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Journal of Cancer Research and Cellular Therapeutics
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Review Article

Evaluation Of Cancer Treatment By Using Doxorubicin Hydrochloride Liposomes

Vinicius LU*, Giovanna Ana Clara, St.ephanie MB

Department of chemotherapy, Brazil.

***Corresponding Author :** **Vinicius LU,** Department of chemotherapy, Brazil. **Email :** vinicius@gmail.com

Received date: June 10,2018;Accepted date : July 20,2018; Published date: July 30,2018.

Citation for this Article: **Vinicius LU, Giovanna Ana Clara, St.ephanie MB**. Evaluation of Cancer Treatment by using Doxorubicin Hydrochloride Liposomes. J Cancer Research and Cellular Therapeutics, **Doi: http://dx.doi.org/ 10.31579/jcrct.2017 /028**

Abstract

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body, to achieve promptly and then maintain the desired drug concentration.

Conventional drug delivery system achieves as well as maintains the drug concentration with in the therapeutically effective range needed for treatment only when taken several times a day. This results in a significant fluctuation in drug level (Chien YM., 1992).

The concept of designing specified delivery system to achieve selective drug targeting has been originated from the perception of Paul Ehrlich, who proposed drug delivery to be as a “magic bullet”.

Controlled & Novel delivery envisages optimized drug in the sense that the therapeutic efficacy of a drug is optimized, which also implies nil or minimum side effects. It is expected that the 21st century would witness great changes in the area of drug delivery. The products may be more potent as well as safer. Target specific dosage delivery is likely to overcome much of the criticism of conventional dosage forms. The cumulative outcome could be summarized as optimized drug delivery that encompasses greater potency & greater effectiveness, lesser side effects and toxicity, better stability, low cost hence greater accessibility, ease of administration and best patient compliance (Jain N K., 2001).

Rationale Of Drug Targeting (Jain N K., 2001)

The site-specific targeted drug delivery negotiates an exclusive delivery to specific pre identified compartments with maximum activity of drugs and concomitantly reduced access of drug to irrelevant non-target cells. The controlled rate & mode of drug delivery to pharmacological receptor and specific binding with target cells as well as bioenvironmental protection of the drug in route to the site of action are specific features of targeting. Invariably, every event stated contributes to higher drug concentration at the site of action and resultant lowers concentration at non-target tissue where toxicity might crop up. The high drug concentration at the target site is relative cellular result of the uptake of the drug vehicle, liberation and efflux of free drug from the target site.

Targeting is signified if the target compartment is distinguished from the other compartments, where toxicity may occur and also if the active drug could be placed predominantly in the proximity of target site. The restricted distribution of the parent drug to the non-target site(s) with effective accessibility to the target site(s) could maximize the benefits of targeted drug delivery.

Introduction To Liposomes

Liposomes (marc J. Ostro., 1987) have reached the clinical only recently, but they are not a new invention Alec D. Bangham of the Agricultural Research Council’s institute of Animal physiology in Cambridge, England, inadvertently produced the first liposome in 1961, while evaluating the effect of phospholipids on blood clotting. When Bangham put water in a flask containing a phospholipid film, the water molecules to arrange themselves in to what he discovered. He found vesicles composed of a bilayered phospholipids membrane surrounding water entrapped from the environment.

Aims and Plan of work

Liposomes have been used to target drug to specific organs, delay the loss of rapidly cleared, drugs, enhances therapeutic potency and offer a host of the other advantages.

Doxorubicin hydrochloride is one of the most commonly used cytotoxic anthracycline antibiotics used in cancer chemotherapy and has been shown to have activity against a wide variety of neoplasms.

Conventional compositions of doxorubicin hydrochloride are available as freeze-dried product (or) as a solution of doxorubicin hydrochloride in water. Both these products have been associated with a number of toxicities when administered intravenously. Severe myelosupression, nausea, vomiting, alopecia, mucosistis & cardio toxicity, limits the use of Doxorubicin Hcl. It also causes extravasations & necrosis at the site of injection.

Doxorubicin hydrochloride:

Doxorubicin is a drug used in cancer chemotherapy, it is an anthracycline topoisomerase inhibitor isolated from streptomyces peucetius var. caesius.

Doxorubicin is commonly used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma, and soft tissue sarcomas.

Clinical Studies

Ovarian cancer

Doxorubicin Hydrochloride was studied in three open-label, single-arm, clinical studies of 176 patients with metastatic ovarian cancer. One hundred forty-five (145) of these patients were refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory ovarian cancer is defined as disease progression while on treatment, or relapse within 6 months of completing treatment.

Patients in these studies received Doxorubicin Hydrochloride at 50 mg/m2 infused over one hour every 3 or 4 weeks for 3-6 cycles or longer in the absence of dose-limiting toxicity or progression of disease.

Ovarian Cancer

Doxorubicin Hydrochloride should be administered intravenously at a dose of 50 mg/m2 at an initial rate of 1 mg/min to minimize the risk of infusion reactions.

Adjuvant Breast Cancer

Doxorubicin HCl is indicated as a component of multi-agent adjuvant chemotherapy for treatment of women with axillary lymph node involvement following resection of primary breast cancer.

Methodology

Standard calibration curve of doxorubicin hydrochloride was developed using phosphate buffer pH 7.4 and estimated by UV-Visible spectrophotometer at 254nm.

COMPATIBILITY STUDIES

IR spectroscopy can be used to investigate and predict any physicochemical interactions between different components in a formulation and therefore it can be applied to the selection of suitable chemically compatible excipients.

Preparation Of Doxorubicin Iposomes

Procedure for the preparation of doxorubicin liposome

The preparation of liposomes with Soybean lecithin was prepared by dried thin film hydration technique using rotary evaporator.

Accurately weighed quantities of Soy lecithin, cholesterol, Stearylamine and Dicetylphosphate are dissolved in chloroform and rotated in a rota-vap by applying vaccum of about 25mmHg at 25 ^{0}c, until it forms a thin film. Required quantities of ammonium sulphate and sucrose (0.3%) are dissolved in W.F.I and it is added to the above thin film in R.B flask and rotated until it forms a milky white suspension. The above solution is homogenized for 15 cycles to reduce particle size of liposomes. The

above solution is undergone for 25 cycles of dialysis, by using sucrose solution (10%) to remove free ammonia and sulphate from the lipid solution. Drug solution is prepared by adding the required quantities of Drug and Histidine in a W.F.I and pH is adjusted to 6.4 to 6.7 and this drug solution is added to the solution in a R.B flask (lipid solution) and rotated for 1hr.

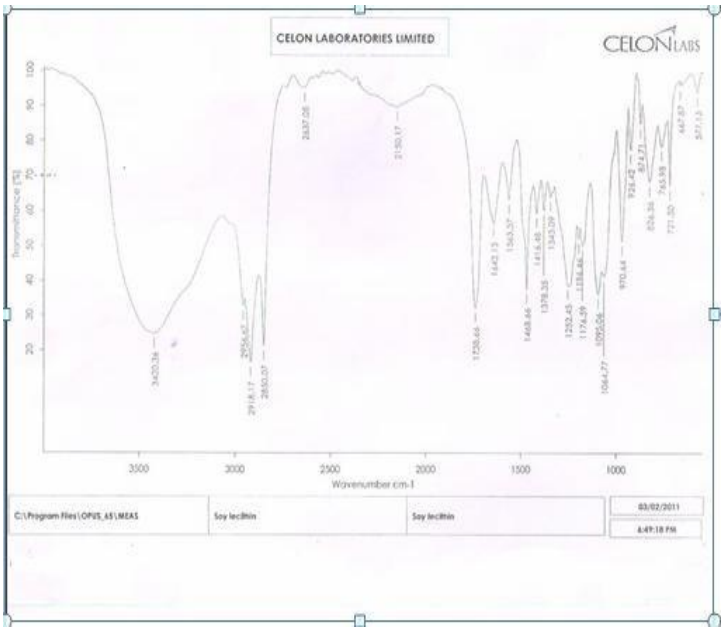
Handling company submissions

All the clinical effectiveness data included in the company submissions from Bristol Myers Squibb, GlaxoSmithKline and Schering-Plough Ltd were assessed. Where this met the inclusion criteria it was included in the clinical effectiveness review. All economic evaluations (including accompanying models) included in the company submissions were assessed and a detailed assessment of the assumptions underlying the submitted analyses was undertaken. A new model was developed to assess the costs of the alternative treatments, the differential mean survival duration and the impact of health-related quality of life. Monte-Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.

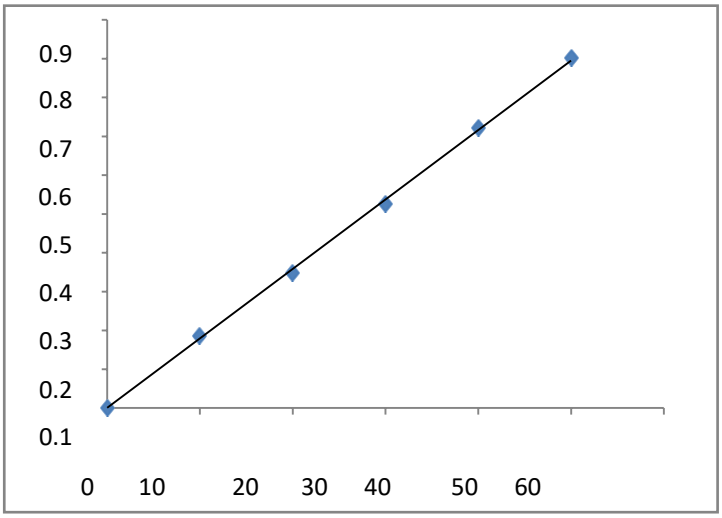
Results And Discussion

S. No.	Concentration(µg/ml)	Absorbance at 254nm
1.	0	0
2.	10	0.184
3.	20	0.348
4.	30	0.526
5.	40	0.721
6.	50	0.901

Standard readings of Doxorubicin hydrochloride in UV



Graph No: 1 Standard graph of Doxorubicin hydrochloride in phosphate buffer of pH 7.4.

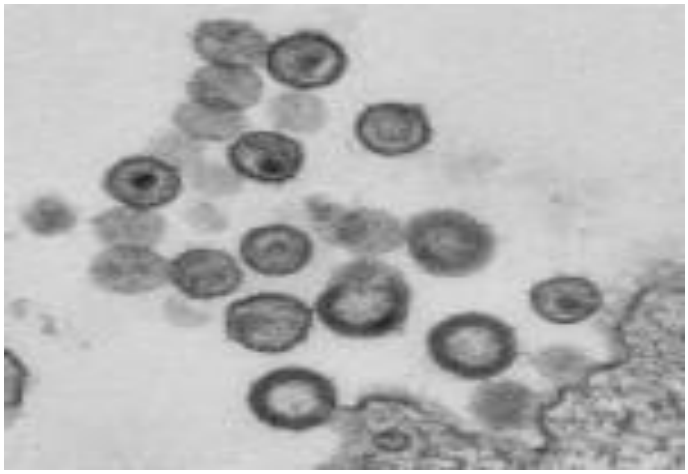


Spectra No: 1 FTIR of Doxorubicin Hcl

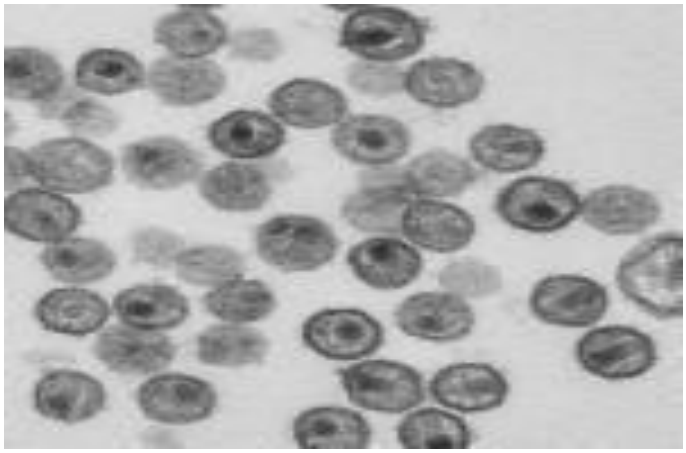
Table : Interpretations of FTIR Spectra for pure drug.

S.No.	FUNCTIONAL GROUPS	ASSESMENT PEAK OF PURE DRUG - CM	RANGE OF GROUPS -1 CM
1.	C=C Streching (Aromatic)	1463.86	1450 – 1600
2.	O-H Bending (Alcohol)	1072.51	1050 - 1150
3.	C=O Streching	1729.84	1705 - 1735
4.	N-H Bending	1617.83	1500 – 1650
5.	C-OStreching (6-Membered cyclic)	1114.46	1100 - 1120

Scanning Electrron Microscopy



SEM photography of Liposomal solution for F2 formulation.



SEM photography of Liposomal solution for F6 formulation.

Conclusion

The main objective of this work was designed to prepare and evaluate the Doxorubicin Hcl Liposomes. This formulation will target the site of action with effect of various stabilizers on drug entrapment efficiency, and to reduce the side effects by formulating non-pegylated Liposomes. This liposomal formulation was formulated using the soyabeanlicithin and cholesterol which has lesser toxicity.

The Liposomes were prepared by dried thin film hydration technique using rotary evaporator with drug, carrier, ammoniumsulphate and stabilizers. The parameters like temperature, vacuum and RPM were maintained accordingly. After preparation, the Liposomes were stored in freezed condition, and given for further evaluation.

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