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DEVELOPMENT AND CHARACTERIZATION OF GASTRO-RETENTIVE MUCOADHESIVE LIPOSOMES LOADED WITH METOPROLOL SUCCINATE, USING NATURAL AND SYNTHETIC POLYMERS

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ABSTRACT

This study focuses on the development and characterization of a gastro-retentive mucoadhesive liposomal formulation of Metoprolol Succinate aimed at enhancing oral bioavailability and patient compliance. Liposomes were prepared using the thin film hydration method and then coated with varying concentrations of Chitosan and Carbopol to improve mucoadhesive properties. The formulations were analysed for compatibility, vesicle size, entrapment efficiency, surface morphology, zeta potential, in vitro drug release, and stability. FTIR analysis confirmed no interaction between the drug and polymers. The optimized formulation (NC1) showed a zeta potential of -34.7 mV and mucoadhesive strength of 70.85%, indicating high stability and effective mucoadhesion, particularly with 1% w/v chitosan. This chitosan-coated liposomal system demonstrates potential for enhancing the oral bioavailability of Metoprolol Succinate through increased] gastric retention and controlled release.

KEYWORDS: Liposomes, Mucoadhesive Liposomes, controlled release, Metoprolol Succinate, FTIR, Chitosan, Carbopol.

INTRODUCTION

Mucoadhesion dosage forms have received substantial attention as novel drug delivery

systems able to improve the bioavailability of drugs by prolonging their residence time and controlling the drug release characteristics. Mucoadhesive Nano particulate systems such as polymer coated liposomes were found to be useful carriers for improved oral delivery because of their prolonged retention in the GI tract excellent pretention into the mucus layer.[1]

The oral route remains to be the most convenient and comfortable way of drug administration. However, the success of liposomal formulating through oral route of administration is limited due to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. It can be achieved by coupling bio adhesion characteristics to liposomes and developing mucoadhesive liposomal delivery system.[2]

Development of mucoadhesive liposomal drug delivery system have advantages such as improved bioavailability of poorly absorbed oral drugs by prolonging their gastric and intestinal residence time, through facilitating the intimate contact of the delivery system with the absorption membrane and specific targeting of drug to the absorption site.

One of the most promising strategies in developing mucoadhesive particulate system is surface modification or coating of the drug carrier particles with mucoadhesive polymers.[3]

Gastro Retentive Drug Delivery Systems (GRDDS) are a type of Controlled Release Drug Delivery System (CDDS) that remain in the stomach to enhance the oral controlled release of medications. By continuously discharging the drug before it reaches the intestinal absorption window, GRDDS improves therapeutic outcomes, reduces dosing frequency, and minimizes drug degradation in the lower gastrointestinal tract. Various methodologies, such as floating, bioadhesive, swelling, and expanding systems, have been developed to extend the gastric retention time of dosage forms, optimizing absorption and overall efficacy.[4]

Hypertension (HTN) otherwise similarly notorious as high blood pressure (BP), occasionally arterial hypertension, remains a chronic medicinal situation and that the BP in the arteries is upraised. This entails the heart to effort durable than regular to circulate blood over the blood vessels. The BP implicates two extents, systolic and diastolic, that are reliant on either the heart muscle remains constricting (systole) or relaxed (diastole) amid beats. Normal BP is at or beneath 120/80 mmHg. High BP is supposed to remain extant if it is obstinately at or

beyond 140/90 mmHg.[5-6]

Metoprolol Succinate is a beta1-selective (cardio-selective) adrenoceptor blocking agent, for oral administration, it is used to treat the chest pain (Angina), Heart failure, and high blood pressure, Metoprolol Succinate is a white crystalline powder and it is freely soluble in water, methanol, sparingly soluble in ethanol, practically insoluble in ethyl-acetate, acetone, diethyl ether and heptane.

Oral bioavailability of Metoprolol Succinate is 40%, Metaprolol Succinate is absorbed in gastro intestinal tract, and so oral absorption of Metaprolol Succinate can be increased by increasing gastric retention time of the drug. Hence, it can be investigated that increasing the residence time at the absorption site can enhance the absorption and bioavailability of the drug.[7]

Hence, the aim of this study is to development and characterization of natural and synthetic polymers assisted development and characterization of gastro retentive mucoadhesive liposomes of Metoprolol Succinate to improve patient compliance by increasing the oral bioavailability.

Table 1: Formulation design for uncoated liposomes.

Formulation code	Drug (mg)	Soya lecithin (mg)	Cholesterol (mg)
F1	50	250	50
F2	50	250	100
F3	50	250	150
F4	50	250	200
F5	50	500	50
F6	50	500	100
F7	50	500	150
F8	50	500	200

Table 2: Formulation design for coated liposomes.

Formulation code	Chitosan (%)	Formulation code	Carbopol (%)
NC1	0.5%w/v	SC1	0.25%w/v
NC2	1%w/v	SC2	0.5%w/v

MATERIALS AND METHOD

Metoprolol succinate was kindly gifted by Hetero labs, Hydrabad. Soya lecithin was provided by Sonic Biochem Extraction Ltd., Indore. Chitosan was provided by Shreeji Chemicals, Mumbai. Carbopol 924, Cholesterol, and other solvents like chloroform and methanol was

purchased from S D Fine Chem limited, Mumbai.

METHODS

PREPARATION OF METOPROLOL MUCOADESIVE LIPOSOME

A. Preparation of liposomes[8]

Cationic multilamellar liposomes can be prepared by hydration of lipid film. The lipid mixture is dissolved in a small amount of chloroform and placed in a rotary evaporator at 40°C until a thin film is obtained, and allowed to stand overnight in a vacuum chamber to ensure complete solvent removal. Hcl buffer pH 1.2 is used to hydrate the thin film. The hydrated thin film is melted in water bath at 70°C for 1 min and blended to obtain multilamellar liposomes. Then prepared liposome will be sonicated to reduce particle size.

B. Coating of liposomes[9]

A volume of 2.0 mL of chitosan/carbopol solution was added drop-wise to the 2.0 mL of liposomes under magnetic stirring at room temperature for 1 hr. followed by incubation in refrigerator overnight.

EVALUATION PARAMETER OF MUCOADHESIVE LIPOSOMES[10, 11]

The prepared liposomes and coated liposomal formulation were evaluated for different parameters like Drug-Excipients compatibility, Surface morphology, Vesicle size analysis, Entrapment efficiency determination, Zeta potential determination, *In vitro* diffusion study, *In vitro* wash-off test for mucoadhesive test and Stability studies as per ICH guidelines.

In-vitro diffusion study

The release of drug was determined by using the treated cellophane membrane mounted on the one end of open tube, containing formulations. The dialysis tube was suspended in 500 ml beaker, containing 150 ml Hcl buffer pH 1.2. The solution was stirred at 100 rpm with the help of magnetic stirrer at 37 ± 0.5 ℃. Perfect sink conditions were maintained during the drug release testing. The samples were withdrawn at suitable time interval (at 1, 2, 4, 6, 8, 12, hrs). The dissolution medium was replaced with same amount of fresh Hcl buffer pH 1.2 solutions to maintain the volume 150 ml throughout the experiment. The drug content in the withdrawn samples (1 ml) were analysed by UV spectrophotometer at λmax 221 nm after making the volume up to 10 ml with Hcl buffer pH 1.2 and cumulative % of drug released was calculated and plotted against time (t). The rate and release mechanism of Metoprolol succinate from the formulations were analysed by fitting the release data in to various kinetic

model.

In-vitro wash-off test for mucoadhesive testing[12-13]

The mucoadhesive property of the polymer-coated liposomes was evaluated by an in-vitro adhesion test. The method used was the modified in-vitro wash-off test. The mucoadhesion of the polymer-coated liposomes was compared with that of a non mucoadhesive material, uncoated liposomes containing Metoprolol succinate. Freshly excised pieces of sheep intestinal mucosa (2 × 2 cm) were tightened onto glass slides (3 × 1 inches) with thread. A volume of 0.5 ml of the liposomes, 0.2 % (w /v) chitosan- coated liposomes; liposomes were spread onto each wet-rinsed tissue specimen and immediately incubated at 37 ℃. The tissue specimens were taken out at 3 hrs. The samples were washed with 10 ml of Hcl buffer pH 1.2 at each time interval.

Determination of mucoadhesive strength

From the 10.0 ml of the eluted buffer containing nonadhered drug, 500 µl aliquots were taken and liposomal lipids were dissolved by methanol. It was measured by a UV spectrophotometer. The concentration of Metoprolol succinate eluted in the Hcl buffer pH 1.2 was measured and the remaining drug was assumed to be present in liposomes adhered to the intestinal mucosa. Hence, the percentage of mucoadhesive strength can be calculated by Equation of

$$Mucoadesion(\%) = \frac{\text{Amount of drug remaining in mucosa}}{\text{Amount of drug taken}} \times 100$$

Stability studies as per ICH guidelines[14]

Stability testing studies was performed at refrigerated condition for 6 months as per ICH guidelines. The optimized formulation was kept at 4 ± 2℃ and 75 ± 5 % RH in stability chamber. At the end of 0, 3, 6 months intervals regularly tested for % entrapment and drug release were fixed as physical parameters for stability testing.

RESULT AND DISCUSSION

Drug-excipients compatibility studies were carried t using FT-IR. The spectrum of pure drug (Metoprolol Succinate) and physical mixture of drug with Soyalechithin, Cholesterol, Chitosan and physical mixture of drug with Soyalechithin, Cholesterol, and Carbopol were obtained from FT-IR spectroscopy studies at wavelength from 4000 to 500 cm-1 And the characteristics peaks obtained showed the was no major changes in position of peak obtained

in drug alone and in the mixture of drug with excipients, which shows that there was no interaction between drug and excipients. FT-IR graph of pure drug and physical mixtures are showed in graphs are showed in fig.1, 2 and 3 and the surface morphology was studied by Scanning electron microscopy (SEM). The SEM photographs of optimized liposomes formulation F1 and NC2 as shown in Fig.4-5. The porous structure in the images of confirmed the formation liposomes that are confirmed the incorporation of lipids and drug. SEM photographs of coated liposomal formulation showed the smooth coating of natural polymer like chitosan over the liposomes as shown in Fig. 5. The size analysis of prepared liposome formulation was done by optical microscope. It was shown in the Table 3. We observed that, increase in the concentration cholesterol in the formulation F1 to F4 and F5 to F8, the vesicle size was increased. The optimized coating of liposomes in concentration of 1% NC2 is 576.4 nm. Shown in the fig. 6-8. The % entrapment efficiency was found to decrease with increasing the cholesterol concentration. It is shown in the Table 4-5. Zeta potential of optimized formulation F1 and NC2 of Metoprolol succinate liposomes shown in fig. 9-10 and it was found to be -32.7 mV and-34.7 mV, respectively which indicate that they are sufficient to be stable. In vitro release behaviour of all formulations is summarized in Table. 6-7. In vitro drug release of Metoprolol succinate liposomes in 1.2N HCL was performed using dialysis tube diffusion technique. The in vitro drug release profile of Metoprolol succinate liposomes formulations obtained from dialysis experiment was shown in Fig. 11-13. The release of Metoprolol succinate containing liposomes Chitosan/Carbopol coated liposomes was varied according to concentration of soya lecithin and cholesterol. The progressive decrease in the amount of drug diffused through cellophane membrane from formulations F1 to F8, NC1 to SC2 attributed to gradual increase in soya lecithin and cholesterol content. It has been concluded that, if we increase the concentration of soya lecithin and cholesterol, the diffusion of drug also decreases. The amount of drug diffused from formulation F4 and F8, was showed 74.79% and 69.43% which was lower among the formulations F1 to F8, NC2 was showed 67.82% which was lower among the formulation NC1 to SC2. The Mucoadhesive strength was measured by a UV spectrophotometer. Mucoadhesive strength optimized formulation NC2. The amount of drug released in the formulation NC2 70.85%. Percent mucoadhesion was calculated and found the mucoadhesive strength was 65% which showed sufficient mucoadhesive property. Stability studies of mucoadhesive liposome formulation NC2 as shown in Table. 8. Respectively, that negligible change in % Entrapment efficiency and % CDR revealed that the formulations are stable on storage. Shown in Table. 9. Respectively.

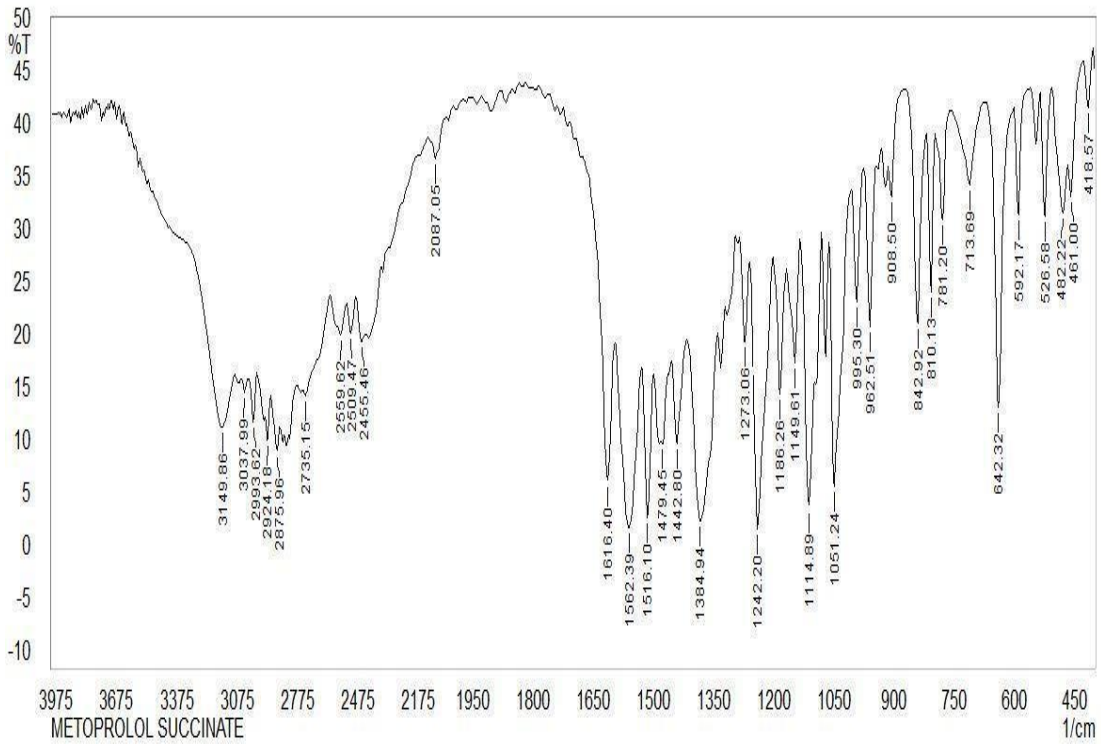


Fig: 1 FT-IR Spectra of Metoprolol succinate.

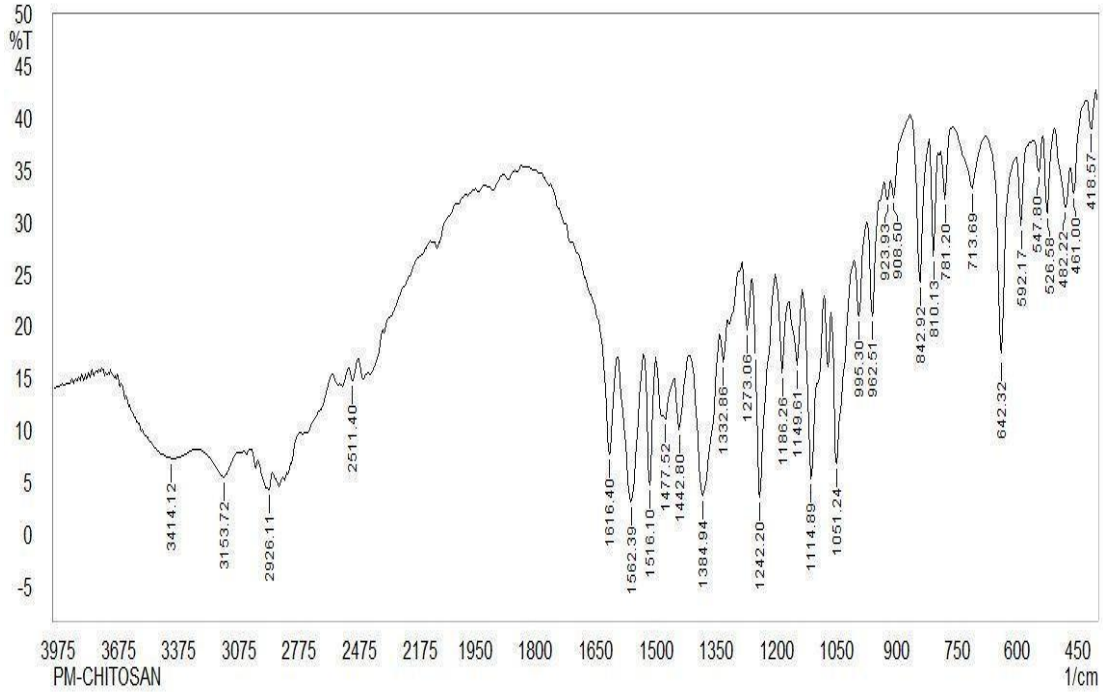


Fig: 2 FT-IR Spectra of Physical mixture of Soyalechithin+ cholesterol+Metoprolol succinate+ Chitosan.

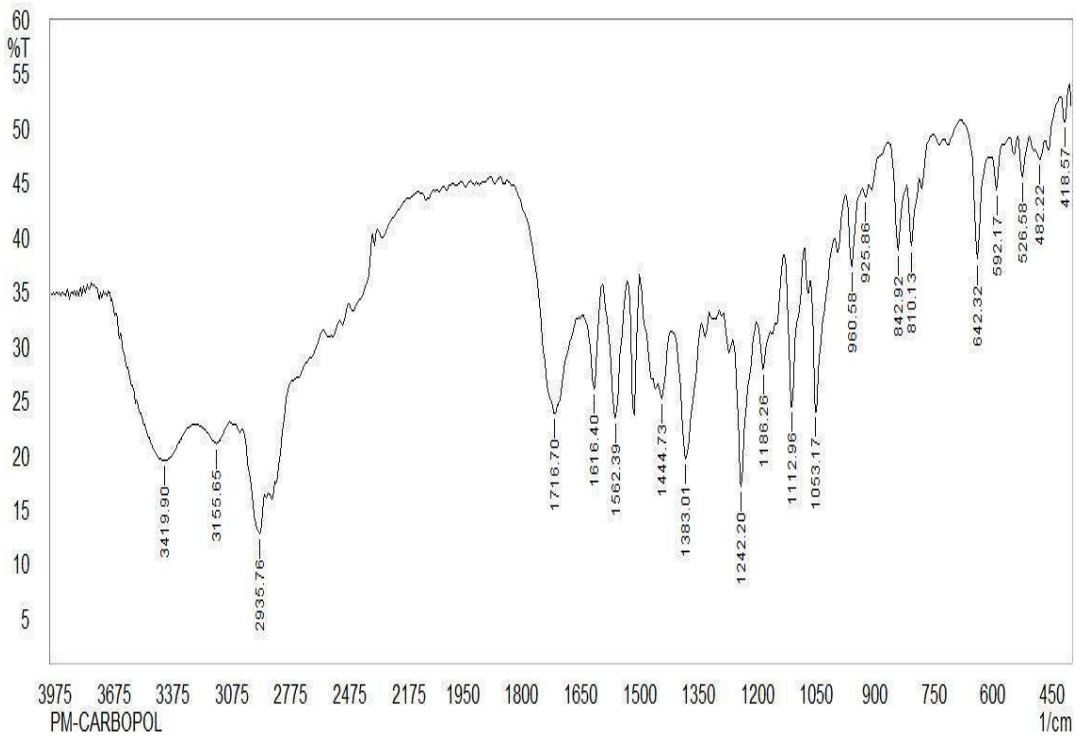


Fig: 3 FT-IR Spectra of Physical mixture of Soyalechithin+ cholesterol+Metoprolol succinate +Carbopol.

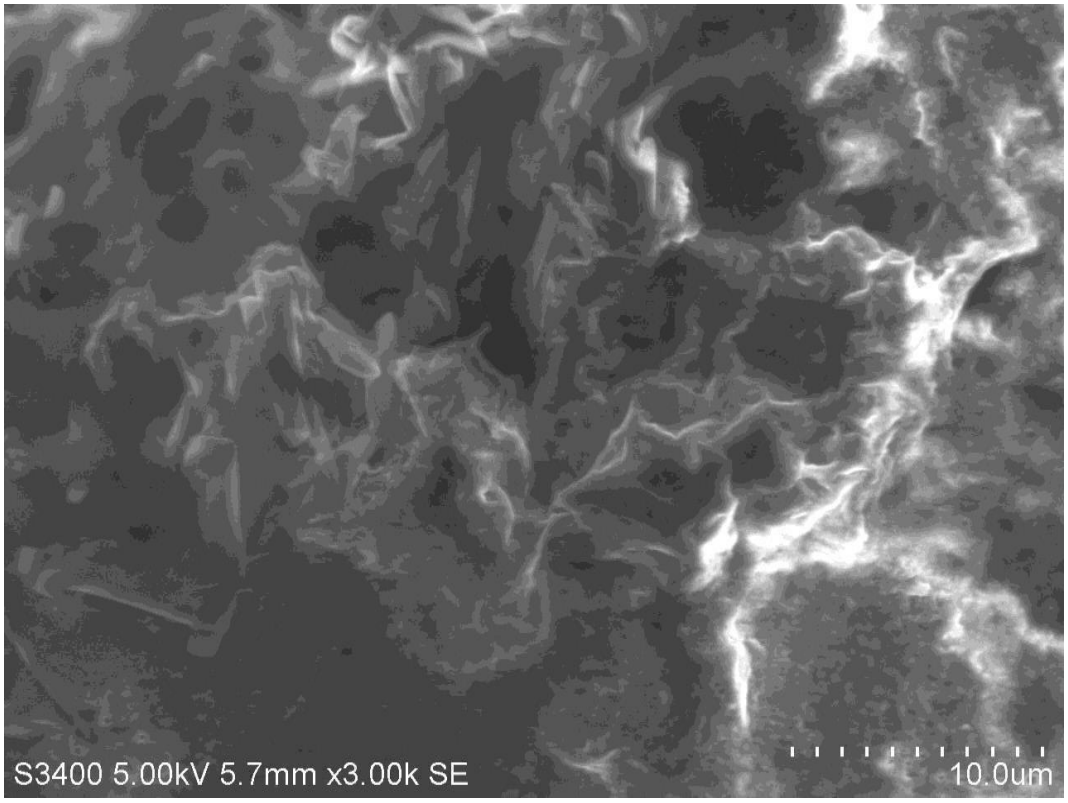


Fig: 4 SEM Image of Coated liposomes formulation.

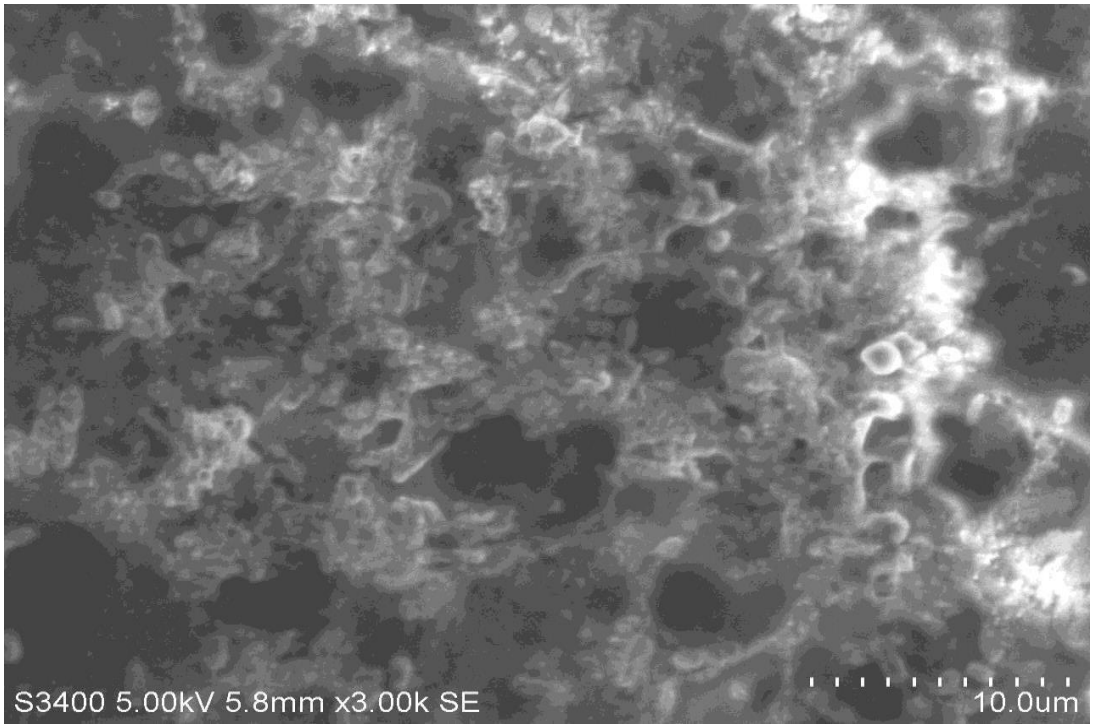


Fig: 5 SEM Image of Uncoated liposomes formulation.

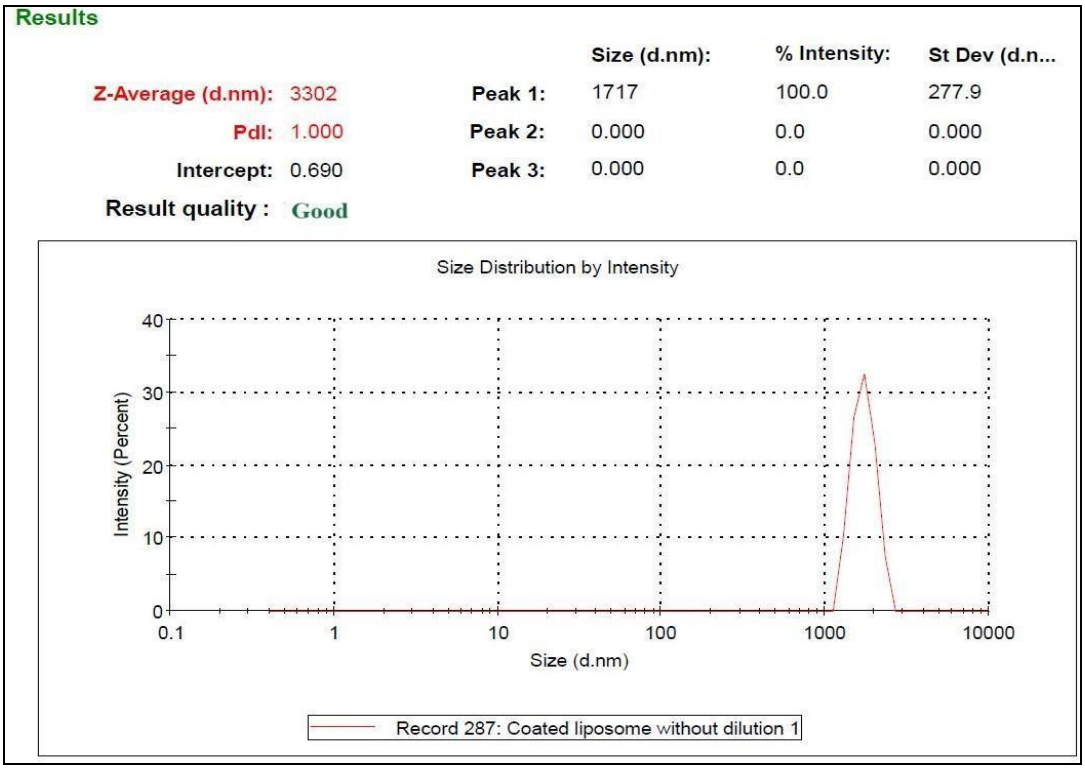


Fig: 6 Particle size analysis for coated liposomes.

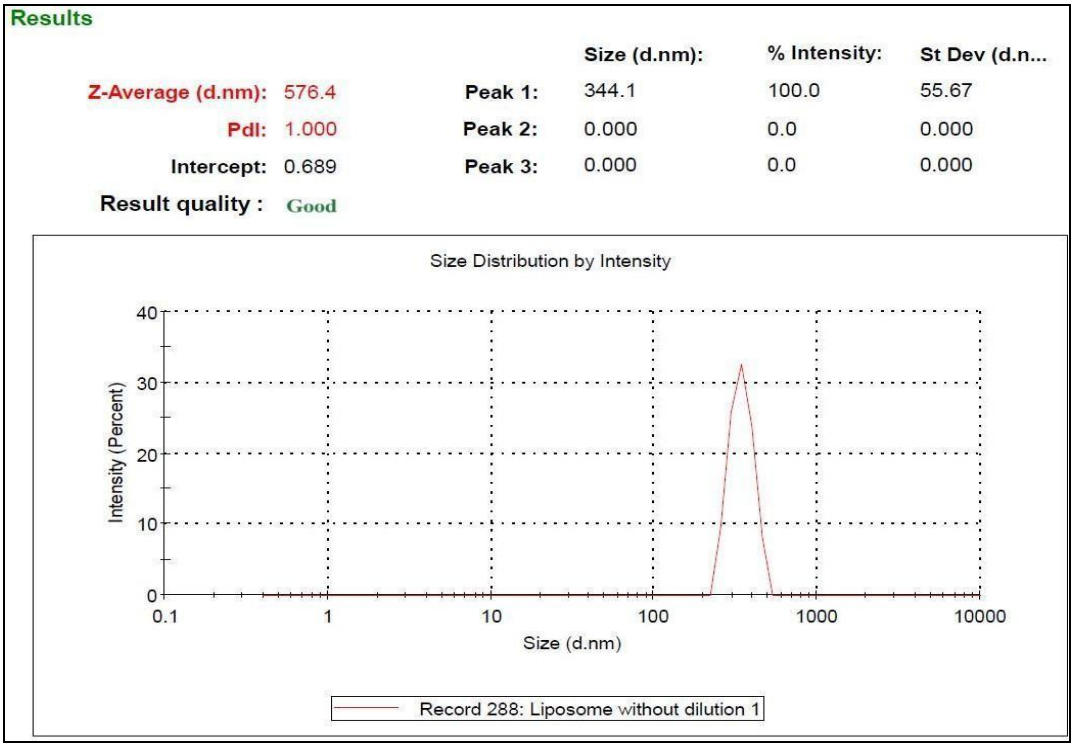


Fig: 7 Particle size analysis for uncoated liposomes.

Table 3: Vesicle size analysis for formulation F1-F8.

Formulation code	0-1.0 µm	1.0 - 2.0µm	2.0 - 3.0µm	3.0 - 4.0µm	4.0 - 5.0µm
F1	85%	10%	5%	3%	1%
F2	70%	20%	5%	3%	1%
F3	65%	20%	10%	3%	2%
F4	30%	63%	45%	5%	2%
F5	73%	13%	7%	5%	2%
F6	65%	15%	10%	5%	2%
F7	55%	25%	20%	15%	10%
F8	35%	30%	25%	25%	10%

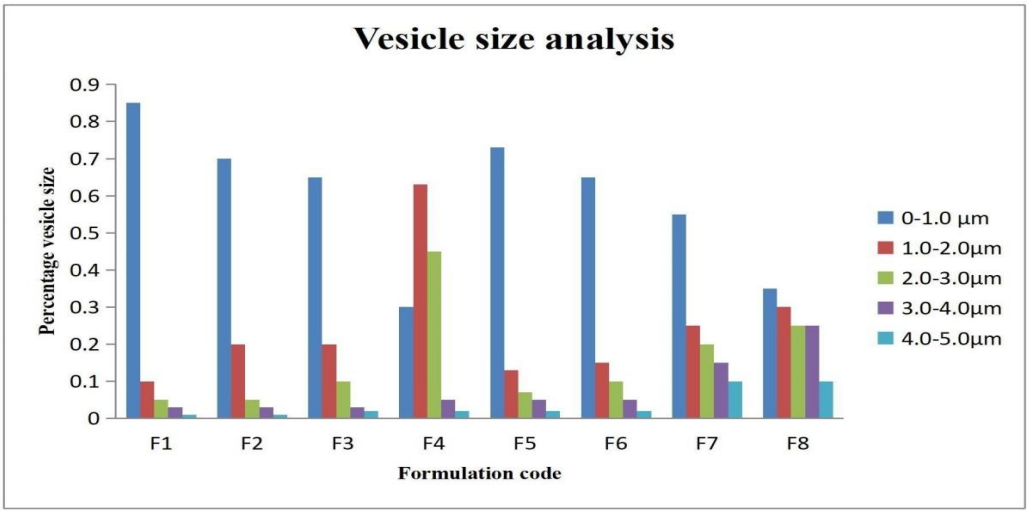


Fig: 8 Vesicle size analysis for formulation F1-F8.

Table 4: Entrapment efficiency of uncoated liposomes.

Formulation code	Entrapment efficiency
F1	95.81
F2	95.19
F3	95.30
F4	94.15
F5	95.74
F6	94.72
F7	95.45
F8	94.37

Table 5: Entrapment efficiency of coated liposomes.

Formulation code	Coating percentage	% Entrapment efficiency
NC1	0.5% w/v	95.21
NC2	1% w/v	95.81
SC1	0.25% w/v	93.8
SC2	0.5% w/v	94.4

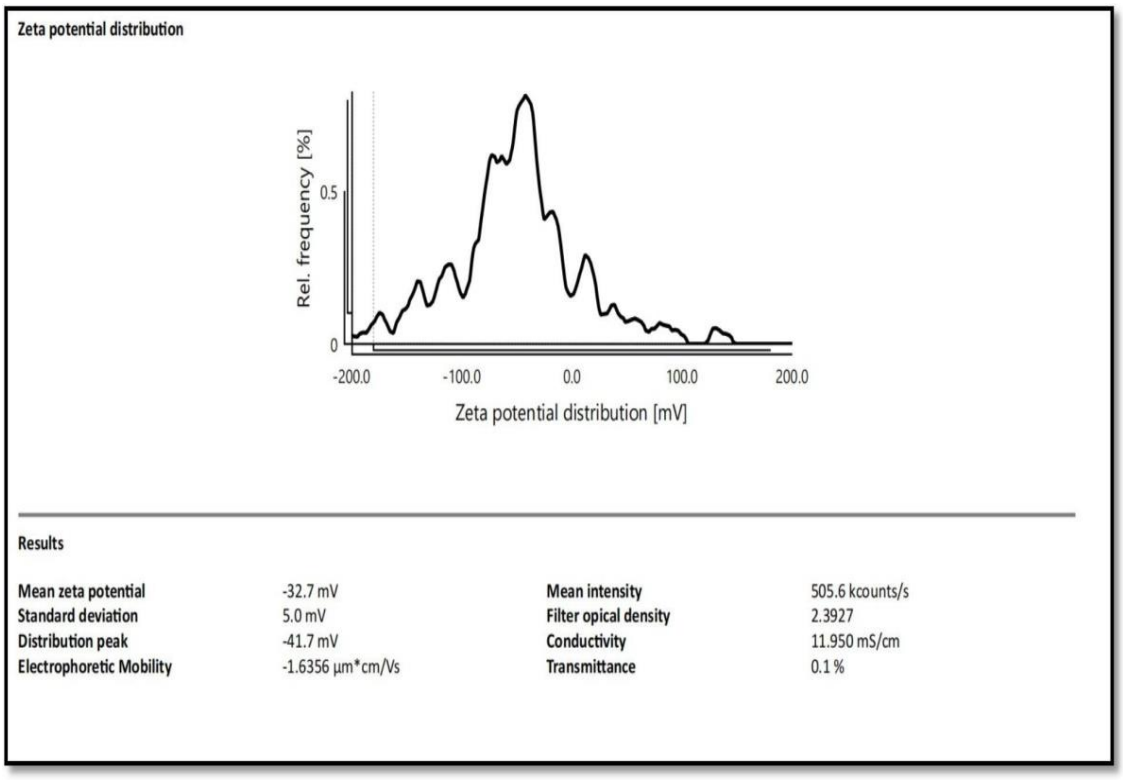


Fig: 9 Zeta potential of optimized uncoated liposomes.

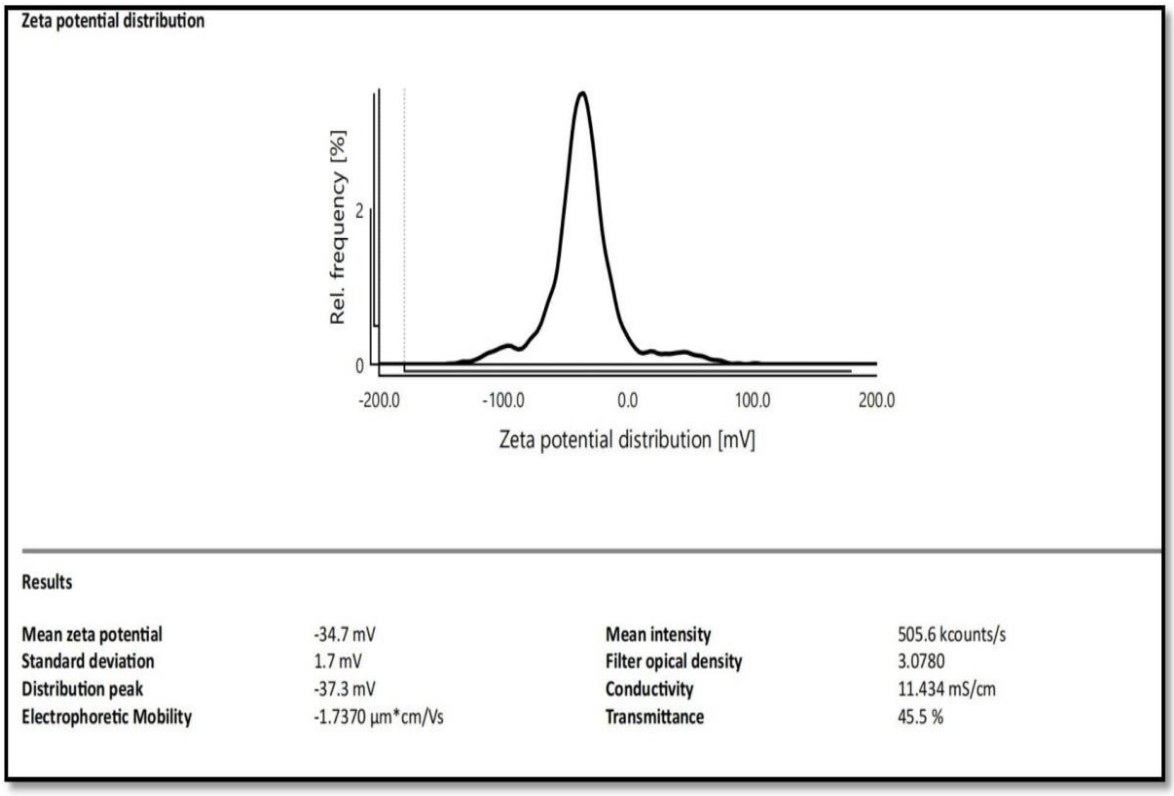


Fig: 10 Zeta potential of optimized coated liposomes.

Table 6: *In-vitro* diffusion study of formulation F1-F8.

Time in (hrs)	% Cumulative Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	9.21	8.36	7.39	6.21	10.50	8.46	7.50	6.64
2	19.07	16.93	15.54	14.14	21.64	21.32	20.25	12.00
4	38.14	34.61	32.57	31.93	42.32	35.89	33.32	24.86
6	51.21	45.32	44.14	42.96	53.36	55.82	53.36	41.46
8	70.07	68.89	65.57	60.54	64.82	69.86	60.75	53.89
12	86.68	82.71	77.46	74.79	81.64	79.50	72.64	69.43

Table 7: *In-vitro* diffusion study of coated liposomal formulation NC1-SC2.

Time in (hrs)	% Cumulative drug release			
	NC1	NC2	SC1	SC2
0	0	0	0	0
1	7.29	6.00	7.61	6.54
2	15.32	13.07	15.21	13.07
4	31.29	26.89	33.32	31.93
6	42.00	39.43	46.93	44.89
8	59.25	52.93	63.64	57.86
12	74.25	67.82	81.75	76.29

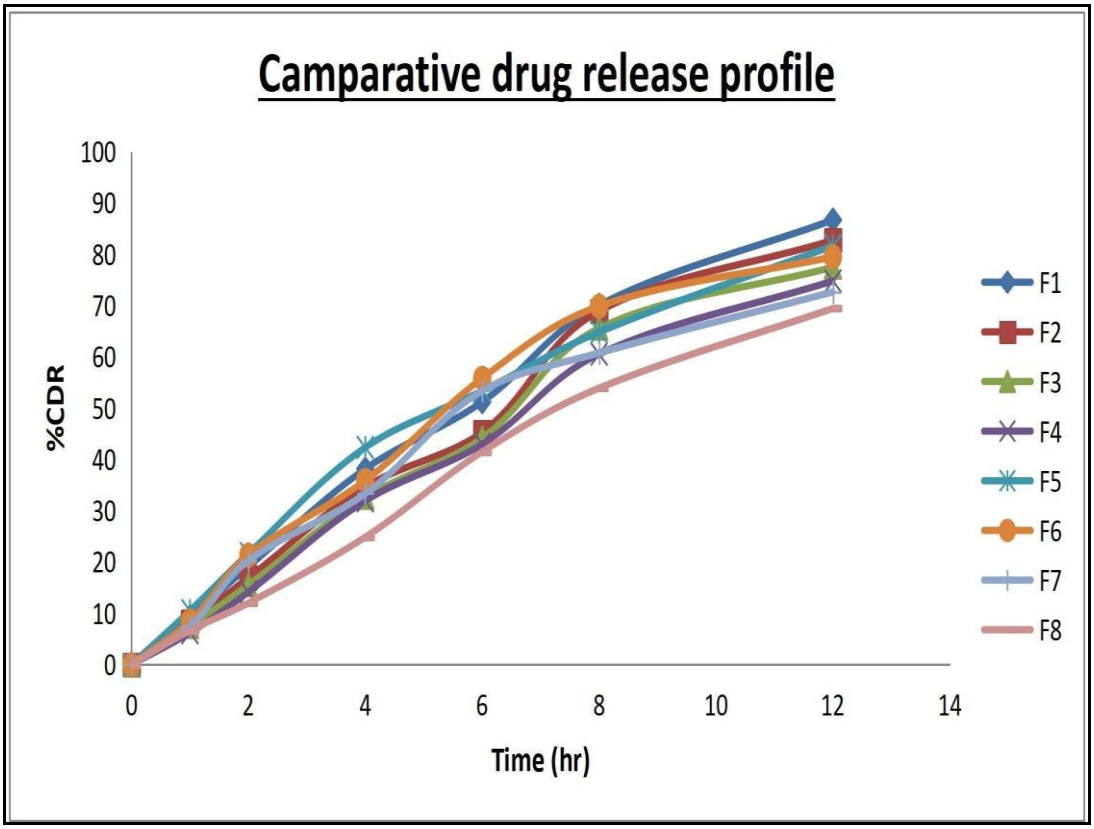


Fig: 11 % Cumulative drug release of formulation F1-F8.

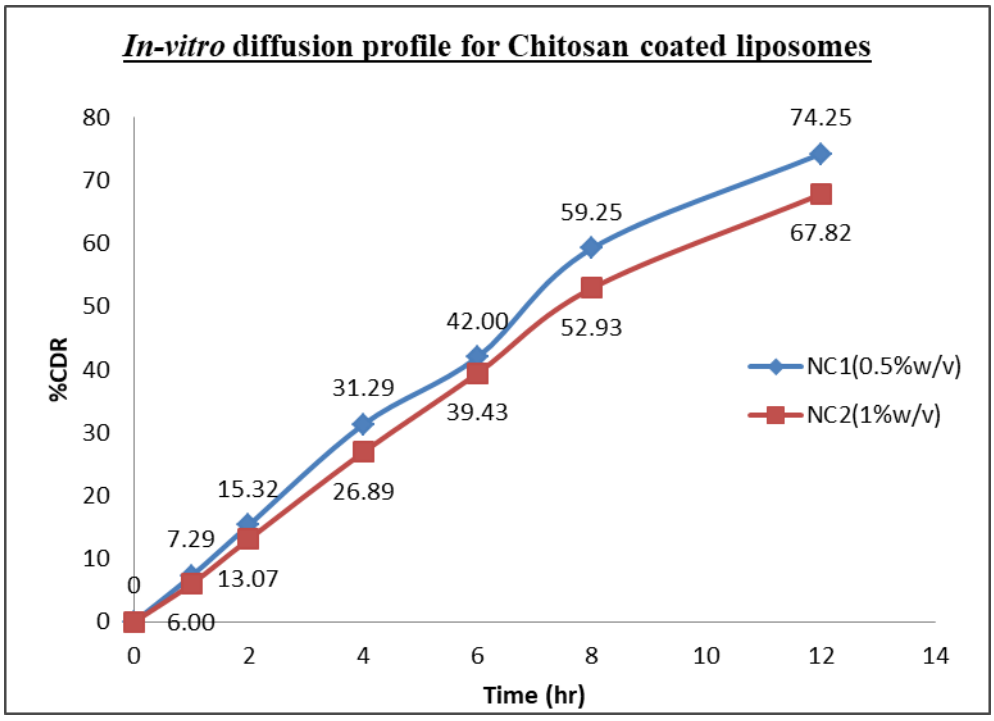


Fig: 12 % Cumulative drug release of coated formulation NC1-NC2.

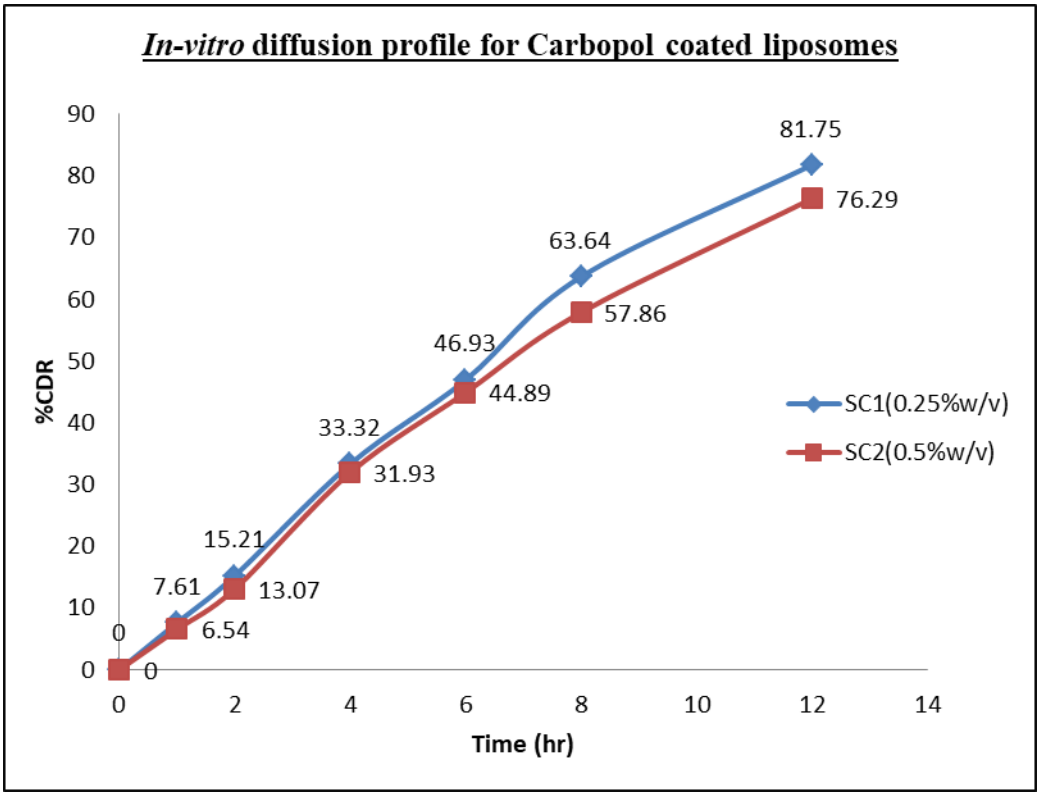


Fig: 13 % Cumulative drug release of coated formulation SC1-SC2.

Table 8: Determination of Mucoadhesion strength.

Formulation code	% Mucoadhesion
F1	4.28
NC1	56.85
NC2	70.85
SC1	53.57
SC2	64.28

Table 9: Refrigerated stability studies for optimized coated formulations.

Parameter	Duration in month											
	0				3				6			
	NC1	NC2	SC1	SC2	NC1	NC2	SC1	SC2	NC1	NC2	SC1	SC2
% Entrapment efficiency	95.21	95.81	93.8	94.4	95.14	95.67	93.6	94.3	95.02	95.44	93.3	94.1
%CDR	74.25	67.82	81.75	76.28	74.12	67.56	81.56	76.20	74.03	67.33	81.23	76.05

CONCLUSION

In this study, a mucoadhesive liposomal formulation of Metoprolol succinate was developed with desirable drug delivery properties. The chitosan -coated liposome had well *in vitro* stability, strong mucoadhesiveness, and enhanced cellular uptake. Therefore, the chitosan-coated liposomal formulation appears to have the potential to improve the bioavailability of Metoprolol succinate.

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