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Review

Formulation and Evaluation of Targeted Drug Delivery system of Doxorubicin Nanopsonges

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Abstract

The aim and objective of the present study was to formulate and evaluate Doxorubicin nanosponges for targeted delivery. Nanosponges were prepared using ethyl cellulose as the polymer and polyvinyl alcohol as the stabilizing agent by solvent evaporation method. The Nanosponges prepared were evaluated for different parameters like the drug: polymer ratio, stirring speed and time. The encapsulation and the diffusion study of the formulation were done. Particle size analysis and scanning electron microscopy of the nanosponges were performed and from this study it was found that the nanosponges were spherical in shape and have porous nature. The nanosponges prepared were incorporated into the gel base of carbapol. In diffusion study of the nanosponge gel was performed. Similarly F6 and F7 exhibited the best release of 90.19% and 87.10% respectively at the end of 48 hours amoung all the five formulations of Doxorubicin – eudragit nanosponges.

Keywords: Doxorubicin, Nanosponges, Solvent Evalporation Method.

INTRODUCTION

Nanosponges have emerged as one of the most promising fields of science because of their perceived application in controlled drug delivery. Nanosponge delivery system can precisely control the release rates or target drugs to a specific body site and have an enormous impact on the health care system. This nanosized delivery system has definite advantages for the purpose of drug delivery because of its high stability, high carrier capacity and feasibility of incorporation of both hydrophilic and hydrophobic substances. The application of nanosponges for targeted and localized delivery of therapeutic agents is the driving force for the research in this area (2). The sponge acts as a three-dimensional network or scaffold. The backbone is long-length polyester. It is mixed in solution with cross-linkers to form the polymer. The net effect is to form spherically shaped particles filled with cavities where drug molecules can be stored. The polyester is biodegradable, so it breaks down gradually in the

body. As it breaks down, it releases its drug payload in a predictable fashion. The nanosponges can be synthesized to be specific size and to release drugs over time by varying proportions of crosslinker to polymer. The main limitation of nanosponges is their ability to include only small molecules (3). Nanosponges are solid in nature and are small particles with porous surface can be formulated as oral, parenteral, topical or inhalational dosage forms.

Drug Excipient Compatibility Studies

T-IR spectrum pf drug was recorded using FT-IR Spectro photometer (Shimadzu JASCO 4100). The diffuse reflectance technique was utilised in the mid IR 4000-400 cm spectral region. The procedure consist of dispersing the sample in KBr(100mg) using a mortar, triturating the materials into a fine powder bed into the holder using compression gauge. The pressure was around 5 tons for 5 minutes. The pellet was placed in the light path and the spectrum was recorded. The characteristic peaks of the functional groups were interpreted.
The FTIR spectrum of Doxorubicin, polymers ethyl cellulose and eudragit were recorded. The spectrum of physical mixture of Doxorubicin, polymer and co-polymer were also documented to check for their compatibility.

II. FORMULATION OF DOXORUBICIN NANOSPONGES BY EMULSION SOLVENT DIFFUSION METHOD:

Emulsion solvent diffusion method was used to formulate Doxorubicin loaded nanosponges by using a suitable polymer. Dispersed phase consist of specified amount of drug and polymer which was dissolved in 20 ml of an organic solvent dichloromethane. Aqueous phase consist 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 nanosponges formed were collected by filtration and dried in oven at 40°c for about 24 hours. They were then kept in the vacuum desiccators to remove the residual solvent. The Doxorubicin nanosponges were formulated using polymers ethyl cellulose and eudragit.

III. 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 drug substance and provide a frame work for the drug combination with pharmaceutical excipients in the fabrication dosage form. This study was carried out by using infrared spectrophotometer to find if there is any possible chemical intraction between the Doxorubicin and polymers.
A few mg of sample (Doxorubicin 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 pressure in hydraulic press to form a pellet was scanned from 4000-400 cm-1 in IR spectrophotometer.

Determination of percentage yield

Doxorubicin loaded nanosponges were weighed after drying. Percentage yield was calculated by

$$\% \text{ yield} = \frac{\text{practical weight of nanosponges obtained}}{\text{Theoretical weight (drug + polymers)}} \times 100$$

Scanning electron microscopy (SEM)

SEM analysis was performed to determine their microscopic characters (shape & morphology) of prepared Doxorubicin nanosponges. Nanosponges were prepared and dried well to remove the moisture 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.

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 Doxorubicin nanosponges.

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 characterisation of stability of the nanosponges.

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. 1ml 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.

$$\text{Entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

In vitro release studies

Drug release was determined by dialysis method; two ml of each formulation (test and control) were poured into dialysis bags and put into 25 ml 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 released Doxorubicin in phosphate buffer were measured by spectrophotometer at 288 nm. Aliquots withdrawn were assayed at each time interval for the drug released at λmax of 288 nm using UV-Visible spectrophotometer by keeping phosphate buffer pH 7.4 as blank and the amount of released drug was estimated by the standard curve.

RESULTS AND DISCUSSIONS

I. PREFORMULATION STUDIES

Physical Characteristics

Doxorubicin was checked for its colour, odour and texture. Doxorubicin is red coloured powder in appearance, odourless and amorphous in nature.

Solubility

Solubility test for Doxorubicin was carried out in different solvents such as ethanol, water, dichloromethane and chloroform and results are given in Table 1.

Table 1: Solubility test for Doxorubicin in different solvents

Sl. No	Solvent	Soluble	Sparingly Soluble	Insoluble
1.	Ethanol	□	-	-
2.	Dichloromethane	□	-	-
3.	Chloroform	-	□	-
4.	Water	□	-	-

Selection of Wavelength

The Doxorubicin stock solution of concentration 100µg/mL was scanned in the range of 200- 400nm for λmax. using double beam UV Spectrophotometer. The absorption peak obtained is shown in Figure 1.

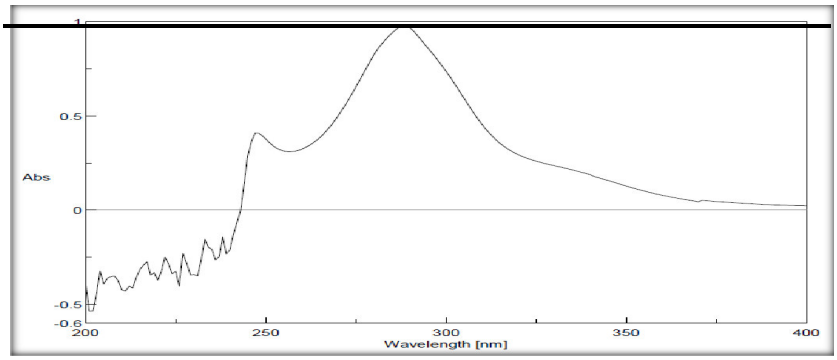

Figure 1: UV spectra of Doxorubicin

The maximum absorption of Doxorubicin was found to be at 232nm and hence it is selected as the wavelength for further studies.

Construction of calibration curve of Doxorubicin

In the calibration curve, linearity was obtained between 5-40 µg/ml concentration of Doxorubicin and the regression value was found to be r^2 = 0.9996. Hence we can conclude that Doxorubicin obeys Beer Lambert's Law at the concentration between 5-40 µg/ml. The results are shown in Figure 5.

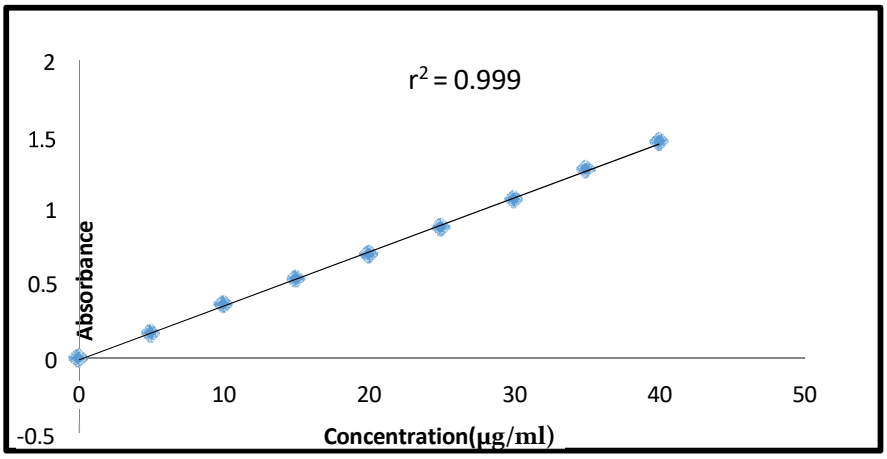

Figure 2: Calibration graph of Doxorubicin

Excipient Compatibility Studies

Fourier Transform Infrared (FT-IR) spectra of the samples were obtained using a SHIMADZU Spectrometer by KBr disc method. The spectrums were recorded for the pure drug and physical mixture of drug and polymer and are shown in Figures 3,4, and 5.

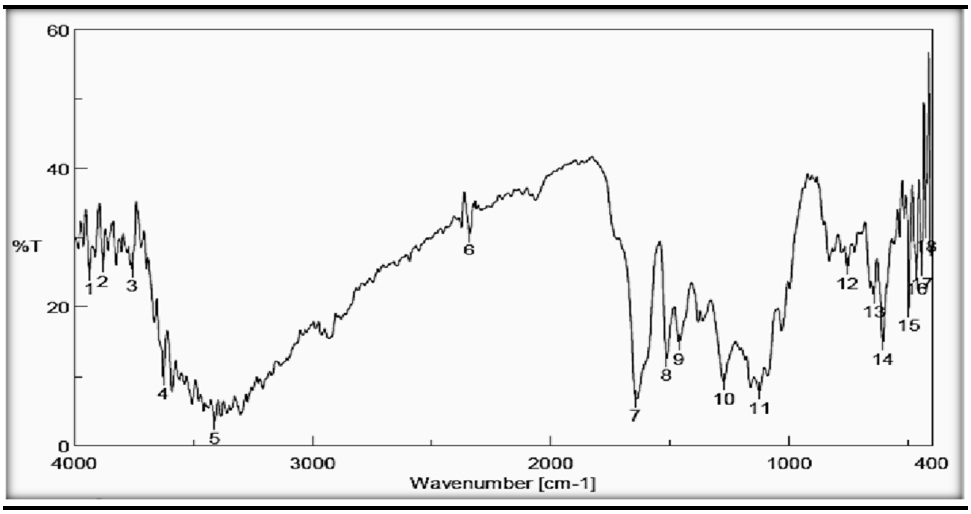

Figure 3: FTIR – spectrum of Doxorubicin

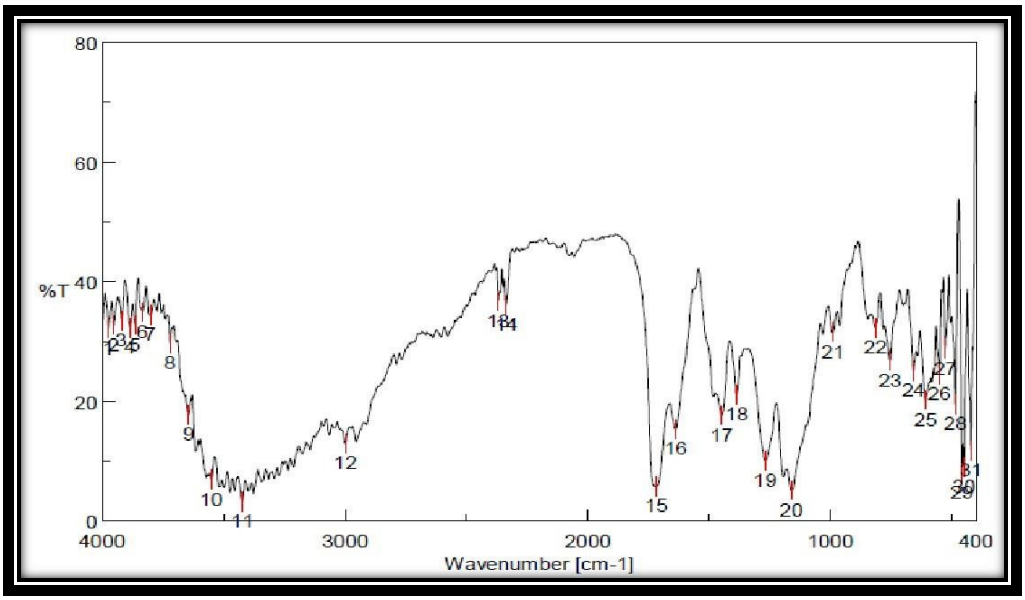

Figure 4: FTIR spectrum of physical mixture containing Doxorubicin, Eudragit and PVA Table

The peaks present in the FTIR spectra of pure Doxorubicin are present in the FTIR spectra of physical mixture containing Doxorubicin with ethyl cellulose and Doxorubicin with eudragit. It is therefore evident that the Doxorubicin is compatible with the excipients ethyl cellulose eudragit and poly vinyl alcohol and can be chosen for the formulation of Doxorubicine

II. FORMULATION OF NANOSPONGES

Selection of polymers for the formulation of Doxorubicin nanosponges by emulsion solvent diffusion method was based on the trial batches carried out by using different polymers such as ethyl cellulose, eudragit, sodium alginate, HPMC, Carbopol, hydroxyl ethyl cellulose, chitosan and pectin and details are depicted in table 15. Drug: polymer ratio was selected based on the literature. The results indicated that ethyl cellulose and eudragit was found to be suitable for the formulation of Doxorubicin nanosponges.

Table 7: Trial batches for formulation of Doxorubicin nanosponge

Drug	Polymer	Ratio	Result observed
DOXORUBICIN	Ethyl cellulose	1:2	Product obtained
	Eudragit	1:2	Product obtained
	Hydroxy propyl methyl cellulose	1:2	Less yield
	Hydroxyl ethyl cellulose	1:2	Less yield
	Carbopol	1:2	Gel like product
	Sodium alginate	1:2	Gel like product
	Chitosan	1:2	No product
	Cyclodextrin	1:2	No product
	Pectin	1:2	No yield

Total ten formulations (F1 – F5 and F6 – F10) of Doxorubicin nanosponges with two different polymers ethyl cellulose and eudragit in different ratios were formulated by emulsion solvent diffusion method as given in Table 16 and Table 17.

Table 8: Formulation of Doxorubicin nanosponges

S. No	Formulation code	Drug	Polymer	Drug: polymer ratio
1	F1	DOXORUBICIN	Ethyl cellulose	1:0.5
2	F2		Ethyl cellulose	1:1
3	F3		Ethyl cellulose	1:1.5
4	F4		Ethyl cellulose	1:2
5	F5		Ethyl cellulose	1:3
6	F6		Eudragit	1:0.5
7	F7		Eudragit	1:1
8	F8		Eudragit	1:1.5
9	F9		Eudragit	1:2
10	F10		Eudragit	1:2.5

Table 9: Formulation of Doxorubicin nanosponges by emulsion solvent diffusion technique

S. No	Formulation code	Weight of drug (mg)	Weight of polymer (mg)	Weight of polyvinyl alcohol(mg)
1	F1	100	50	200
2	F2	100	100	200
3	F3	100	150	200
4	F4	100	200	200
5	F5	100	300	200
6	F6	100	50	200
7	F7	100	100	200

8	F8	100	150	200
9	F9	100	200	200
10	F10	100	250	200

III. CHARACTERISATION OF DOXORUBICIN NANOSPONGES

Percentage yield analysis

Percentage yield of the formulated Doxorubicin nanosponges were calculated using the formula:

$$Percentage\ Yeild = \frac{Practical\ yield}{Theoritical\ yield} \times 100$$

The percentage yield was minimum for formulation F6 (32.08%) and maximum for formulation F5 (80.34%). From the results we can conclude that as the concentration of polymer increases the percentage yield also increases. It can also be noted that the yield obtained while using ethyl cellulose as polymer is much higher when compared with eudragit. The percentage yield of all formulations is depicted in Figure 9.

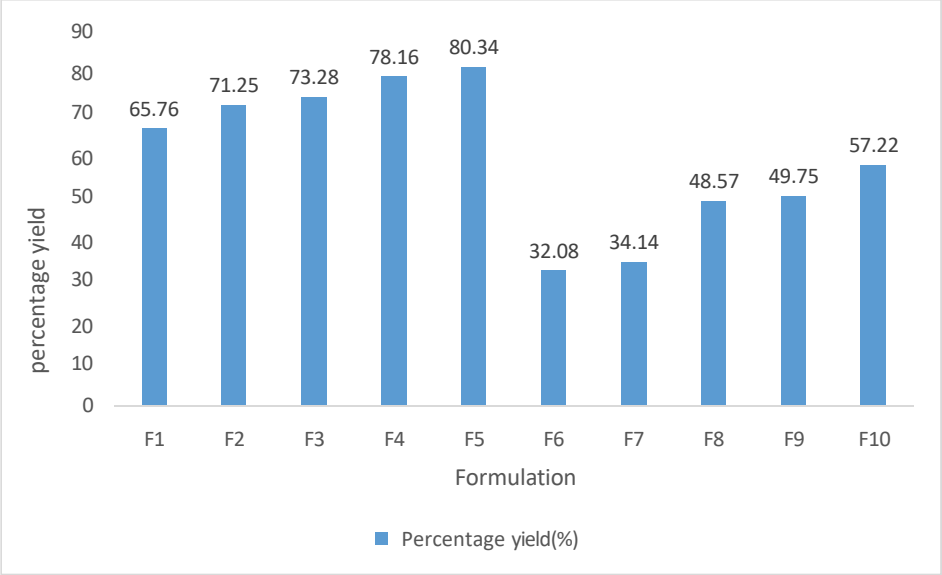

Figure 5: Percentage yield analysis of Doxorubicin nanosponges

Scanning Electron Microscopy

SEM analyses of the formulated Doxorubicin nanosponges were performed to evaluate the surface morphology of nanosponges. The SEM images of formulation F9 are shown in Figure 10.

SEM images showed the nanosponge was porous with a smooth surface morphology and spherical in shape. The spongy and porous nature of the nanosponges can be seen in the above figures.The presence of pores was due to the impression of diffusion of the solvent dichloromethane.

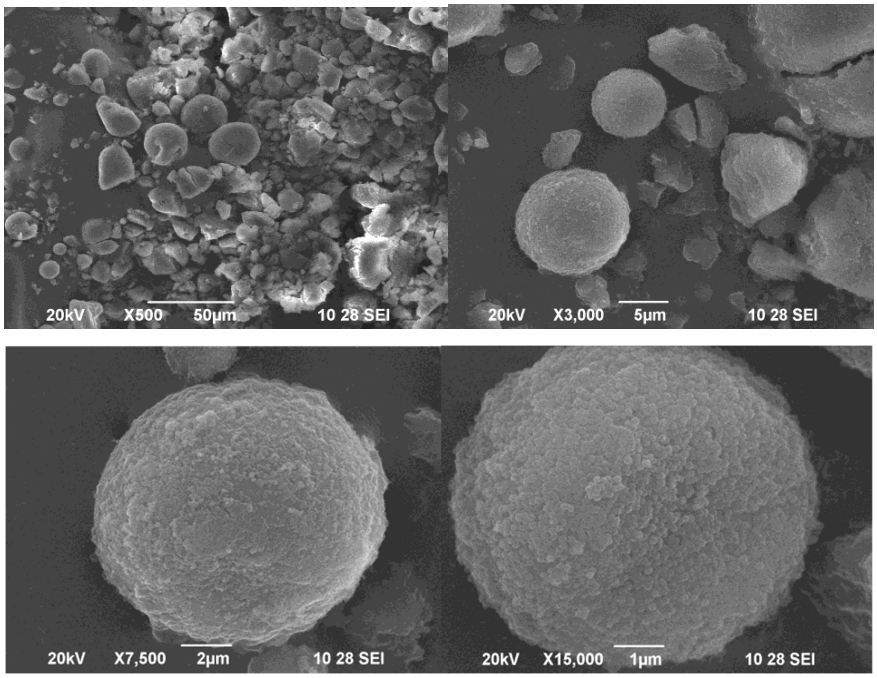

Figure 6: SEM images of Doxorubicin nanosponges using eudragit

Particle Size Measurement

The particle size is one of the most important parameter for the characterisation of nanosponges. The average particle sizes of the prepared Doxorubicin nanosponges were measured using Malvern zeta sizer.

Particle size analysis showed that the average particle size of Doxorubicin nanosponges formulated using eudragit (F9) was found to be 4097 nm with polydispersity index (PDI) value

1.00 and with intercept 1.41. The zeta size distribution of ethyl cellulose –Doxorubicin nanosponges is depicted in Figure 11.

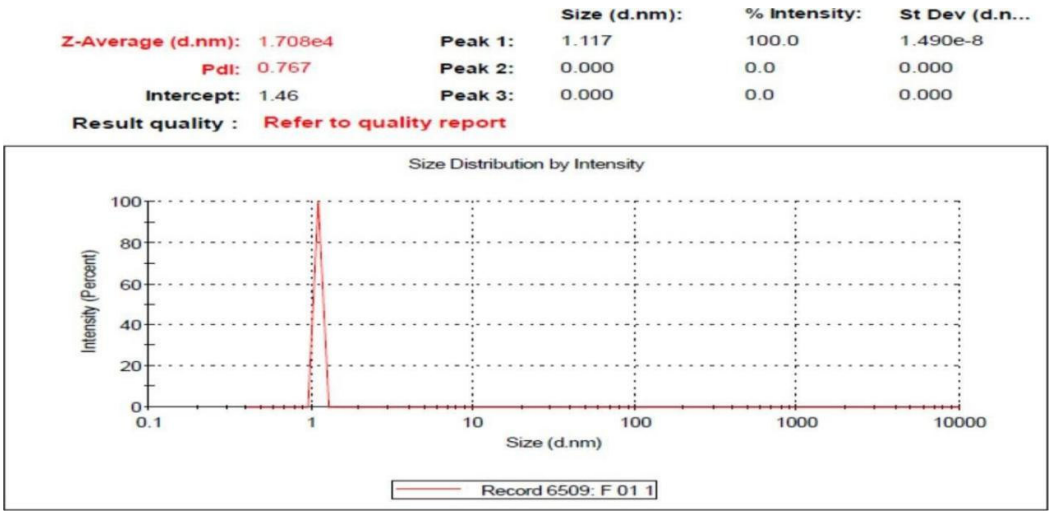

Figure 7: Zeta size distribution of Doxorubicin nanosponges

The average particle size analyses of eudragit-Doxorubicin nanosponges are 1.708which is lesser than 5µm.

Determination of Zeta Potential

Zeta Potential was determined using Malvern zeta-sizer instrument. Zeta potential analysis is carried out to find the surface charge of the particles to know its stability during storage. The magnitude of zeta potential is predictive of the colloidal stability. Nanoparticles with zeta potential value greater than +25 mV or less than -25 mV typically have high degrees of stability.

For Doxorubicin nanosponges using eudragit zeta potential was found to be -24.3mV with peak area of 100% intensity. These values indicate that the formulated Doxorubicin nanosponges are stable. Zeta potential distribution of Doxorubicin nanosponges prepared using eudragit is depicted in Figure 12.

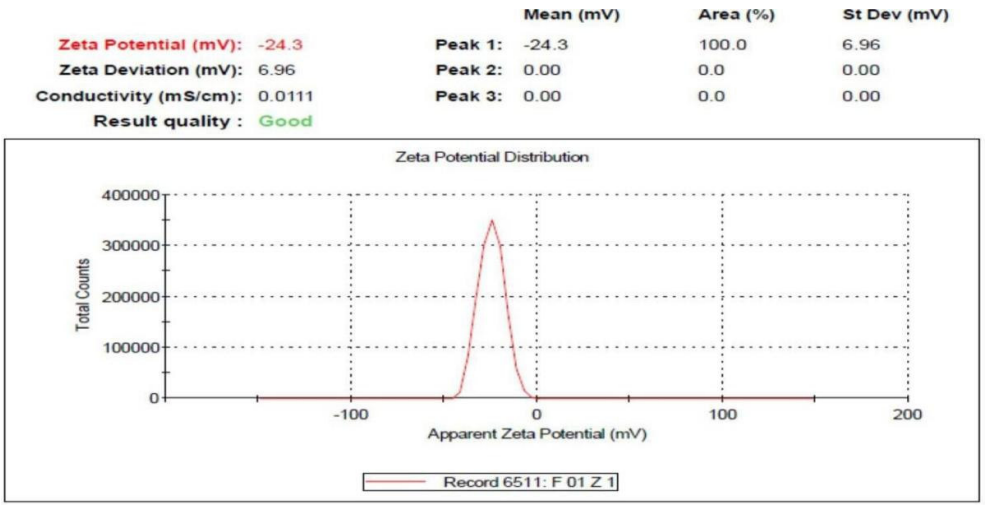

Figure 8: Zeta potential of Doxorubicin nanosponges Entrapment efficiency

The amount of entrapped drug was calculated from the equation:

$$\%\ Drug\ Entrpment = \frac{Practical\ drug\ content}{Theoretical\ drug\ content} \times 100$$

Entrapment efficiency of prepared formulation is given in Table 14 and Figure 13.

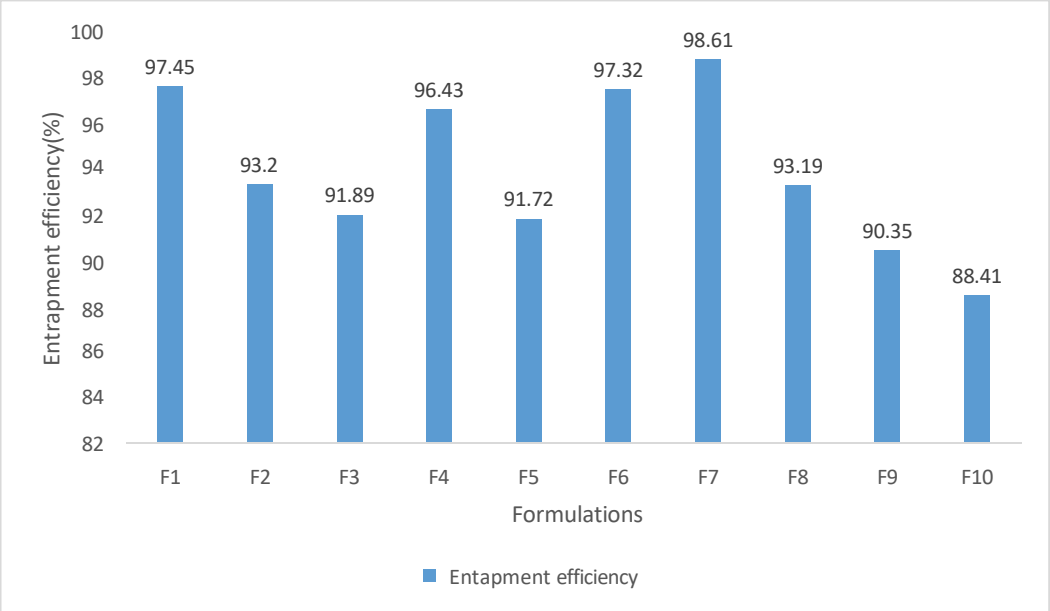

Figure 9: Entrapment efficiencies of Doxorubicin nanosponges

Table 15: *In vitro* drug release profile of Doxorubicin nanosponges (F1-F5)

Sl.No	Time (hrs)	Cumulative percentage drug release (%)				
		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

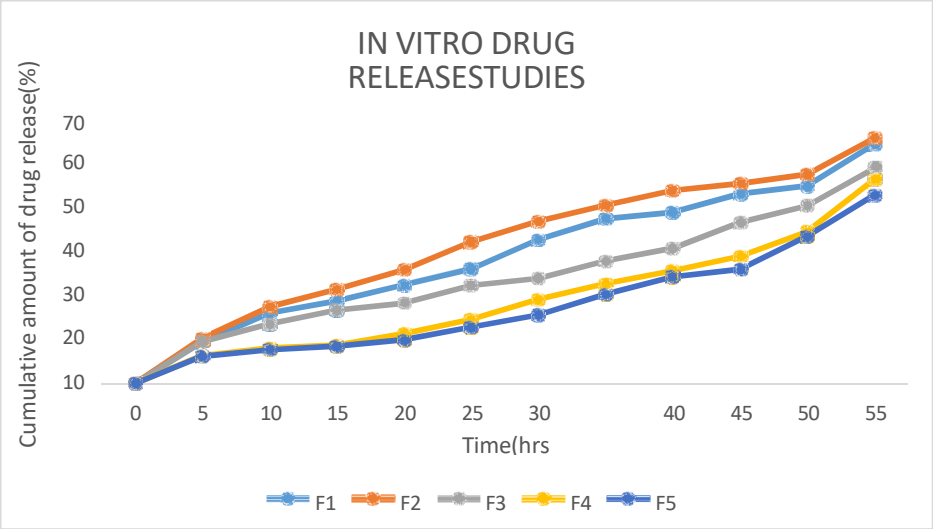

Figure 10: *In vitro* drug release profile of Doxorubicin nanosponges (F1-F5)

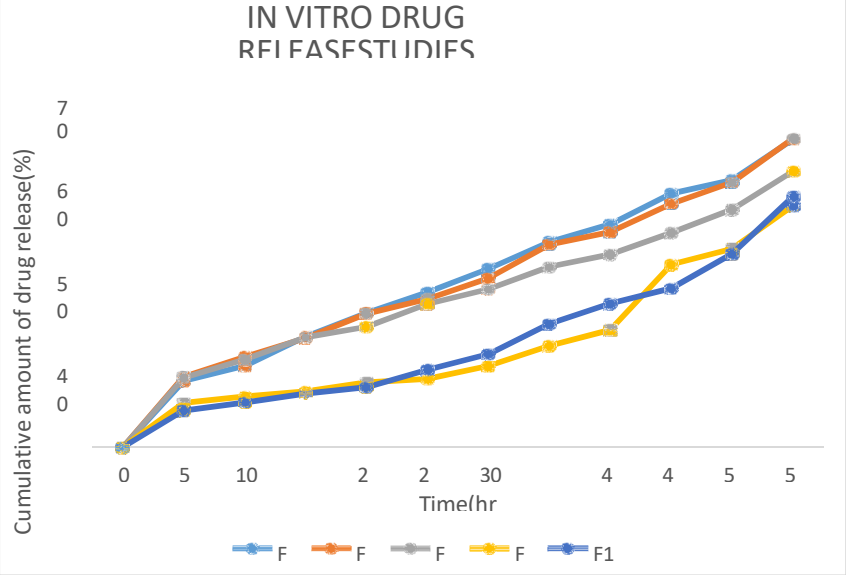

Figure 11: In vitro drug release profile of Doxorubicin nanosponges (F6-F10)

In vitro drug release profile data of Doxorubicin nanosponges containing eudragit (F6- F10) are given in Table 16 and Figure 15.

Table 16: In vitro drug release profile of Doxorubicin nanosponges (F6-F10)

Sl. No	Time (hrs)	Cumulative percentage drug release (%)				
		F6	F7	F8	F9	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

The entrapment efficiency was found to be highest for F7 formulation which is 98.61 and the lowest entrapment of drug was found for F10 formulation. This might be due to the fact that the variation in entrapment efficiency was due to the changes in the polymer concentration and difference in the degree of cross linking. The prepared nanosponges possess high drug entrapment efficiency and were found to be in the range of 88.40%-98.61%.

***IN VITRO* DRUG RELEASE STUDIES**

In vitro drug release study of the prepared. Doxorubicin nanosponges was carried out using dialysis bag diffusion method. Amount of drug released in different time intervals were observed.

In vitro drug release profile data of Doxorubicin nanosponges containing ethyl cellulose (F1-F5) are given in Table 15 and Figure 16.

From the in vitro release data it was found that formulation F1 and F2 showed the best release of 89.90% and 88.79% respectively at the end of 48 hours among all the five formulation of Doxorubicin – ethyl cellulose nanosponges. Similarly F6 and F7 exhibited the best release of 90.19% and 87.10% respectively at the end of 48 hours amoung all the five formulations of Doxorubicin – eudragit nanosponges. The release rate was related to drug: polymer ratio. Increase of drug release was observed as a function of drug: polymer ratio. It was observed that the drug release decreased with an increase in the amount of polymer for each formulation. This may be due to the fact that the release of drug from the polymer matrix takes place after complete swelling of the polymer and as the amount of polymer in the formulation increases the time required to swell also increases. These result are in agreement with the release pattern of Doxorubicin nanoparticles observed by Hui-ping-sun et al (2016).

The newly developed nanosponges exhibit a core shell structure with a hydrophobic core formed by either ethyl cellulose (F1-F5) and eudragit (F6-F10) and a hydrophilic shell formed by PVA macromolecules. The release showed a bi-phasic pattern with an initial burst effect may due to the unentrapped drug adsorbed on the surface

of the nanosponges, while remaining drug released for further few hours say around 7-8 hours may stem from drug molecule physically entrapped with in hydrophilic outer shell. At the same time, hydrophilic PVA molecules that from the shell could also solubilize within aqueous medium and release part of drug. Remaining drug is probably entrapped within the core of nanosponges and are released in the later time period.

CONCLUSION

The Doxorubicin nanosponges can be formulated by cost effective and easy emulsion solvent diffusion method using hydrophobic polymers such as eudragit. The formulated Doxorubicin nanosponges can be used in the treatment of breast cancer. This can be targeted to the cancer cells and produce sustained drug delivery which in turn reduces the dose, frequency of administration and the side effects.

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