Bexarotene: A Novel Drug Delivery System for Cutaneous T-cell Lymphoma (CTCL)

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Abstract---Bexarotene is an analogue which is used as skin manifestations therapy of the "cutaneous T-cell lymphoma (CTCL)". Its therapy is highly associated with the enhancement in the concentration of serum enzyme and reduces the chances of acute liver iunjury. "Cutaneous T-cell lymphoma (CTCL)" is a member of the family "non-Hodgkin lymphomas" (which are related to the B-cells), and is caused by the mutation of T-cells. They are predominantly found in the skin and are a heterogeneous and relatively rare family of extranodal non-Hodgkin's lymphomas (NHLs). Some patients have dermal spots, plaques, tumors and erythroderma more rarely. The most important prognostic factors in CTCL patients are the type of skin lesions and the surface extent of skin infection and extracutaneous disease. Early-stage patients can only be treated effectively by skin-directed therapies. In this paper, we have talked about the development and characterization of Polymeric-zeinnanomicelles base formulation of Bexarotene for the treatment of "cutaneous T-cell lymphoma (CTCL)". The Pegylated-zeinnanomicelles were evaluated as nanocarriers to improve the efficacy, reduced toxicity in vivo, protection of encapsulated agent against degradation and enhanced water solubility of hydrophobic bexarotene as a novel delivery system for "cutaneous T-cell lymphoma (CTCL)". For this, the formulation of nanomicelle drug delivery comprising the Pegylated-zeinnanomicelles encapsulates the bexarotene in two different ratios and then the results were evaluated accordingly.

Keywords--- Bexarotene, skin manifestations, "cutaneous T-cell lymphoma (CTCL)", non-Hodgkin lymphomas (NHLs), extracutaneous disease, polymeric-zeinnanomicelles, nanocarriers, nanomicelles

I. INTRODUCTION

Cancer is a type of disease which involves the growth of abnormal cells with the potential to spread or invade to other parts of the body. According to the studies on cancer, it has been demonstrated the case of cancer among the people suffering from cancer is 17.5 million and the mortality rate of approximately 8.7 million in the year 2015. The incidence of cancer has rapidly increased between the year 2005 and 2015 [1]. Currently, cancer is the world's second leading cause of death, and is expected to reach 27 million by 2030-particularly in the developed countries [2][3]. Now the question of "what causes cancer" has intrigued people from many years. The main reason for the cause of cancer is associated with the diseases such as smoking, alcoholism and sedantrism[4].

Cancer is classified into the following types – "Carcinoma, Sarcoma, Myeloma, leukemia and Lymphoma" [5].

"Carcinoma" is a type of cancer of an inner or outer body's neoplasm of malignancy of the epithelial origin or cancer. Epithelial tissue malignancies, carcinoma, account for between 80% and 90% of all cases of cancer. It is

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present in the skin and on tissues, including the gastrointestinal tract and on the lining of internal passages.

"Sarcoma" is the cancer of bone, tendon, cartilage, muscle and fat that comes from supportive tissue and connective tissue. The most common sarcoma usually develops as a painful mass on the bone in young adults [6].

"Myeloma" is a type of cancer which is found in the plasma cells of bone marrow. Some of the proteins found in the blood are produced by plasma cells [7].

"Leukemia" is the type of cancer found in bone marrow, either liquid cancer or blood cancer. In this type of cancer, there is an overproduction of immature white blood cells, which do not perform their function properly and thus, the patient is affected to the infection. "Leukemia" also affects the RBCs of a person, which causes the blood clotting and fatigue due to anemia [8].

"Lymphomas" is a type of cancer which grows in the glands or nodes of the lymphatic system, and is a network of vessels, nodes and organs which purifies the fluid in the body and produces the white blood cells, or lymphocytes for fighting against infections [9]. In contrast to leukemia, which is the liquid cancer, the lymphoma is the solid cancer. Lymphoma occurs in the specific organs of the body such as "stomach, breast and brain". The Lymphomas are considered as the extranodal lymphomas. Lymphoma is divided into two classes – Hodgkin and non-Hodgkin lymphomas". The difference between the "Hodgkin and non-Hodgkin lymphomas is known by the presence of "Reed-Sternberg cells". Lymphomas are a large and heterogenous group of biological and medical neoplasms, with treatment and prognosis [10]. "Non-Hodgkin lymphoma" (NHL) accounts for nearly 90% of the lymphoma of hematological malignancy.

Nanomicelles are the self assembled nanosized (particle size range from 10 to 100 nm) copolymer, characterized by amphiphilic molecule with hydrophobic inner core loaded with lipophilic drug and hydrophilic outer shell layer (like PEG). Nanomicelles consists of the good thermodynamically stability in physiological solution, as indicated by their low critical micelle concentration (CMC) of 10^{-6}-10^{-7} M, responsible for its stability and prevents its fast dissociation *in vivo*. This low concentration after the dilution (during intravenous administration) suggested slower dissociation rate, around 1000-times slower than that of ordinary surfactant micelles which allow them to move in the bloodstream and reaches their molecular target sites.

"Bexarotene, 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8- tetrahydro-2-naphtalenyl)vinyl]" benzoic acid (figure 1) is the first US-FDA-approved retinoid which belongs to a subclass arotinoids called rexinoids. It specifically binds to the retinoid X receptors and activates it, as opposed to the retinoic acid derivative and is responsible for controlling cell differentiation, apoptosis and prevents development of drug resistance. Bexarotene is not a retinoic acid derivative; it has one carboxylate moiety and its structure is similar to other RAR specific agonists. It is a drug of choice for the treatment of cutaneous manifestations of "cutaneous T-cell lymphoma (CTCL)" in patients who are prone to at least one prior systemic therapy.
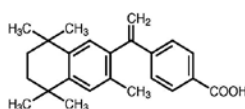

Fig.1. Bexarotene

The C-3 position has methyl substituted on its tetrahydro-naphthalenyl moiety which is believed to contribute to its retinoid X receptors (RXR) affinity. Activation of RXR modulates chain of "gene expression pathways" which finally modulate coincides with signaling pathways responsible for cell differentiation, apoptosis and proliferation. The central role of RXR in regulating retinal receptor signaling, as well as the proof that rexinoids can play an important role in the therapy of lung disease, has resulted in significant clinical interest in the anti-tumor and tolerability of bexarotene. Bexarotene is highly protein bound (99.8-99.9%). Its metabolites have been found in plasma, which are "6- & 7-hydroxybexarotene" and "6- & 7-oxo-bexarotene". The *in vitro* studies suggest that mainly the "cytochrome P450 3A4" is responsible for generation of the oxidative metabolites which may be glucourinated.

Therapeutic use of bexarotene is hampered due to its poor bioavailability because of its lipophilic nature and highly protein binding property but elimination of bexarotene and its metabolite is mainly hepatobiliary, their excretion via renal pathway is minimal. To enhance the bioavailability hydrophobic drug bexarotene may be encapsulated in pegylated-zein micelle shell. Zein is considered as the prolamine protein of corn consisting of the hydrophobic character. It is well known for its high thermal resistance and high oxygen barrier property. Zein is first conjugated to a polymer PEG (polyethylene glycol) chain which conjugates to prepare micelle assemblies into which poorly water-soluble drug molecules are encapsulated into polymer nanomicelles.

So the aim of this study is to prepare "bexarotene loaded pegylated-zeinnanomicelles", a novel drug delivery system for cutaneous t-cell lymphoma (CTCL) by two methods (dialysis method & film method). Nanomicelles were characterized for CMC estimation, TEM, degradation studies, drug loading and percentage drug release analysis was done using developed high performance liquid chromatography (HPLC) method.

II. MATERIALS AND METHODS

1. *Preparation and Characterization of PEG-Zein polymer*

The PEGylated-zein polymer was prepared by dissolving desired quantity of PEG of selected PEG (PEG 200, PEG 4000 and PEG 6000) and desired quantity of zein (in ratio 1:1, 1:2, 1:3, 2:1, 3:1) having specific molecular weight in 90% v/v ethanol. The resultant mixture was vortexed for 2 minutes and was then incubated for 3 hours at 37℃. After 3 hours, 1M glycine was added to quench excess of PEG ester. Afterwards 5 ml of citrate buffer was added to precipitate PEGylatedzein. This aqueous suspension of PEGylatedzein was dialyzed (M.W. cut off 10 KDa) against water for 24 hours at room temperature, to remove glycine and ester. The dialyzed aqueous dispersion was then freeze dried to a solid cake at –80 ℃. It was then lyophilized (12-72 hours, as required) at -47℃ and under 60mTorr vacuum and PEGylated-zein polymer was stored in refrigerator in a desiccator at 4℃ till further use.

Developed pegylated-zein polymer was characterized by determining CMC and encapsulation efficacy. The critical micelle concentration of various ratios of PEGylated-zein polymers was determined by plotting graph of concentration v/s conduction. To determine the encapsulation efficacy UV spectral analysis of non PEGylatedzein and PEGylatedzein was carried out. Percentage of PEGylation efficiency was calculated using formula: % of PEGylation efficiency = 100

where, Slope of concentration of non-PEGylatedzein versus absorbance = Slope of concentration of PEGylatedzein versus absorbance.

2. *Preparation and characterization of Bexarotene loaded PEGylated-zeinnanomicelles*

Bexarotene loaded PEGylatedzeinnanomicelles was prepared by two selected methods, i.e., dialysis method and film method. Various formulations were prepared using the different polymer ratios of PEGylatedzein. Bexarotene loaded PEGylated-zeinnanomicelles ratio 1:2 (Dialysis and film method) was selected as the best ratio with maximum drug loading content, i.e., 97%.

3. *By dialysis method*

Dissolved PEGylatedzein (50mg), bexarotene (300mg) and BHT (1mg) in 90% v/v ethanol. Then vortexed the mixture for 2 minutes and incubated the mixture overnight at 37ºC. Dialyzed (mol. wt. cut off 10 KDa) mixture against water (containing 1µg/ml BHT) for 8hrs. Aqueous dispersion was freeze dried to a solid cake at -80ºC. Lyophilized (for about 24hrs) at -100ºC under 100mTorr vacuum and stored in a desiccator in refrigerator at 4ºC till further use.

4. *By film method*

Dissolved PEG-zein and bexarotene (1:1) in 90% v/v ethanol. Then vortexed the mixture for 2 minutes and incubate the mixture overnight at 37ºC. The ethanol is completely evaporated at 37ºC in a "rotary evaporator" to form a dry film. Dialyzed (mol. wt. cut off 10 KDa) the mixture against water (containing 1µg/ml BHT) for 8hrs. Aqueous dispersion was Freeze dried to a solid cake at -80ºC. Lyophilized (12 to 14 hrs) at -47ºC and under 60mTorr vacuum and stored in refrigerator in a desiccator at 4ºC till further use.

Developed bexarotene loaded PEGylatedzeinnanomicelles was characterized by determining morphological characteristic, TEM, %drug loading capacity, in-vitro release. A "high performance liquid chromatography (HPLC)" method for bexarotene was developed and applied to measure the drug loading, solubility and to quantity bexarotene in release. To determine the concentration of entrapped bexarotene within the core of nanomicelle formulation, RP-HPLC analysis was performed using C18 column of qualisil gold (250x4.6mm, 5µ) with mobile phase in mixture of "acetonitrile": ammonium acetate buffer: DMSO (98:1.5:0.5%v/v) pH4.5 at flow rate of 1ml/min and injection volume was 20µl, a UV detector (Agilient) set at 279nm.

Various morphological characteristics were studied by physical analysis like: appearance, odor, texture, etc. The TEM analysis of selected best ratios of bexarotenePEGylated-zeinnanomicelles was done by Hitachi, Japan MSW-301. The nanomicelles were dissolved in solvent [acetonitrile: ammonium acetate buffer: DMSO (98:1.5:0.5) pH 4.5]. Drug loading (drug incorporated) was calculated by using the formula:

Drug incorporated % = 100

Where, a = Amount of drug loaded in micelle; b = Total amount of drug used in micelle.

The artificial in vivo evaluation of bexarotenenanomicelles is done using "franz diffusion cell". The cell is composed of two components: donor and receptor. The receptor compartment has a capacity of 30ml volume and an

effective surface area of 33 cm2. The diffusion buffer is continuously stirred by a magnetic bar. The samples are then taken from "franz diffusion cell" for calculating the "percentage cumulative drug release" for 24 hours. Percent drug release is studied using the "franz diffusion cell" which was filled with the phosphate buffer saline solution pH 7.4 samples which are taken from "franz diffusion cell" replaced with the same volume of fresh saline phosphate buffer to maintain the sink condition and the sample is analyzed by RP-HPLC method.

5. *Stress degradation studies*

i) *Hydrolysis under acidic conditions*

To determine the stress degradation caused due to the hydrolysis under acidic conditions of 3 ml of stock solution (1000µg/ml) of drug was pipette out in 10 ml of volumetric flask, to this 1 ml of 3N hydrochloric acid is added and the volume was made up to 10 ml along with methanol. The volumetric flask is then kept under the room temperature for 90 minutes. After 60 minutes, 1 ml of solution is pipetted out, neutralized and diluted with methanol to 10 ml. Then after 90 minutes of time interval again, 1 ml solution is taken and same steps are repeated thereafter. Blank used for this consist of 0.5ml of 3N hydrochloric acid mixed with 0.5 ml of 3N sodium hydroxide solution and diluted to 10ml with methanol.

ii) *Hydrolysis under alkaline conditions:*

To determine the stress degradation caused by hydrolysis under the alkaline conditions, 3 ml of stock solution (1000µg/ml) of drug is added into the 10 ml of volumetric flask and to this 1 ml of 0.1 N sodium hydroxide solutions is added and the volume was made up to 10 ml with methanol. The volumetric flask was then kept under the room temperature for 90 minutes. After 60 minutes, 1ml solution is pipetted out, neutralized and diluted with methanol up to 10 ml. Then after 90 minutes of time interval again 1 ml solution was taken and same procedure was repeated. Blank used for this contained 0.5ml of 0.1N hydrochloric acid mixed with 0.5 ml of 0.1 N sodium hydroxide solutions and diluted to 10ml with methanol.

iii) *Oxidative degradation:*

To determine the oxidative degradation, 1.5 ml of stock solution (1000µg/ml) of drug is pipette out in 10 ml of volumetric flask, to this 1 ml of 30 % hydrogen peroxide solution is added and the volume is made up to 10 ml with methanol. The volumetric flask was then kept under the room temperature for 15 minutes. After 15 minutes, the dilutions are made and the analysis is carried out under the UV conditions. Blank used for this contained 1ml of 30% w/v hydrogen peroxide, and volume up to 10ml is made with methanol. Both (sample and blank solution) are heated on the boiling water bath to remove excess of hydrogen peroxide, for 15 minutes.

iv) *Dry heat induced degradation kept under normal conditions overnight:*

To determine the "dry heat induced degradation", standard drug and bexarotenenanomicelles samples are taken in the petriplates and are exposed to a temperature of 70 ºC for 48 hours in oven. After 48 hours, 10 mg of sample from each is weighed and dissolved in the methanol and diluted up to a mark with methanol. Further, the dilutions are made to achieve desired concentrations. Drug content analysis was carried out by RP-HPLC method.

v) *Stability studies:*

The stability of solution was investigated at different time intervals. All the sample solutions were stored at 4 ºC in a desiccator. The experiment was carried out to demonstrate the specificity of the developed method for

determining the quantity of bexarotene under the controlled conditions. The sample of specific concentration was drawn at 3, 6, 8, 24, 48, 72 and 96 hours and after 1 month and the sample solutions were analyzed by RP-HPLC method.

vi) Statistical analysis:

The data is expressed as the mean ±SD (standard deviation) of at least three repeation of every experiment.

III. RESULTS AND DISCUSSION

1. *Preparation and Characterization of Nanomicelles*

For optimizing the preparative process of pegylated-zein polymer, it is studied by varying the polymer and zein ratio. PEGylated-zein polymer were prepared by varying the ratio of PEG and zein (1:1, 1:2, 1:3, 2:1, 3:1) using different polymers i.e PEG 200, PEG 4000, PEG 6000. Characterization was carried out by CMC determination and encapsulation efficacy.

Critical micelle concentration (CMC) criticizes the micelle stability in *in-vitro* and *in-vivo* experiments. The micelle stability depends upon the CMC values of micelle forming materials and CMC is an effective parameter for the preparation of micelle. The critical micelle concentration was studied using conductivity meter. The critical micelle concentration of various ratios of PEGylated-zein polymers was determined by plotting graph of concentration v/s conduction. CMC of PEGylated-zein polymer in ratio 1:2 was 24 µg/ml at 25°C, indicating that the plain micelles might be stable in-vitro. (figure 2).
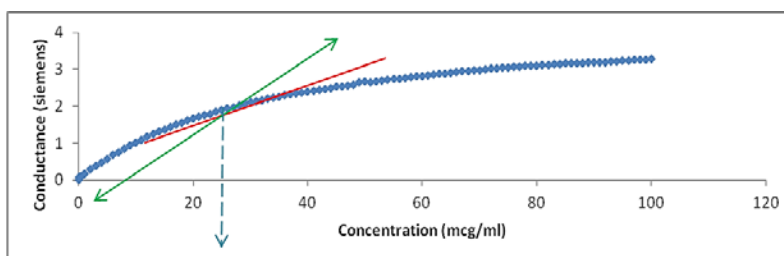

Fig.2. CMC of PEGylated-zein polymer in ratio 1:2

The encapsulation efficacy was determined by UV analysis of non PEGylatedzein and PEGylatedzein was carried out. Percentage of PEGylation efficiency was calculated using formula: % of PEGylation efficiency = $[(a - b) \div a] \times 100$ where, a = Slope of concentration of non-PEGylatedzein versus absorbance; b = Slope of concentration of PEGylatedzein versus absorbance.

The results observed were revealed that except ratio 1:3 all other ratios showed 100% encapsulation efficiency.

Table 1: Encapsulation efficacy of PEGylated-zein in different ration

Ratio of PEGylated-zein	Encapsulation Efficacy
1:1	100%
1:2	100%
1:3	0%
2:1	100%
3:1	100%

Bexarotene loaded PEGylatedzeinnanomicelles was prepared by two selected methods, i.e., dialysis method and film method. Various formulations were prepared using the different polymer ratios of PEGylatedzein. Bexarotene loaded PEGylated-zeinnanomicelles ratio 1:2 (Dialysis and film method) was selected as the best ratio with maximum drug loading content, i.e., 97%. Developed formulation was characterized by studying morphological characteristics, TEM, percentage loading capacity, in-vitro release.

Prepared nanomicelles were found to be of yellow color, odorless, and soluble in acetonitrile: ammonium acetate buffer: DMSO (98:1.5:0.5) pH 4.5 which was used for evaluation of formulation by HPLC.

The morphology of the optimal formulation under "transmission electron microscope (TEM)" represents the homogeneous spheres as photographed (figure 21-22). The average diameter of micelles as measured with Hitachi, Japan MSW-301 nanoparticle analyzer was in range 20 nm – 195 nm. Homogeneous and small sized particles (<200nm) provide efficient passive tumor-targeting ability. Hydrogen bond occurs between the carboxyl group of bexarotene and NH_2 group of zein chains in bexarotene loaded micelles leading to slightly lowered in particle size compared with that of blank micelle (150 nm-265 nm). The TEM analysis of selected best ratios of bexarotenePEGylated-zeinnanomicelles (i.e. bexarotenePEGylated-zeinnanomicelles 1:2 prepared by both dialysis and film method) was done by Hitachi, Japan MSW-301. The nanomicelles were dissolved in solvent [acetonitrile: ammonium acetate buffer: DMSO (98:1.5:0.5) pH 4.5]. Figure 3,4 shows the morphology and shape of bexarotene loaded nanomicelles. The microphotographs show homogenous population of spherical nanomicelles.
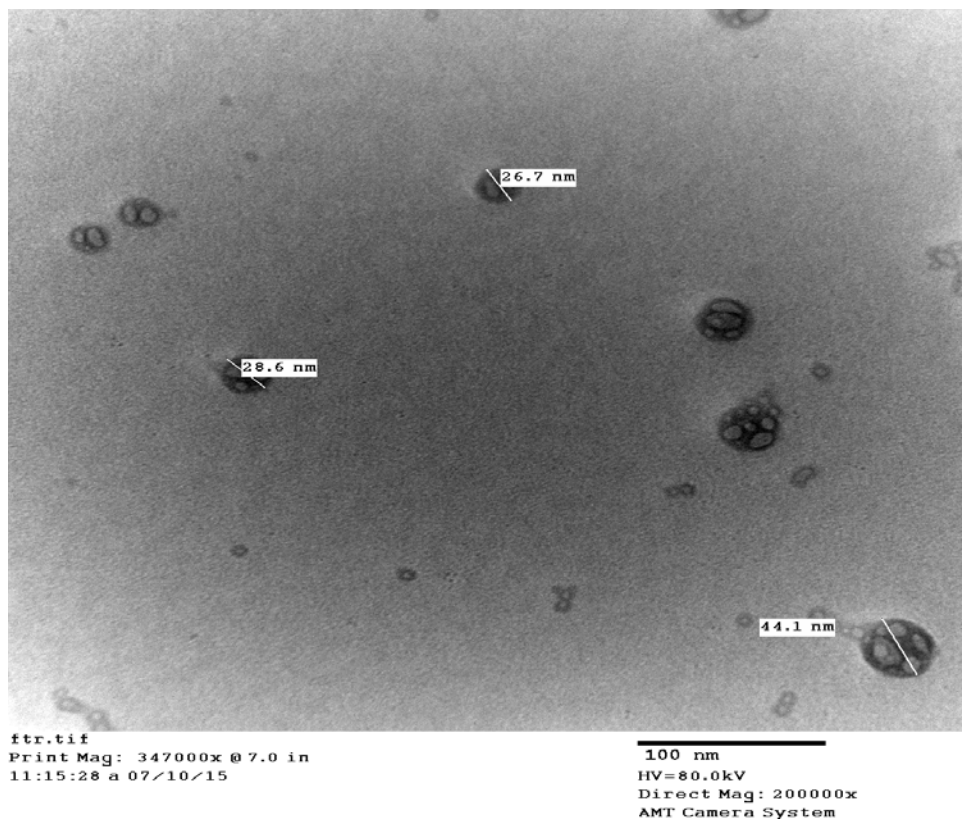

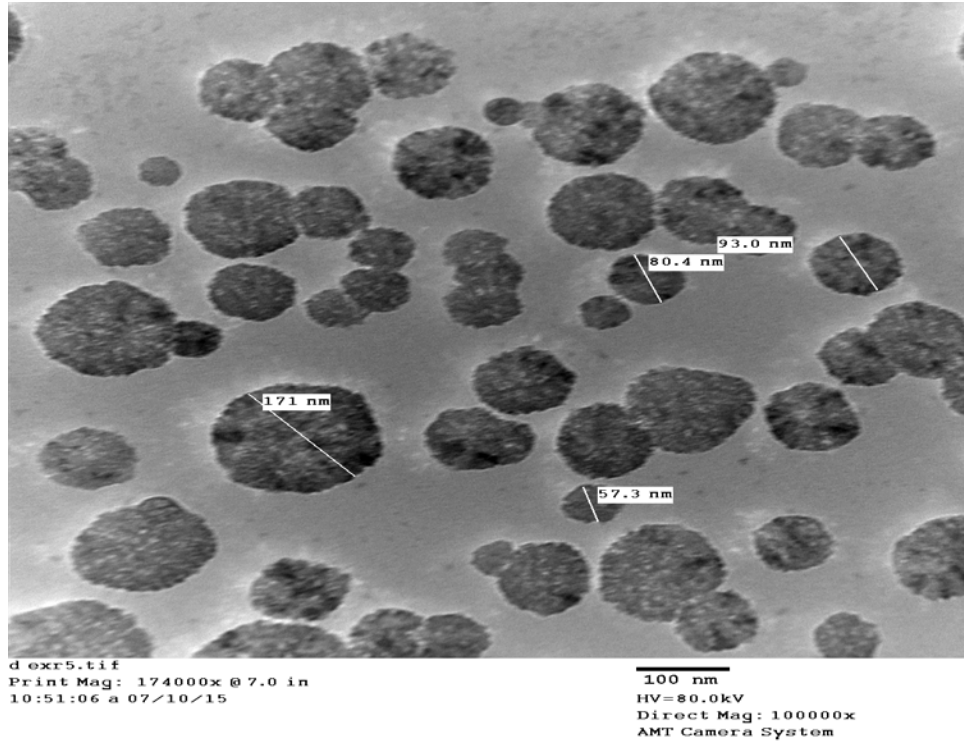**Fig.3. TEM of PEGylated-zeinbexarotenenanomicelles (Film method)**

Fig.4. TEM of PEGylated-zeinbexarotenenanomicelles (Dialysis method)

2. *Drug loading%:*

Results revealed that the drug loading capacity was found best with bexarotenePEGylated-zeinnanomicelles (PEG 4000) 1:2 of both dialysis method and film method. (Table 2). Drug loading (drug incorporated) was calculated by using the formula: Drug incorporated % = $\dfrac{a}{b} \times 100$

Where, a = Amount of drug loaded in micelle; b = Total amount of drug used in micelle.

Table 2: Bexarotene loaded capacity of PEGylated-zeinnanomicelles.

	Dialysis method drug loading %			Film method drug loading %		
Ratio	PEG-200	PEG 4000	PEG 6000	PEG-200	PEG 4000	PEG 6000
1:1	84.22	89.00	85.22	82.78	88.11	84.67
1:2	86.33	97.44	86.00	87.33	98.11	86.78
1:3	67.87	82.56	69.11	69.67	85.67	70.44
2:1	73.78	79.89	75.55	75.67	84.78	77.11
3:1	66.11	77.00	67.78	65.33	75.67	67.00

The drug loading capacity ranges from 65- 98% but was found best with PEG4000 in 1:2 by both dialysis & film method about 97.44% and 98.11% respectively.

3. *In vitro release profile:*

The artificial *in- vivo* evaluation of bexarotenenanomicelles was done using a "Franz diffusion cell". The cell consists of two components: "donor and receptor". The receptor compartment has a capacity of 30ml volume and an effective surface area of 3×3 cm^2. A magnetic bar constantly moves the diffusion buffer. For the calculation of cumulative drug release percentage for 24 hours, the samples were taken from the "Franz diffusion cell". "Franz diffusion cell" was filled with phosphate buffer saline solution having pH 7.4; the samples are taken from the "Franz diffusion cell" and replaced with the same volume of fresh saline phosphate buffer to maintain the sink condition. The sample is withdrawn at various time intervals were analyzed by using optimized chromatographic conditions by RP-HPLC method at 279nm. From the results it was observed that permeability increases in formulation (bexarotenePEGylated-zein 1:2, Film method), which exhibited greatest % of drug release value, while formulation (bexarotenePEGylated-zein 1:2, Dialysis method) exhibited lowest % drug release values than the latter in 24 hours.

Bexarotene loaded PEGylatedzeinnanomicelles prepared by both the methods, i.e., dialysis and film method revealed comparable release but maximum release was obtained with formulation prepared by film method, i.e., a high release amount of drug permeation at the end of 12 hours (74.513%) and 24 hours (97.941%). [Figure 5] figure shows release profile of bexarotene from nanomicelle. When the nanomicelle was dispersed in phosphate buffer saline solution pH 7.4, bexarotene was released following a zero kinetic order. In 2 hrs, around 20% of loaded bexarotene was released from nanomicelle prepared by both film and dialysis method. At the end of 12 hrs 74.513% and at 24 hrs 97.941% of bexarotene was released.
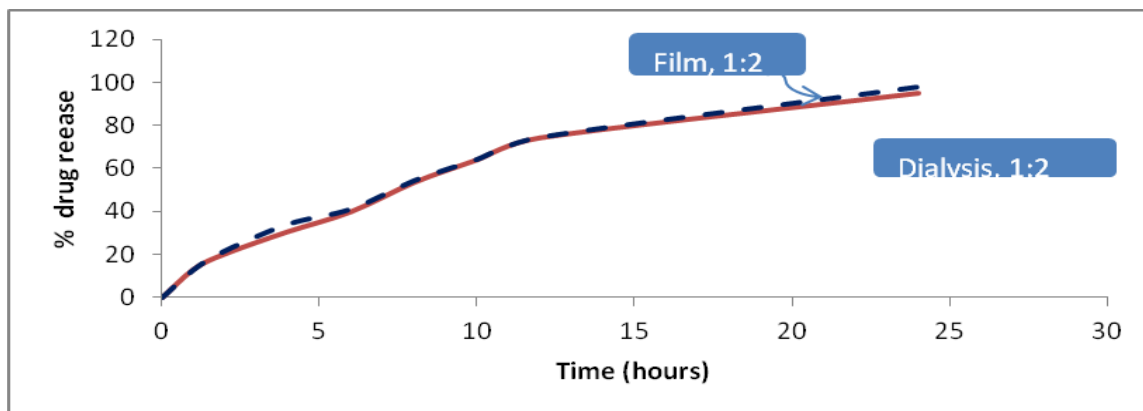

Fig.5. Percentage Drug release curve showing maximum and minimum drug release from the formulation.

4. *Stress degradation studies:*

i) *Stress degradation studies by hydrolysis under acidic, alkaline and oxidative conditions*:

The procedure for stress degradation study by hydrolysis under acidic, alkaline and oxidative conditions was performed as described under section 5 (C). [Table 3] Results revealed maximum degradation under acidic condition, i.e., 80.29 % and 91.57% drug degradation after 90 min for dialysis and film method respectively.

Table 3: Stress degradation studies by hydrolysis under acidic, alkaline and oxidative conditions.

Condition for stress degradation studies	Time (minutes)	% Degradation	
		Dialysis method (1:2)	Film method (1:2)
Acidic	60	61.25%	48.43%
	90	80.29%	91.57%
Alkaline	60	62.14%	50.55%
	90	68.12%	68.83%
Oxidative	60	75.02%	69.39%
	90	81.49%	78.17%

5. *Dry heat induced degradation kept under normal conditions overnight:*

To determine the dry heat induced degradation, standard drug and bexarotenenanomicelles samples were taken in petriplates and were exposed to a temperature of 70 °C for 48 hours in oven. After 48 hours 10 mg of sample from each was measured and diluted with methanol q.s. to 10 ml. From this solution further dilutions were made to achieve desired concentrations. Afterwards UV spectral analysis was carried out and the results observed indicates that the % degradation after exposure to temperature of 70° C for 48 hrs was found to be 86.84% (100 µg/ml, Dialysis method) and 81.77 % (100 µg/ml, Film method) respectively [Table 4].

Table 4: Dry heat induced degradation kept under normal conditions overnight observations

Concentration µg/ ml	Dialysis Method (% degradation)	Film Method (% degradation)
100	86.21%	81.01%
150	86.84%	81.77%

From the stability studies it was revealed that both the formulations were found to be stable as per literature.

6. *Stability studies of Bexarotene loaded PEGylatedzeinnanomicelles:*

The stability of solution was investigated at different time intervals. All the sample solutions were stored at 4 °C in a desiccator. The experiment was carried out to demonstrate the stability of prepared formulation for the

determination of bexarotene under controlled conditions. The sample of specific concentration was drawn at 3, 6, 8, 24, 48, 72 and after 2190 hours (1 month) and the absorbance of sample solutions were recorded. The solution was found to be stable for days. The %RSD values were found to be less than 2.

Table 5: Stability data of PEGylated-zeinbexarotenenanomicelles 1:2(dialysis method) by HPLC Method

TIME	P4D-1:2 PEAK AREA	P4-F-1:2 PEAK AREA
DAY 1	13025.82	13099.13
DAY2	13024.73	13098.75
DAY3	13024.72	13098.17
1 month	12083.16	12193.11
Avg	12789.61	12872.29
STD. DEV.	0.003761	0.001976
%RSD	1.856487	1.594532

IV. CONCLUSION:

In summary, pegylated –zeinnanomicelle have been appeared to be the adequate carriers for the topical delivery of bexarotene. In this study, bexarotene loaded pegylated-zeinnanomicelle were prepared by two methods (dialysis and film method). The nanomicelle preparation did not require the use of organic solvents or other toxic chemicals only ethanol was used.

To the best of our knowledge this is the first time that pegylatedzeinbexarotenenanomicelle were developed and characterized and evaluated *in-vitro*; opening the door for novel strategies in the treatment of cutaneous T-cell lymphoma (CTCL).

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