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Formulation and Evaluation of Idarubicin Nanosponges

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Abstract

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. The hydrophobic nature of most of the drugs presents a challenge for effective in vivo delivery. Shrinking materials to nano size has profoundly enhanced the efficacy of such drugs. 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 input rate. 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 studies conducted in this field proves that the tiny mesh-like structures called nanosponges may revolutionise the treatment of many diseases and early trials suggest this technology is up to five times more effective at delivering drugs for breast cancer than conventional methods.

Keywords
Nanosponges, lipophilic, hydrophilic.

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INTRODUCTION:

Targeting Sites by Nanosponges

"Tagging" drug-loaded nanosponges ensures desired pharmacological response by targeting only disease affected cells and leaving the healthy ones unharmed. Drugs encapsulated within the nanosponge pores are shielded from premature destruction and stability of drug is enhanced. This tiny sponge circulates around the tumour cell until they encounter the surface to release their drug cargo in a sustained manner. Nanosponge is three to five times more effective at decreasing tumour growth than direct injection. The targeted delivery systems of nanosponge have several basic advantages like, the drug is released at the tumour instead of circulating widely through the body, and it is more effective for a given dosage. The nanosponges have basic features such as fewer harmful side effects as smaller amounts of the drug will come into contact with healthy tissue.

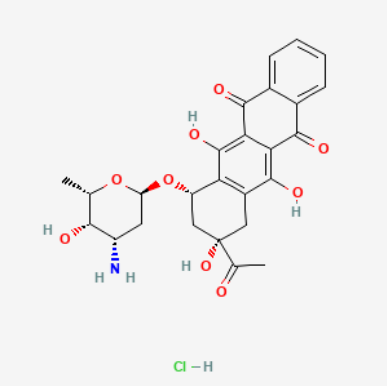
MARKETED FORMULATIONS

Table 1: Marketed formulations of nanosponges

Drug	Administration Route	Trade Name	Dosage Form
Dexamethasone	Dermal	Glymesason	Tablet
Iodine	Topical	Mena- gargle	Solution
Alprostadil	I.V	Prostavastin	Injection
Piroxicam	Oral	Brexin	Capsule

DRUG PROFILE

DRUG NAME: Idarubicin



MECHANISM OF ACTION:

Idarubicin binds directly to DNA via intercalation between base pairs on the DNA helix.2 Idarubicin also inhibits DNA repair by inhibiting topoisomerase II. These actions result in the blockade of DNA and RNA synthesis and fragmentation of DNA.4 Idarubicin is also a powerful iron-chelator. The iron-Idarubicin complex can bind DNA and cell membranes producing free radicals that immediately cleave DNA and cell membranes. Although maximally cytotoxic in S phase, Idarubicin is not cell cycle-specific.2

SUPPLY AND STORAGE:

Injection3: Mayne Pharma supplies Idarubicin in single-dose vials of sterile, preservative- free, lyophilized red powder of 10 mg, 50 mg and 150 mg sizes.3 The formulation contains lactose.41 Store vials between 15-20ºC and protect from light (keep intact vials in their carton until use).

Novopharm supplies Idarubicin in single-dose vials of sterile, isotonic, preservative-free solution of 10 mg/5 mL, 50 mg/25 mL and 200 mg/100 mL sizes.41 The formulation contains hydrochloric acid for pH adjustment. Refrigerate vials and protect from light (keep intact vials in their carton until use).

EXCIPIENTS PROFILE

EUDRAGIT® E 100

1. **Commercial form**

EUDRAGIT® E 100

Solid substance

EUDRAGIT® E 100 is described in the monographs quoted above.

EUDRAGIT® E PO

Solid substance obtained from EUDRAGIT® E 100.

EUDRAGIT® E PO is described in the Ph. Eur. and JPE monographs quoted above. The polymer conforms to the USP/NF monograph quoted above.

EUDRAGIT® E 12,5

Solution of EUDRAGIT® E 100 with 12.5 % (w/w) dry substance in a mixture of 60 % (w/w) Isopropyl Alcohol Ph. Eur. / USP and 40 % (w/w) Acetone Ph. Eur. / NF.

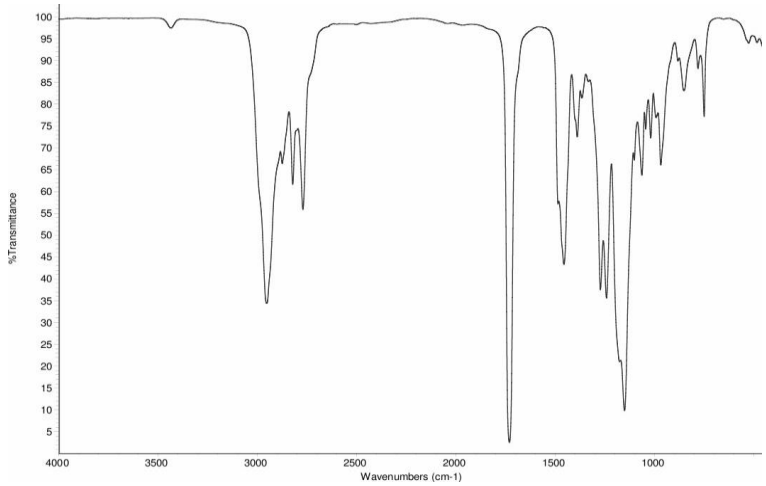
Monomers

EUDRAGIT® E 100 / EUDRAGIT® E PO total of monomers: < 2500 ppm Butyl methacrylate: < 1000 ppm

Methyl methacrylate: < 500 ppm Dimethylaminoethyl methacrylate: < 1000 ppm

EUDRAGIT® E 12,5: total of monomers max. 0.04 %

The test is performed according to the Ph. Eur., USP/NF or JPE monograph on 1 g EUDRAGIT® E 100 / EUDRAGIT® E PO or 8 g EUDRAGIT® E 12,5.



ETHYL CELLULOSE
Functional uses: Tableting aid, binder, filler, diluent of colour and other food additives

RESULTS AND DISCUSSION:
1.PREFORMULATIONSTUDIES Physical Characteristics

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

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

Table 2: Solubility test for Idarubicin in different solvents

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

Selection of Wavelength
The Idarubicin 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.

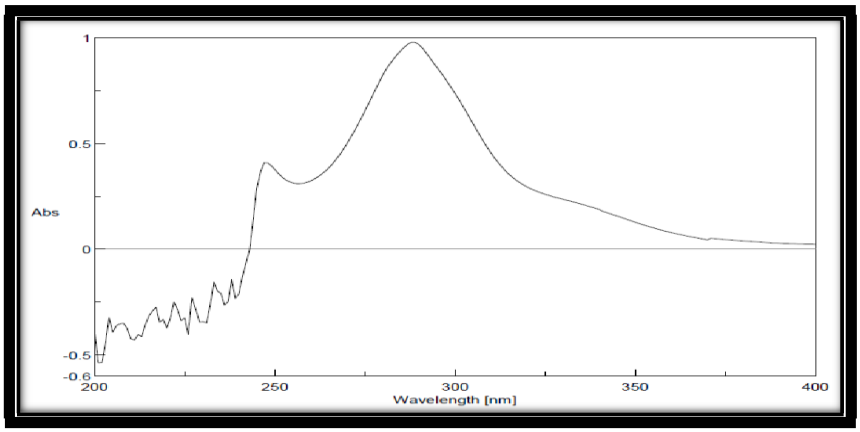


Figure 1: UV spectra of Idarubicin

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

Construction of calibration curve of Idarubicin
In the calibration curve, linearity was obtained between 5-40 µg/ml concentration of Idarubicin and

the regression value was found to be r2 = 0.9996. Hence, we can conclude that Idarubicin obeys Beer Lambert's Law at the concentration between 5-40 µg/ml. The results are shown in Table 2 and Figure 5.

Table 2: Concentration and absorbance values for estimation of Idarubicin

Sl.No	Concentration (µg/ml)	Absorbance (AU) at 232nm
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

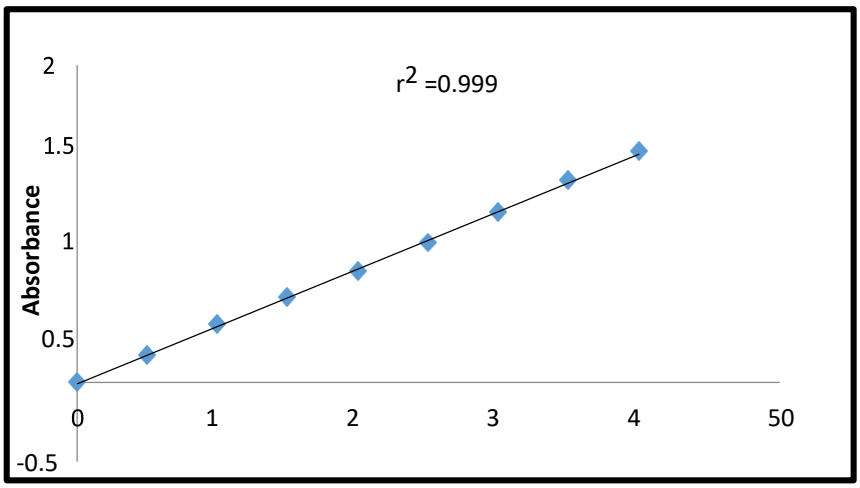


Figure 2: Calibration graph of Idarubicin

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.

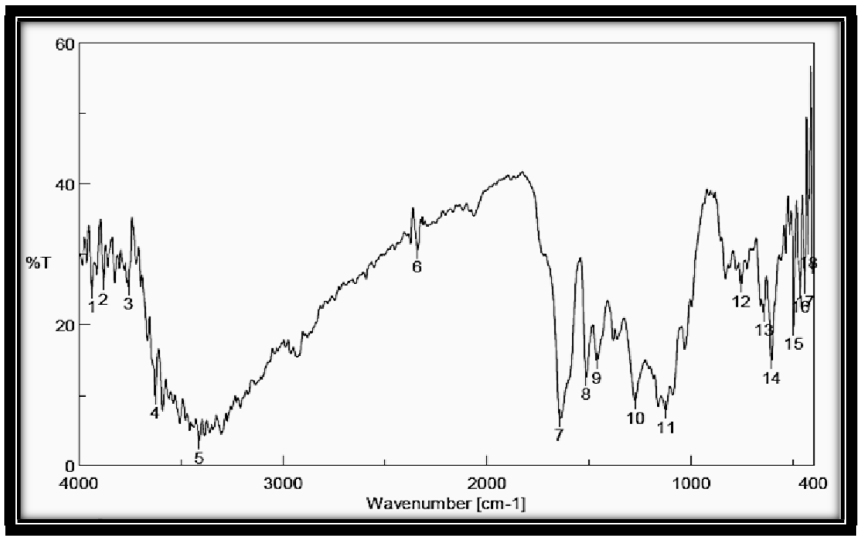


Figure 3: FTIR – spectrum of Idarubicin

Table 3: FTIR interpretation of Idarubicin

Materials	Standard wave number (cm-1)	Test wave number (cm^{-1})	Functional group assignment
Idarubicin	3650-3200	3410.49 3625.52	OH stretching
	1820-1665	1643.05	C=O stretching
	1320-1210	1273.75	C-O-C stretching
	1161-1029	1121.4	In plane =C-H bending

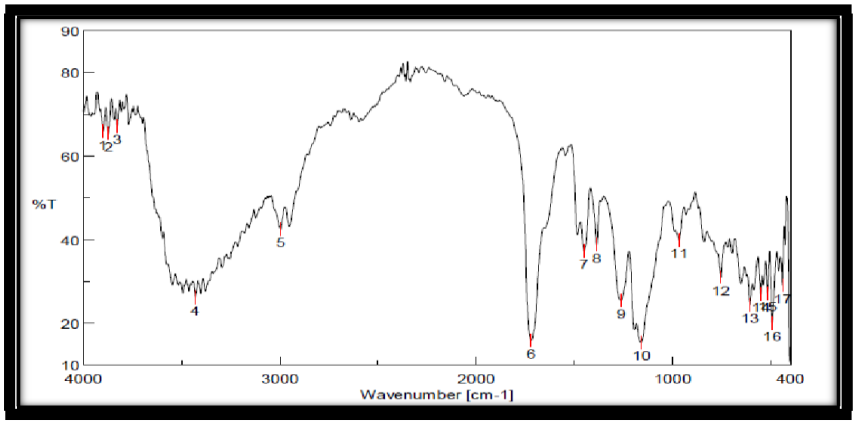


Figure 4: FTIR spectrum of Eudragit Table

4: FTIR interpretation of Eudragit

Materials	Standard wave number (cm^{-1})	Test wave number (cm^{-1})	Functional group assignment
EUDRAGIT	3000-3700	3430.74	O-H stretching
	1500-1800	1720.19	N-H bending
	2700-3300	2995.87	C-H stretching
	1300-1500	1451.17 1386.57	C-H bending
	1000-1300	1262.18 1159.01	C-O stretching

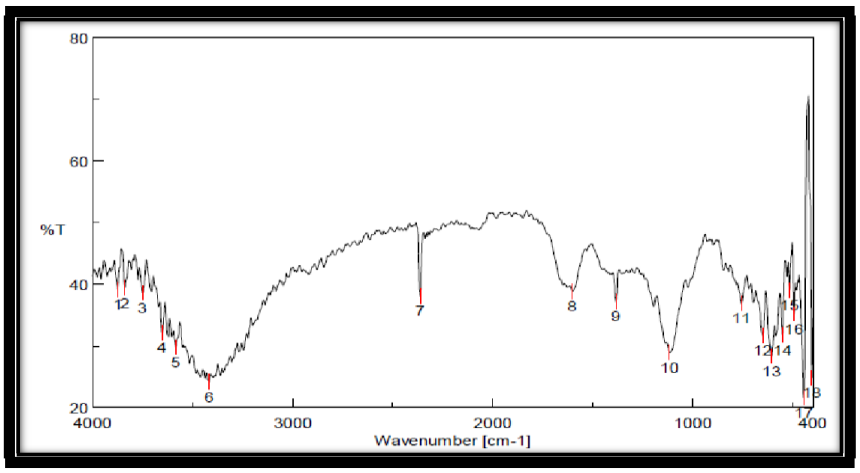


Figure 5: FTIR spectrum of Poly Vinyl Alcohol (PVA)

Table 5: FTIR interpretation of Poly Vinyl Alcohol

Materials	Standard wave number (cm-1)	Test wave number (cm-1)	Functional group assignment
POLYVINYL ALCOHOL	3300-3600	3584.06	OH stretching
	2850-2970	2862.37	CH3 stretching
	1500-1760	1600.63	COOH
	1340-1470	1383.68	Alkanes bending
	1000-1300	1116.58	C-O stretching
	600-800	757.888 648.929	C-H rocking

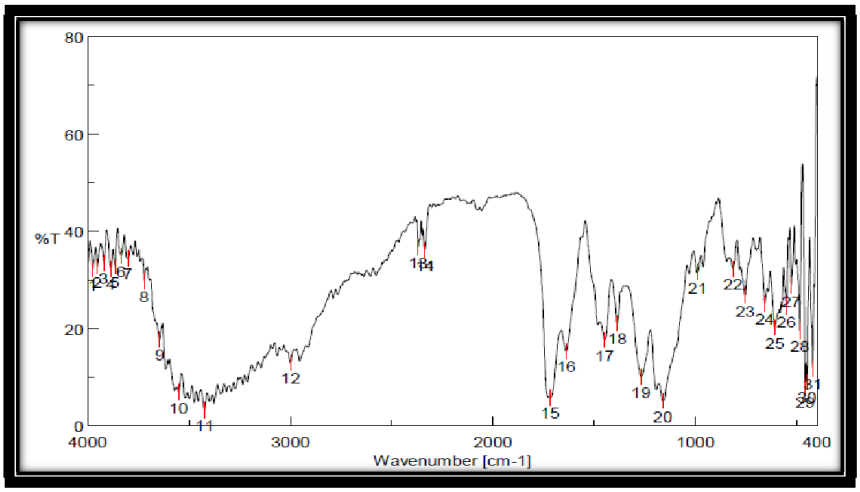


Figure 6: FTIR spectrum of physical mixture containing Idarubicin, Eudragit and PVA Table

6: FTIR interpretation of mixture containing Idarubicin, Eudragit and PVA

The peaks present in the FTIR spectra of pure

Materials	Standard wave number (cm^{-1})	Test wave number (cm^{-1})	Functional group assignment	
MIXTURE CONTAINING IDARUBICIN, EUDRAGIT and PVA	3650-3200	3642.87 3423.033	OH stretching	
	3300-2700	2999.73	C-H stretching	
	1820-1665	1718.26	C=O stretching	
	1800-1500	1639.2	N-H bending	
	1500-1300	1386.57	C-H bending	
	1320-1210	1268.93	C-O-C stretching	
	1161-1029	1161.9	In plane bending	=C-H
	800-600	814.777 658.571	C-H rocking	

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

I. FORMULATION OF NANOSPONGES

Selection of polymers for the formulation of Idarubicin 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 Idarubicin nanosponges.

Table 7: Trial batches for formulation of Idarubicin nanosponge

Drug	Polymer	Ratio	Result observed
IDARUBICIN	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 Idarubicin 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 Idarubicin nanosponges

S. No	Formulation code	Drug	Polymer	Drug: polymer ratio
1	F1	IDARUBICIN	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 Idarubicin 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

II. CHARACTERISATION OF IDARUBICIN NANOSPONGES FTIR Spectroscopy of Idarubicin nanosponges
FTIR Spectrum of Idarubicin nanosponges using ethyl cellulose is given in figure 7.

Figure 7: FTIR interpretation of Idarubicin nanosponges using Ethyl cellulose

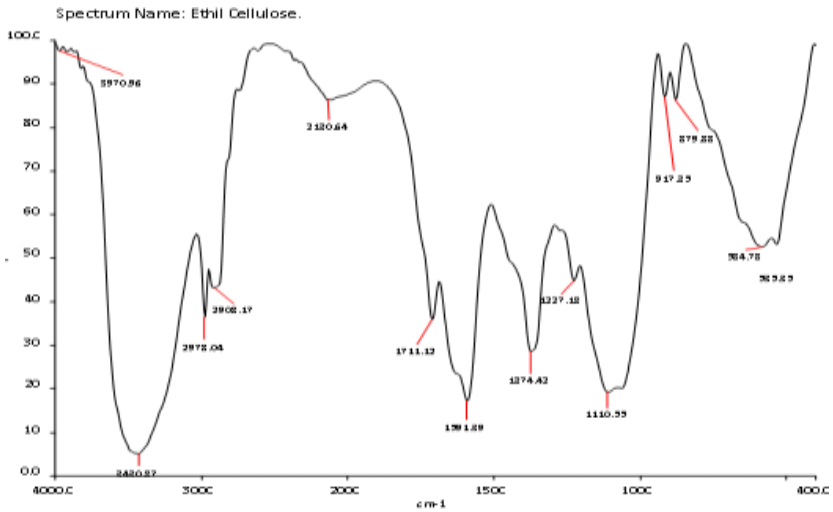


Table 10: FTIR interpretation of Idarubicin nanosponges using Ethyl cellulose

Materials	Standard wave number (cm-1)	Test wave number (cm-1)	Functional group assignment
FORMULATION F4	3650-3200	3615.88 3478.95	OH stretching
	2970-2850	2876.31	C-H stretching
	1725-1665	1668.2	C=O stretching
	1161-1029	1114.65	Inplane =C-H bending
	800-600	876.488 643.144	C-H rocking

FTIR Spectroscopy of Idarubicin Nanosponges
FTIR spectrum of Idarubicin nanosponge using eudragit is given in Figure 8.

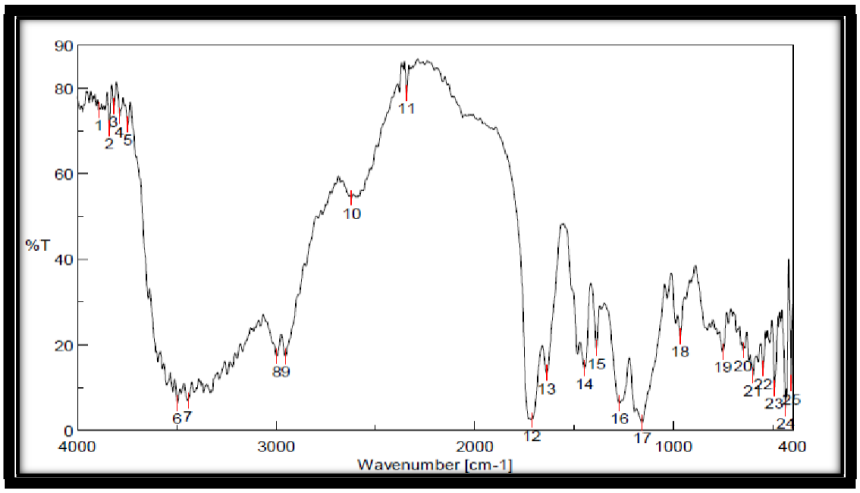


Figure 8: FTIR spectrum of Idarubicin nanosponges using Eudragit

Table 12: FTIR interpretation of Idarubicin nanosponges using Eudragit

Materials	Standard wave number(cm-1)	Test wave number(cm-1)	Functional group assignment
FORMULATION F9	3650-3200	3497.27 3444.24	OH stretching
	3300-2700	2993.94 2951.52	C-H stretching
	1820-1665	1714.41	C=O stretching
	1800-1500	1638.23	N-H bending
	1500-1300	1449.24	C-H bending
	1320-1210	1271.82	C-O-C stretching
	1161-1029	1159.01	In plane =C-H bending
	800-600	753.066 648.929	C-H rocking

The peaks present in the FTIR spectra of pure Idarubicin are present in the FTIR spectra of formulations. The FTIR interpretations indicated that the Idarubicin is compatible with the excipients eudragit and poly vinyl alcohol and no interactions observed in all formulations of nanosponges.

Percentage yield analysis

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

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

Table 13: Percentage yield of Idarubicin nanosponges

S. No	Formulation code	Percentage yield (%)
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

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.

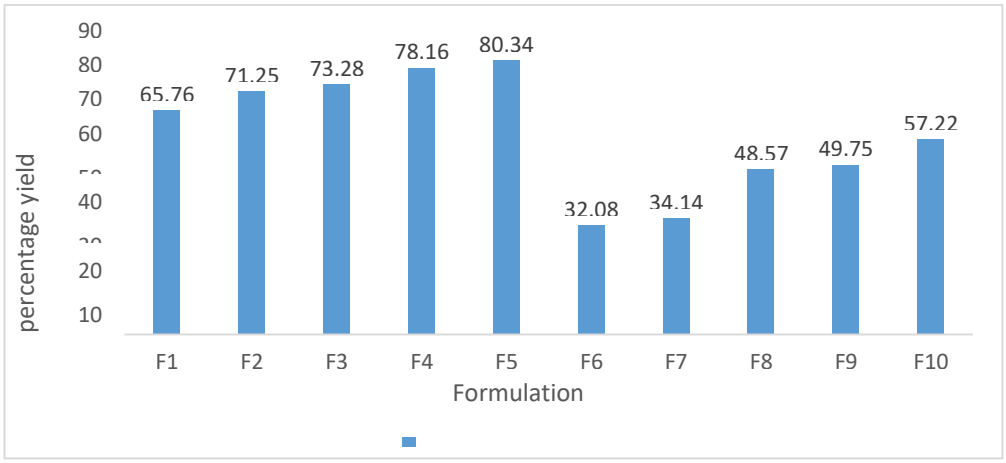


Figure 9: Percentage yield analysis of Idarubicin nanosponges

Scanning Electron Microscopy

SEM analyses of the formulated Idarubicin 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.

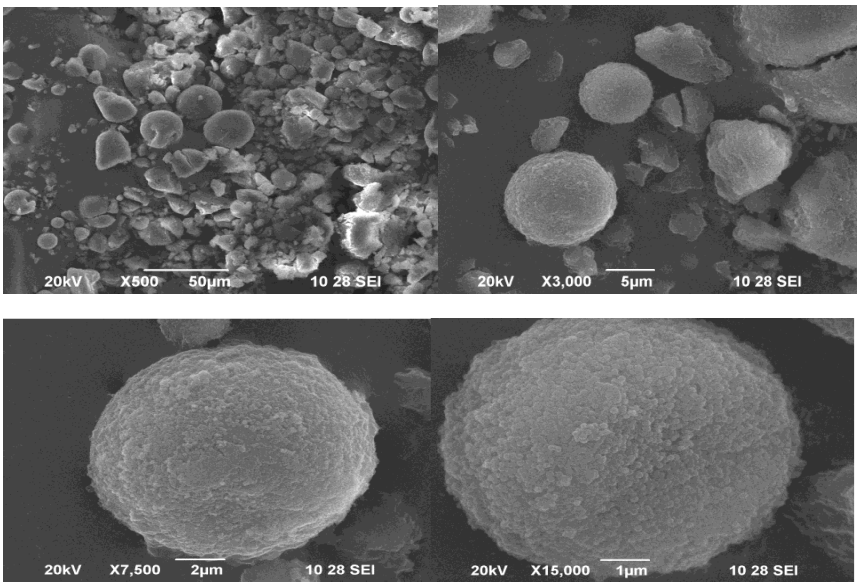


Figure 10: SEM images of Idarubicin nanosponges using eudragit

Particle Size Measurement

The particle size is one of the most important parameters for the characterization of nanosponges. The average particle sizes of the prepared Idarubicin nanosponges were measured using Malvern zeta sizer.

Particle size analysis showed that the average particle size of Idarubicin nanosponges formulated using eudragit (F9) was found to be 4097 nm with polydispersity index (PDI) value 1.01 and with intercept 1.41. The zeta size distribution of ethyl cellulose –Idarubicin nanosponges is depicted in Figure 11.

			Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	1.708e4	Peak 1:	1.117	100.0	1.490e-8
PdI:	0.767	Peak 2:	0.000	0.0	0.000
Intercept:	1.46	Peak 3:	0.000	0.0	0.000
Result quality :	Refer to quality report				

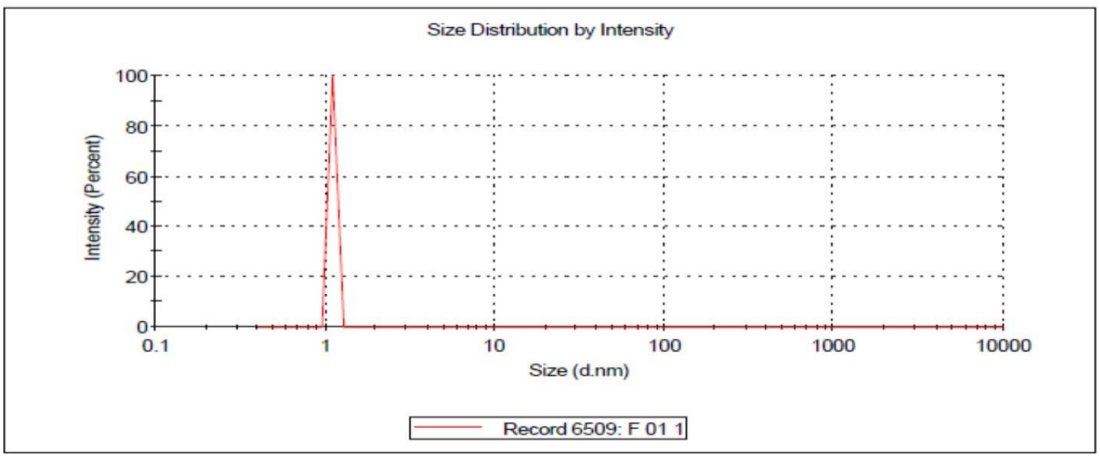


Figure 11: Zeta size distribution of Idarubicin nanosponges

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

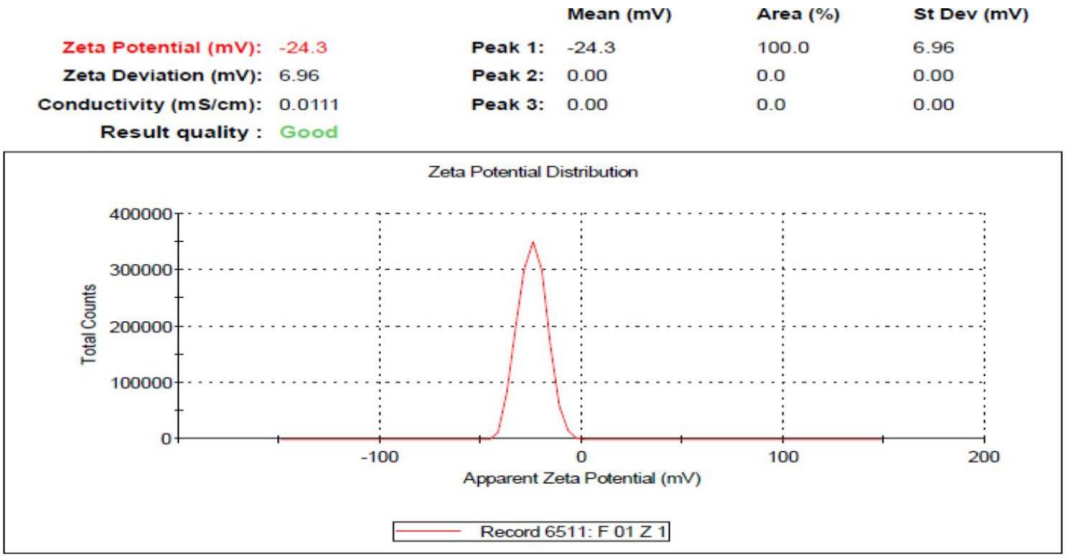


Figure 12: Zeta potential of Idarubicin nanosponges

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.

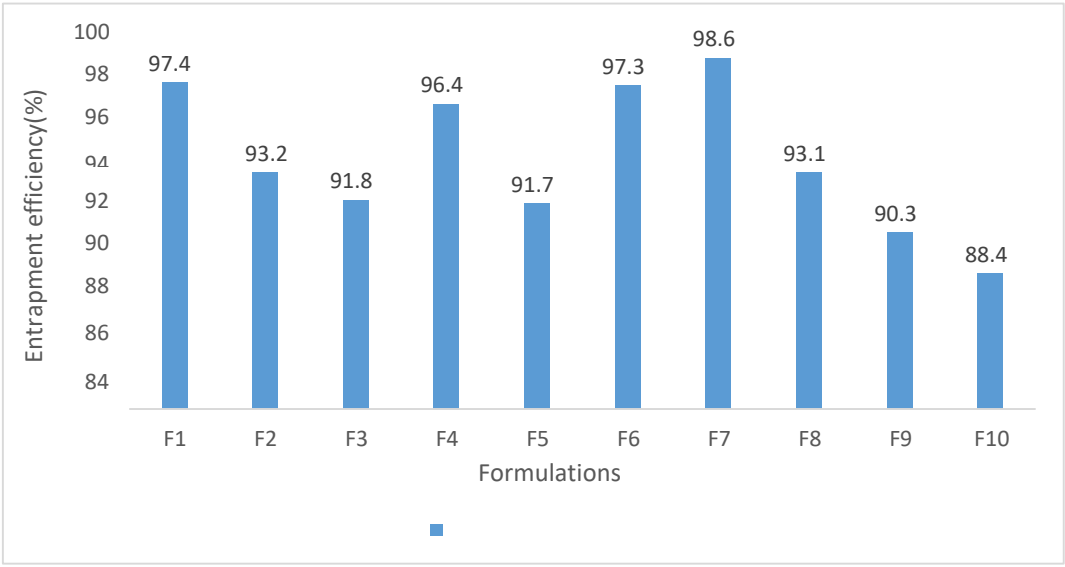


Figure 13: Entrapment efficiencies of Idarubicin nanosponges

Table 14: Entrapment efficiencies of Idarubicin nanosponges

S. No	Formulation code	Entrapment Efficiency (%)
1.	F1	97.45
2.	F2	93.20
3.	F3	91.89
4.	F4	96.43
5.	F5	91.72
6.	F6	97.32
7.	F7	98.61
8.	F8	93.19
9.	F9	90.35
10.	F10	88.41

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. Idarubicin 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 Idarubicin nanosponges containing ethyl cellulose (F1- F5) are given in Table 15 and Figure 16.

Table 15: *In vitro* drug release profile of Idarubicin 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

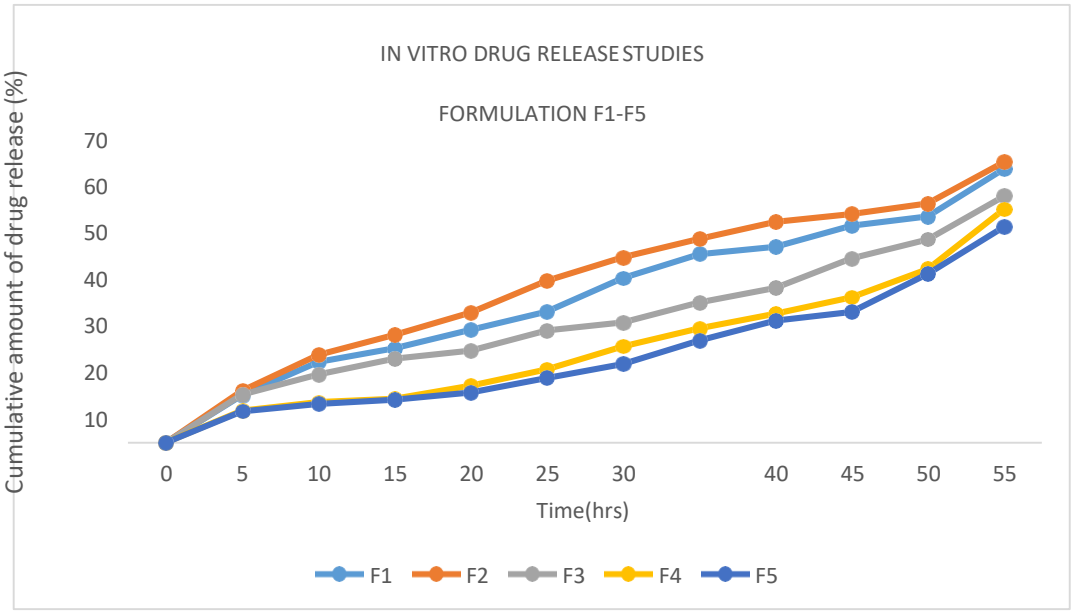


Figure 14: *In vitro* drug release profile of Idarubicin nanosponges (F1-F5)

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

Table 16: In vitro drug release profile of Idarubicin 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

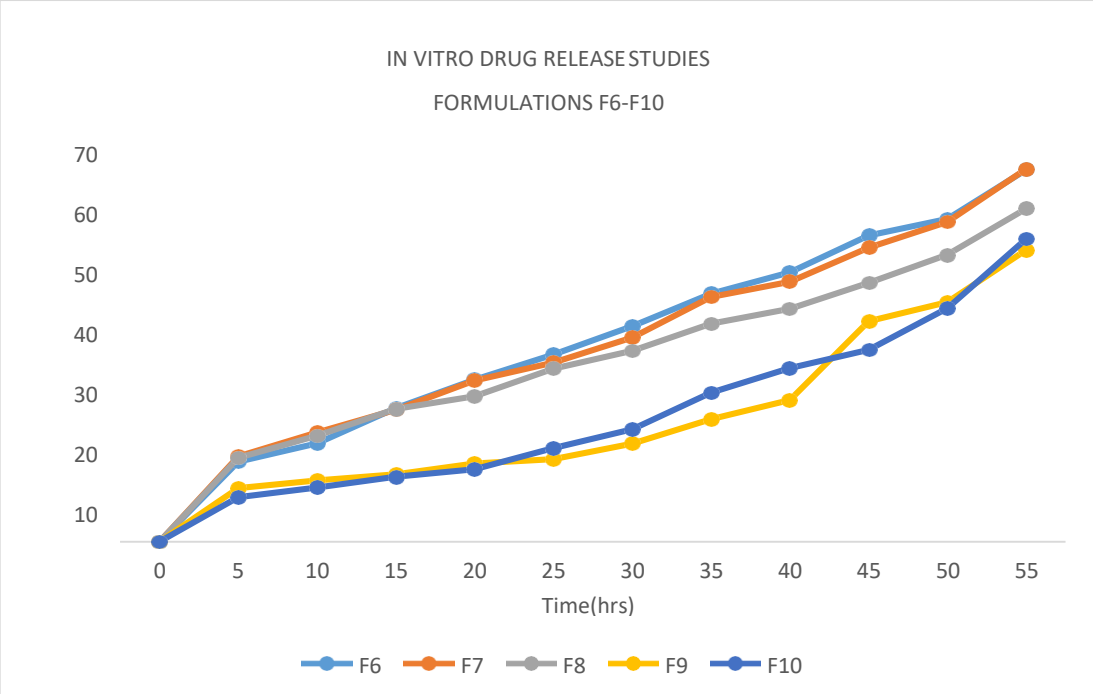


Figure 15: In vitro drug release profile of Idarubicin nanosponges (F6-F10)

SUMMARY AND CONCLUSION:

Nanosponges are 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. Drugs encapsulated within the nanosponge pores are shielded from premature destruction and stability of drug is enhanced.

Main objective of this study was to formulate Idarubicin loaded nanosponges using polymer to target cancer cells (breast cancer, colorectal cancer or oesophageal cancer) and release the drug in a controlled manner. This formulation reduced the side effects, minimized the dosing frequency and dose.

The present work aimed at formulating Idarubicin nanosponges with polymer name hydrophobic polymer using emulsion solvent diffusion method. This method was simple and cost effective.

Preformulation studies were carried out to find out the solubility of Idarubicin. Solubility test gave an idea that Idarubicin is water soluble and soluble in solvents like acetone, dichloromethane etc.

FTIR and UV spectral studies authenticate the spectra obtained with the sample drug matched with standard pure drug. UV spectra gave the maximum absorption peak at 232nm.

The comparison of FTIR spectra of Idarubicin and mixture of Idarubicin and polymer confirms that there is no appearance of additional new peaks and disappearance of existing peaks from that of the drug. This indicates that there is no interaction between the drug and polymer used in the study.

Formulation was carried out by emulsion solvent diffusion method. Trial batches indicated that hydrophilic polymers are not suitable for the Idarubicin nanosponges. The hydrophilic polymers produced no yield or very less yield. Hydrophobic polymers produced good formulations. Eudragit were selected for further studies.

Scanning electron micrograph of the prepared nanosponges at different magnification showed that the nanosponges were porous with a smooth surface morphology and spherical shape. The spongy and porous nature of nanosponges was clearly observed in the SEM images.

Particle size and zeta potential was determined by Malvern Zeta sizer. The particle size analysis confirmed that the prepared sample were in the nanometer range. Average particle size obtained for the formulations F9 is 1.708e4. Zeta potential values of nanosponges indicated that the formulated nanosponges are stable.

The amount of drug being entrapped in nanosponges was calculated and all the prepared nanosponges were found to possess very high entrapment efficiency.

From the *in-vitro* release data from the dialysis bag diffusion method it was found that formulations F1 to F5 & F6 to F10 showed the best release of 89.90,

88.79, 81.75, 72.86, 67.56 and 90.18, 87.10, 77.94, 70.14, 69.86 respectively at the end of 48 hours. 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 is because the newly developed nanosponges is believed to exhibit a core shell structure with a hydrophobic core formed by eudragit and a hydrophilic shell formed by PVA macromolecules.

CONCLUSION:

The Idarubicin nanosponges can be formulated by cost effective and easy emulsion solvent diffusion method using hydrophobic polymers such as eudragit. The formulated Idarubicin 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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