivery among other formulations.

The results presented in this study indicate that the long circulation of niosomes offer a potential application to improve the pharmacokinetic parameters.

However, niosomes offer new and interesting perspectives of drug delivery systems. Niosomes can be used sustained drug delivery system that remains at the

injection site over a period of around 24 hours and slowly release drug in to the blood and retaining the drug higher in tumor, thus enhanced the therapeutic action of Methotrexate, Tamoxifen and Cisplatin niosmes.

Niosomes could be one of the promising drug delivery systems to delivery of antitumor drugs like Methotrexate, Tamoxifen and Cisplatin niosmes to tumor.

Findings of this investigation suggest that niosomal formulation of Methotrexate, Tamoxifen and Cisplatin can provide consistent and prolonged anticancer effect and may help in improving therapeutic index of the drugs and is also expected to minimize the side effects due to selective built up of drug concentrations at the site of action.

The optimized formulation is characterized by small vesicles size, high percentage of entrapment with the desired sustained release of Methotrexate, Tamoxifen and Cisplatin. *Invitro* release from niosomal formulations showed extended release of drug for 24hours. The optimized formulation of Methotrexate, Tamoxifen and Cisplatin niosomes entrapment efficiency of 93.72%, 94.72% and 92.39% respectivel.

The optimized formulation was found to follow zero order release pattern which was revealed by the linearity shown from the plot of time Vs concentration.

The stability tests were carried out for a period of 3 months at various storage conditions. The results showed that the formulation remains stable throughout the period of study. Niosomes were stable with respect to the amount of drug retained for a period of 3 months at 4ºC and affirm that the drug leakage increased at a higher temperature.

Anti-cancer studies by using cell lines namely DAC optimized formulation of Methotrexate, Tamoxifen and Cisplatin niosomes posses significant anti-cancer activity. This is due to prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability of Methotrexate, Tamoxifen and Cisplatin, niosomes. The targeting effect may increase the anticancer activity of the drug and potentially improve its therapeutic benefits. Invivo studies show encouraging results.

In future the suitability for marketing of Methotrexate, Tamoxifen and Cisplatin niosomes formulations should be subjected to bioequivalence studies.