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Formulation And Evaluation of Etoposide Nanosponges

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ABSTRACT

The main objective of the study is to formulate Etoposide Nanosponges. The nanosponges were prepared by Emulsion solvent diffusion method using various concentrations of Eudragit and Ethyl cellulose. An ideal drug therapy attains effective drug concentration at the target site for a specified period of time and minimizes general and local side effects. To obtain a desirable therapeutic response, the correct amount of drug should be transported and delivered to the site of action with subsequent control of drug release.Nanosponges are made of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles possess the ability to carry both lipophilic and hydrophilic substances and thereby improving the solubility of poorly water soluble molecules. The prepared nanosponges were evaluated for particle size, zeta potential, entrapment efficiency and in vitrodrug release. The prepared nanosponges using Ethyl Cellulose an Eudragit have the average particle size was found to be 192.6 nm and 100.81nm which are lesser than 5µm, zeta potential was found to be -15.2mV and -23.4mV respectively. The formulatedEtoposide nanospongescanbeused inthetreatment ofcancersuchasleukemiaandothercancers.This canbe targeted to the cancerous cells and produce sustained drug delivery which in turn reduces the dose, frequency of administration and the side effects.

Keywords: *Nanosponges, Etoposide, Eudragit, Ethyl Cellulose, Emulsion Solvent Diffusion Method, Dialysis Bag Diffusion Method.*

1. INTRODUCTION

The pharmaceutical and health care industry has been creating and using nano-scale materials for resolving many physical, biological and chemical problems related with the treatment of disease. Shrinking materials to nano size has profoundly enhanced the efficacy of such drugs. Targeted drug delivery is the delivery of drug to receptor, organ or any part of the body to which one wishes to deliver the drug exclusively[1]. Nanosponges are made of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles possess the ability to carry both lipophilic and hydrophilic substances and thereby improving the solubility of poorly water soluble molecules.

The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. Based on the method of associating with drugs, the nanoparticles are classified into encapsulating nanoparticles, conjugating nanoparticles and complexing nanoparticles. The nano sponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms[2]. For oral administration, these may be dispersed in a matrix of excipients, diluents,

lubricants and anticaking agents which is suitable for the preparation of tablets or capsules. For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions. For topical administration, they can be effectively incorporated into topical hydrogel. When compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non- toxic and stable at high temperatures up to 300oC. They are capable of capturing, transporting and selectively releasing a huge variety of substances because of their specific 3D structure containing cavities of nanometric size and tunable polarity[4].

The simple chemistry of polymers and cross linkers poses no problems in the preparation and this technologycanbeeasilyrampedupto commericalproductionlevels.Theycanbemixedwithwater and used as a transport fluid. The nanosponges can be formulated to be of specific size and to release drugs over time by varying the proportionofcrosslinkertopolymer. Drugs encapsulated within the nanosponge pores are shielded from premature destruction and stability of drug is enhanced. This tiny spongecirculatesaroundthetumourcelluntiltheyencounterthesurfacetoreleasetheirdrugcargoina sustained manner[5]. Nanosponge is three to five times more effective at decreasing tumour growth than direct injection. The targeted deliverysystems of nanosponge have several basic advantages like, thedrugisreleasedatthetumourinsteadofcirculatingwidelythroughthebody,anditis moreeffective fora givendosage. Nanosponges of specific size can be synthesized by changing the cross linker to polymer ratio. They are nontoxic, porous particles, insoluble in most organic solvents and stable up to 300°C. They are stable at the pH range of1-11.They form clear and opalescent suspension in water. They can be reproduced by simple thermal desorption, extraction with solvents, byusing microwaves and ultrasounds[6,25].Their three-dimensional structure allows capture, transportation and selective release of a variety of substances. Chemical linkers permit nanosponges to bind preferably to the target site. By complexing with different drugs nanosponges can form inclusion and non-inclusion complexes. By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges[7].

2. MATERIALS AND METHODS

MATERIALS

Etoposide - Gift sample, **Ethyl Cellulose** - Himedia, Mumbai, **Eudragit** - Yarrow Pharma, **Polyvinyl Alcohol** - Sigma Aldrich, **Dimethyl Formamide** - Zhuhai Chemico Industries, **Di-Sodium Hydrogen Orthophosphate** - SD Fine Chemical Limited, **Potassium Dihydrogen Orthophosphate** - Qualigens Fine Chemicals, Mumbai.

Magnetic Stirrer - REMI-2MLH, **Optical Microscope** - MOTICB1SERIES, **UV Spectrophotometer** - JASCOV-530, **FT-IR Spectrometer** - FTIRJASCO-4100, **pH Meter**– pHTESTER1, 2(EUTECH), **Zeta Sizer** – MALVERN, **SEM** - HITACHIX650,Tokyo, Japan, **Dialysis membrane50mm** - Himedia, Mumbai.

METHODOLOGY

Preparationofstocksolution

ThestandardstocksolutionofEtoposidewaspreparedbytransferringaccuratelyweighedquantity(10 mg) of Etoposide raw material in 100 ml of volumetric flask[8]. The drug was dissolvedin few ml of ethanol and the volume was made up to 100 ml with ethanol to get a stock solution of 100 µg/mL.

Selection of Wavelength

Thestandardstocksolutionwasscannedintherangeof200to400nminUVspectrophotometerusing methanol as blank.

Construction of calibration curve of Etoposide:

From the standard stock solution of Etoposide 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 ml were withdrawn to 10 ml volumetric flask and then made up volume with methanol to get a concentration range of 5-40 µg/mL[22-24]. The absorbance of these solutions was measured at 288nm using JASCO V-530 UV 1600 UV- visible spectrophotometer methanol was used as blank. The calibration curve was plotted between concentration and absorbance.

Formulation of Etoposide Nanosponges by Emulsion Solvent Diffusion Method:

Emulsion solvent diffusion method was used to formulate Etoposide loaded nanosponges by using a suitable polymer. Dispersed phase consists of specified amount of drug and polymer which was dissolved in 20 ml of an organic solvent, dichloromethane. Aqueous phase consists of specified amount of poly vinyl alcohol dissolved in 100 ml distilled water. Disperse phase was added drop by drop into aqueous phase by stirring on magnetic stirrer at 1000 rpm for about 2 hours. The nanospongesformed were collected by filtration and dried in oven at 40°C for about 24 hours[10]. They were then kept in the vacuum desiccators to remove the residual solvent. The Etoposide nanosponges were formulated using polymers Ethyl Cellulose and Eudragit.

Evaluation of Formulations

1. **Characterization of Nanosponges FTIR Spectroscopy of Nanosponges**

Before formulating a drug substance into dosage form, it is essential that it should be chemically and physically compatible. Compatibility studies give information needed to define the nature of the drug substance and provide a frame work for the drug combination with pharmaceutical excipients in the fabrication of a dosage form. This study was carried out by using infrared spectrophotometer to find if there is any possible chemical interaction between the Etoposide and polymers[11,16-18]. A few mg of sample (Etoposide Nanosponges) was weighed and mixed with 100 mg of potassium bromide (dried at 40-50°C). The mixture was taken and compressed under 10- ton pressurein hydraulic press to form a pellet. The pellet was scanned from 4000-400cm^{-1} in IR spectrophotometer.

Percentage yield was calculated by

$$\text{Percentage yield} = \frac{\text{Practical weight of nanosponges obtained}}{\text{Theoretical weight (drug + polymers)}} \text{ X } 100$$

2. Scanning Electron Microscopy (SEM)

SEM analysis was performed to determine their microscopic characters (shape & morphology) of prepared Etoposide nanosponges. Nanosponges were prepared and dried well to remove themoisture content and images were taken using scanning electron microscopy (Hitachi X650, Tokyo, Japan) in different magnifications .Samples were placed on glass slide kept under vacuum and then by using sputter coater unit, samples were coated with a thin gold layer, operated at 15kv acceleration voltage[12-14].

3. Particle Size Determination

The average mean diameter and size distribution of loaded nanosponges is found by Dynamic Light Scattering method using Malvern zeta sizer at 25°C.The dried nanosponges were dispersed in water to obtain proper light scattering intensity for Etoposide nanosponges[5,13].

4. Determination of Zeta Potential

Zeta potential is a measure of surface charge. The surface charge (electrophoretic mobility) of nanosponge can be determined by using Zeta sizer (Malvern Instrument) having zeta cells, polycarbonate cell with gold plated electrodes and using water as medium for sample preparation. It is essential for the characterization of stability of the nanosponges[28,29].

5. Determination of Entrapment Efficiency

The entrapment efficiency of nanosponges were determined by adding 10 ml of phosphate buffer of pH 7.4 and sonicated in a bath sonicator and filtered. 1 ml of filtrate is made up to 10 ml with phosphate buffer and was assayed spectrophotometrically at 288 nm (UV visible spectrophotometer, model UV- 1601 PC, Shimadzu). The amount of entrapped drug was calculated from the equation[27].

Entrapment efficiency = (Practical drug content/Theoretical drug content) X 100

6. In Vitro Release studies

Drug release was determined Dialysis Bag Diffusionmethod :

Two ml of each formulation (test and control) were poured into dialysis bags and put into 25ml phosphate buffer (pH 7.4) and stirred (100 rpm, room temperature). At predetermined time intervals, 2 ml of phosphate buffer was taken and then substituted by fresh phosphate buffer. Finally, the amounts of Etoposide released in phosphate buffer were measured by spectrophotometer at 288 nm[15,31]. Aliquots withdrawn were assayed at each time interval for the drug released at λ max of 288 nm using UV-Visible spectrophotometer by keeping phosphate buffer pH 6.8 as blank and the amount of released drug was estimated by the standard curve.

3. RESULTS AND DISCUSSION

ConstructionofcalibrationcurveofEtoposide

Inthe calibrationcurve,linearitywas obtainedbetween5-40µg/mlconcentrationofEtoposideand theregressionvaluewasfoundtober2=0.9996.hencewecanconcludethatEtoposideobeysBeerLambert'sLawattheconcentration between5-40µg/ml.TheresultsareshowninTable8 andFigure5.

Table1:ConcentrationandabsorbancevaluesforestimationofEtoposide

S.NO	Concentration	Absorbance(AU)at 288nm
1	5	0.1686

2	10	0.3624
3	15	0.5357
4	20	0.6963
5	25	0.8770
6	30	1.0693
7	35	1.2700
8	40	1.4516

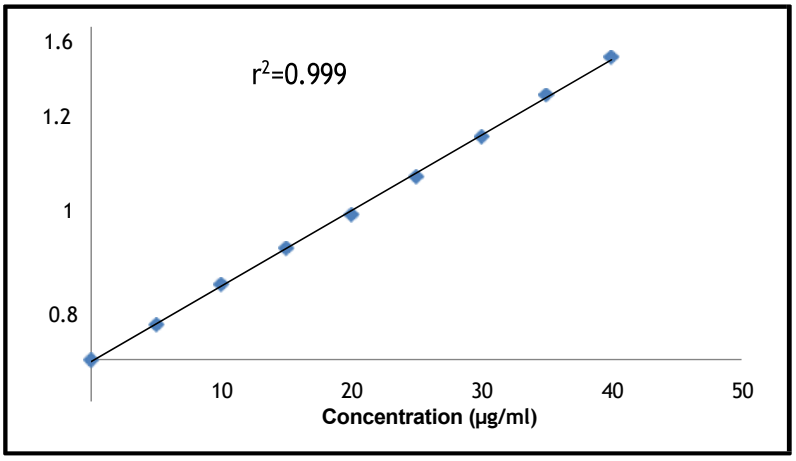


Figure1:CalibrationgraphofEtoposide

Table2: Optimised FormulationofEtoposide NanospongesbyEmulsion Solvent DiffusionTechnique

S.No	Formulation code	Drug in mg	Polymer in mg	Drug:polymer ratio
1	F1	ETOPOSIDE (100)	Ethylcellulose (50)	1:0.5
2	F2		Ethylcellulose (100)	1:1
3	F3		Ethylcellulose (150)	1:1.5
4	F4		Ethylcellulose (200)	1:2
5	F5		Ethylcellulose (250)	1:2.5
6	F6		Eudragit (50)	1:0.5
7	F7		Eudragit (100)	1:1
8	F8		Eudragit (150)	1:1.5
9	F9		Eudragit (200)	1:2
10	F10		Eudragit (250)	1:2.5

Table3:PercentageyieldofEtoposidenanosponges

S.No	Formulationcode	Percentageyield(%)
1.	F1	65.76
2.	F2	71.25
3.	F3	73.28
4.	F4	78.16
5.	F5	80.34
6.	F6	32.08
7.	F7	34.14
8.	F8	48.57
9.	F9	49.75
10.	F10	57.22

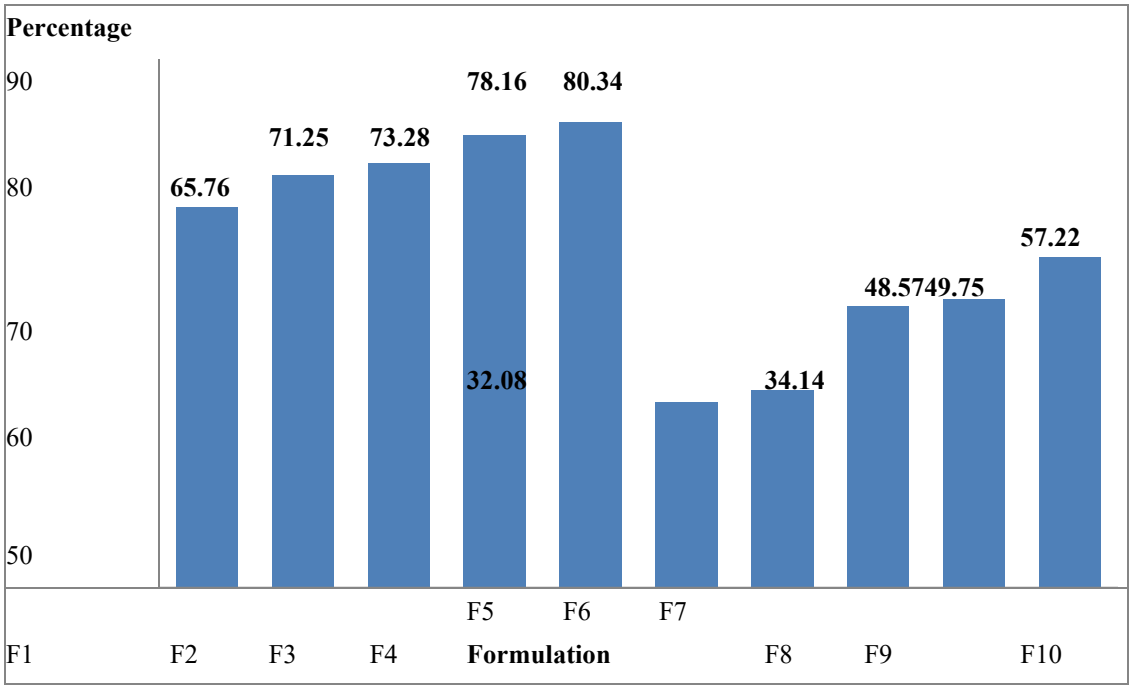


Figure 2 : PercentageyieldanalysisofEtoposidenanosponges

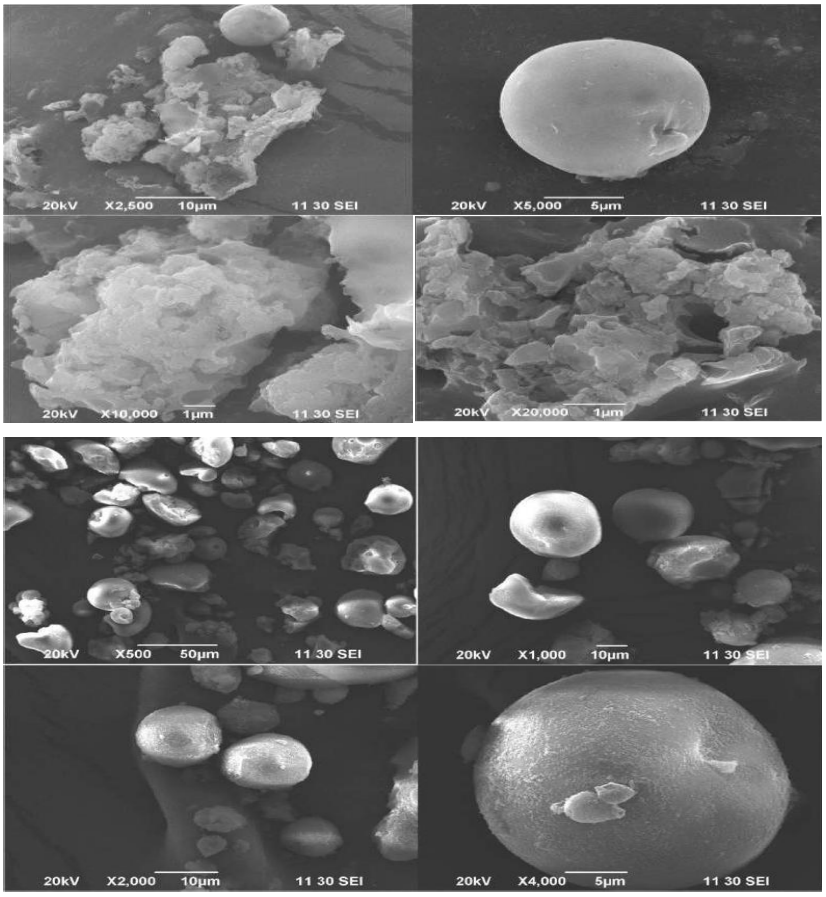


Figure 3 : SEMimagesofEtoposidenanospongesusing Ethyl Cellulos

Figure 4 : SEM imagesofEtoposidenanospongesusing eudragit

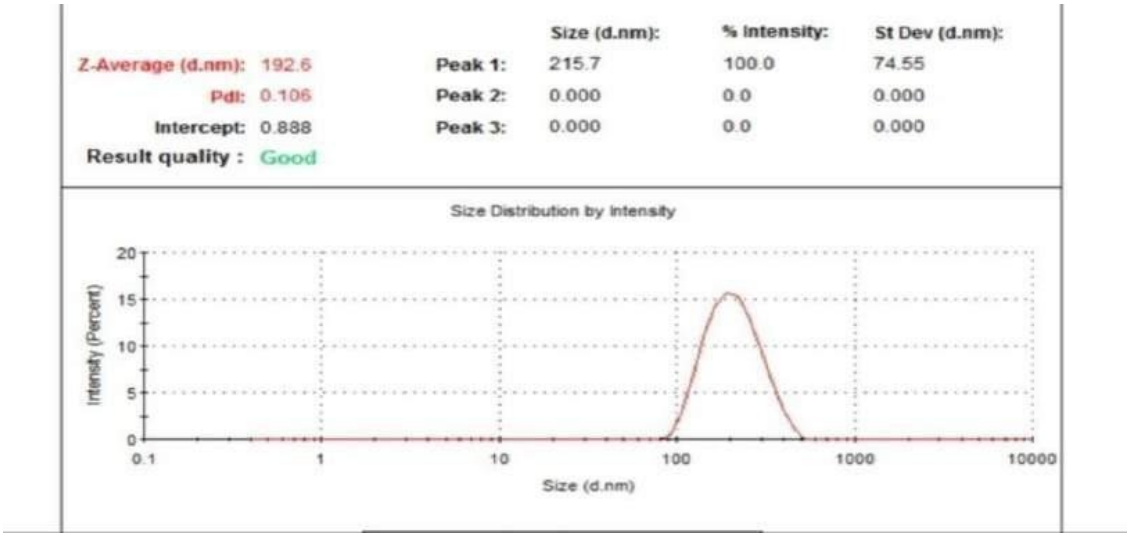
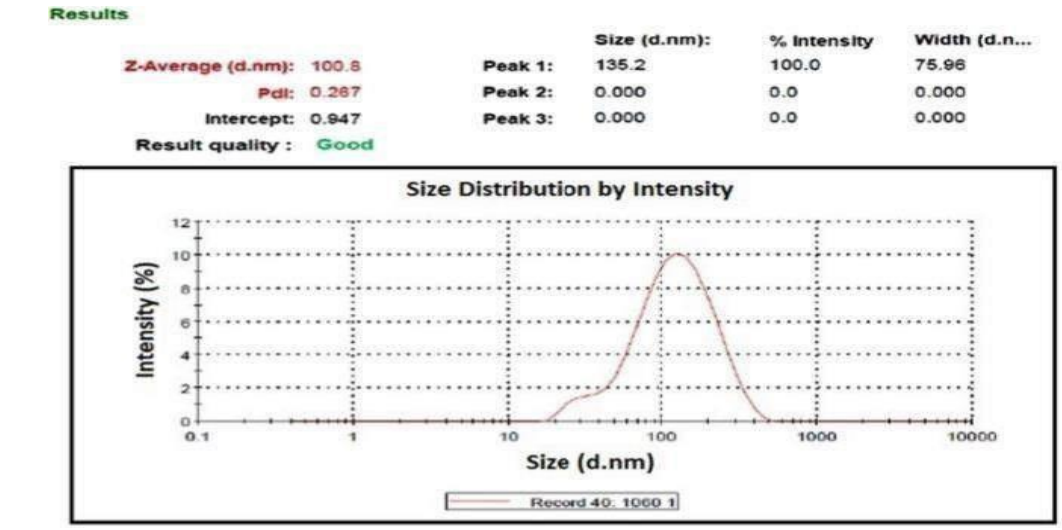


Figure 5 : ZetasizedistributionofEtoposidenanosponges(F4)



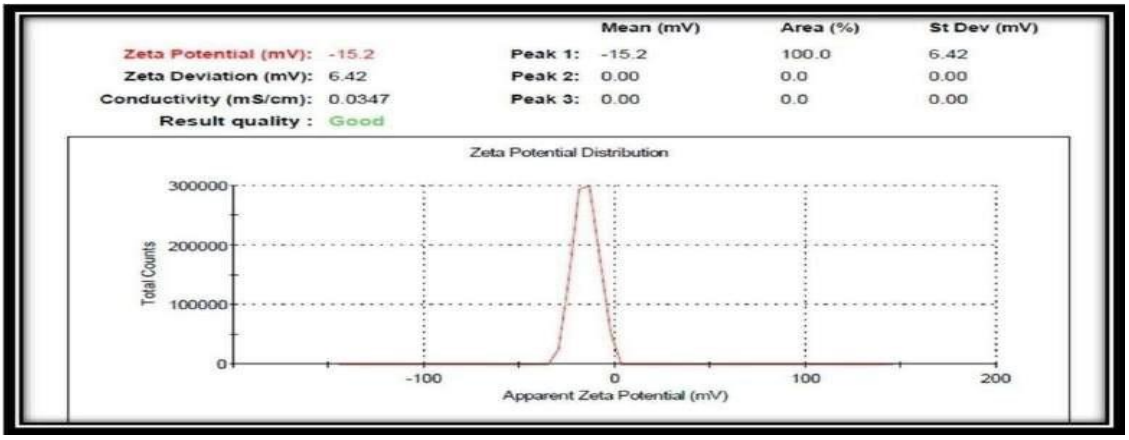


Figure 6 : ZetasizedistributionofEtoposidenanosponges(F6)

Figure 7 : Zeta potential of Etoposide Nanosponges (F4)

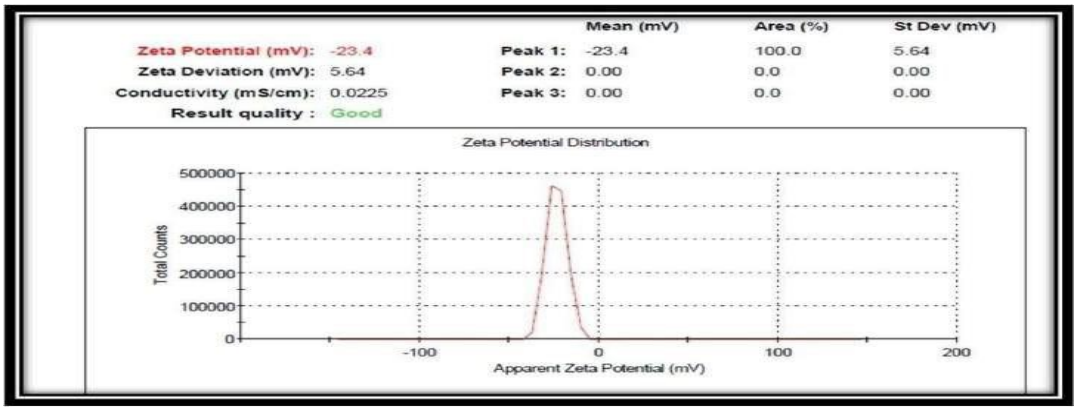


Figure 8: ZetapotentialofEtoposidenanosponges (F9)

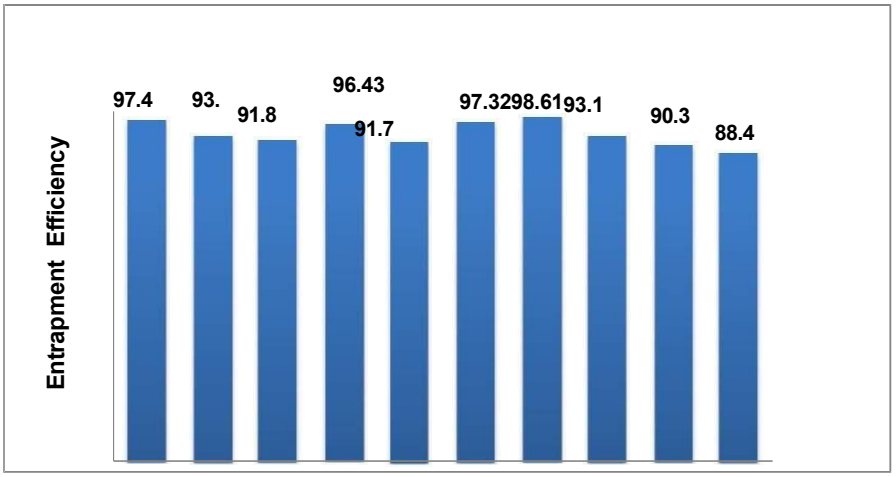


Figure 9 : EntrapmentefficienciesofEtoposidenanosponges

Table 4:In-vitrodrugreleaseprofileofEtoposidenanosponges(F1-F5)

Sl.No	Time(hrs)	Cumulativepercentagedrugrelease(%)				
		F1	F2	F3	F4	F5
1	0	0	0	0	0	0
2	1	10.90	11.93	11.08	7.36	7.23
3	2	18.62	20.26	15.7	9.33	8.96
4	3	21.76	24.89	19.39	10.13	9.89
5	4	26.00	30.01	21.24	13.11	11.54
6	5	30.23	37.37	25.86	16.93	14.89
7	6	37.94	42.73	27.71	22.19	18.16
8	7	43.47	47.03	32.33	26.35	23.54
9	8	45.18	50.96	35.68	29.71	28.18
10	10	50.04	52.74	42.46	33.53	30.13
11	12	52.14	55.16	46.89	40.05	38.91
12	24	63.17	64.73	56.86	53.83	49.75
13	32	69.90	69.16	64.90	58.12	53.67
14	36	77.18	75.44	69.17	61.92	59.11
15	48	89.90	88.79	81.75	72.86	67.56

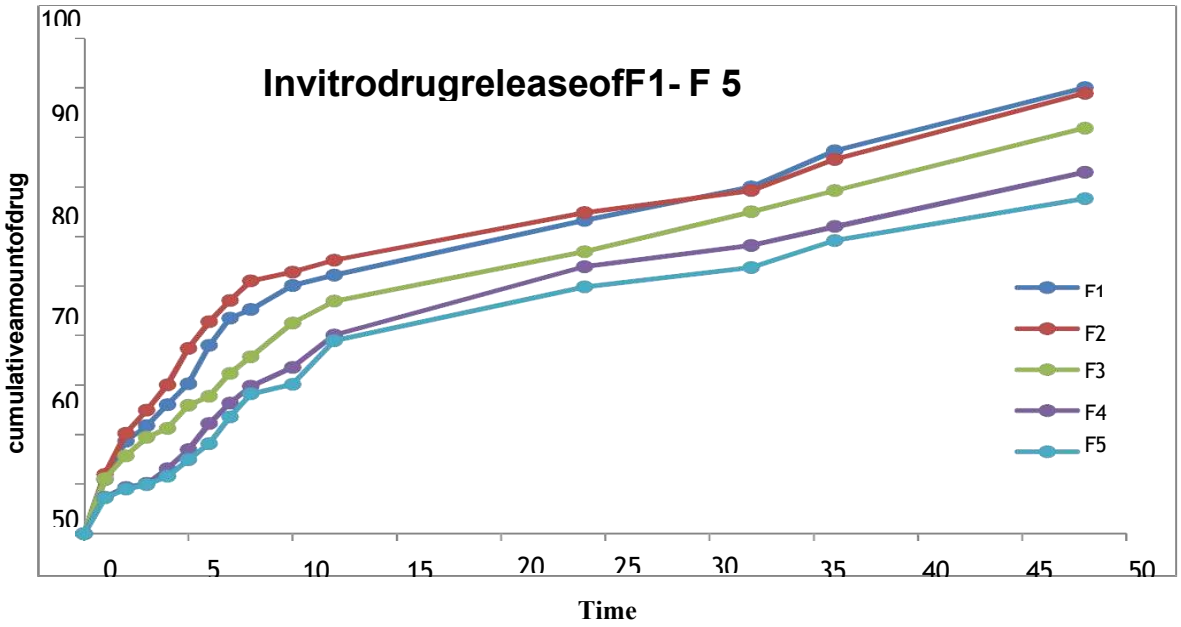


Figure 10 : InvitrodrugreleaseprofileofEtoposidenanospongescontaining Ethyl Cellulose (F1-F5)

Table 5 : InvitrodrugreleaseprofileofEtoposidenanosponges(F6-F10)

Sl.No	Time(hrs)	Cumulativepercentagedrugrelease(%)				
		F6	F7	F8	F8	F10
1	0	0	0	0	0	0
2	1	13.44	14.32	14.06	8.99	7.45
3	2	16.48	18.35	17.77	10.27	9.06
4	3	22.39	22.14	22.26	11.30	10.87
5	4	27.18	27.04	24.41	13.10	12.12
6	5	31.4	30.05	29.05	13.87	15.68
7	6	36.16	34.24	32.02	16.44	18.86
8	7	41.64	41.08	36.57	20.55	24.98
9	8	45.19	43.61	39.09	23.76	29.12
10	10	51.4	49.35	43.43	36.99	32.19
11	12	54.16	53.67	48.13	40.18	39.16
12	24	62.41	62.53	55.89	48.91	50.80
13	32	70.85	68.51	61.24	55.16	54.89
14	36	76.18	73.27	66.75	61.19	60.23
15	48	90.18	87.10	77.94	70.14	69.86

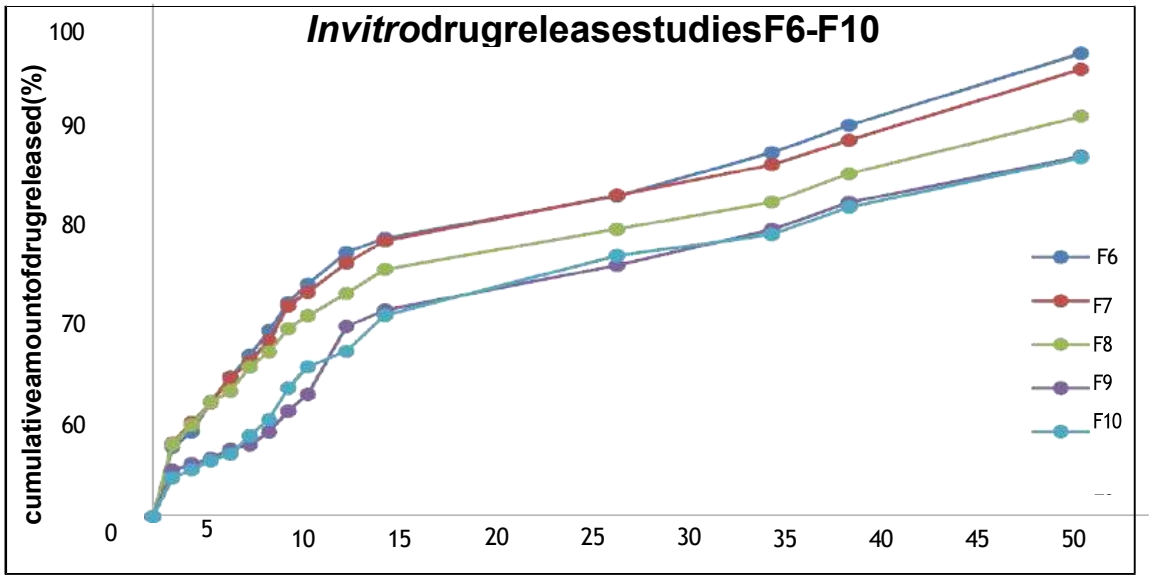


Figure 11: InvitrodrugreleaseprofileofEtoposidenanospongescontaining Eudrajit (F6-F10)

4. CONCLUSION

The Etoposide Nanosponges can be formulated by cost effective and easy emulsion solvent diffusion method using hydrophobic polymers such as Ethyl Cellulose and Eudragit. TheEtoposidenanospongescanbeformulatedbycosteffectiveandeasyemulsionsolventdiffusion methodusinghydrophobicpolymerssuchasethylcelluloseandeudragit.TheformulatedEtoposide nanospongescanbeused inthetreatment ofcancersuchasleukemiaandothercancers.This canbe targeted to the cancerous cells and produce sustained drug delivery which in turn reduces the dose, frequency of administration and the side effects.

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6. CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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