Research Article

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DESIGN, DEVELOPMENT, AND CHARACTERIZATION OF LIPOSOMES LOADED WITH CEFUROXIME.

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Abstract

Liposomes have emerged as a promising drug delivery system due to their biocompatibility, biodegradability, and ability to enhance drug stability while minimising adverse effects. This study focuses on the formulation and characterisation of cefuroxime-loaded liposomes prepared using the thin lipid film hydration method. Nine formulations were developed using varying concentrations of soya lecithin and cholesterol, followed by vortexing for different durations. The prepared liposomes were evaluated for drug-excipient compatibility using DSC, particle size distribution, zeta potential, drug entrapment efficiency, and in vitro drug release kinetics. The optimized formulation (F9) demonstrated high drug entrapment efficiency (87.36%), nanoscale particle size (1246.4 nm), and a stable zeta potential (-47.2 mV). In vitro release studies revealed a controlled and sustained drug release profile following zero-order kinetics. The results indicate that increasing lipid concentration enhances drug encapsulation but slows drug release. These findings highlight the potential of liposomal formulations for improving cefuroxime delivery, stability, and therapeutic efficacy.

Keywords: Liposomes, Differential Scanning Calorimetry (DSC), Cefuroxime, Drug delivery system, Encapsulation efficiency (EE).

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Introduction

Liposomes have been investigated in several pharmaceutical research studies as drug delivery systems and continue to constitute an intense field of research [1]. Liposomes are a powerful drug delivery system due to their structural versatility, biocompatibility, biodegradability, and non-toxic and non-immunogenic nature [2]. The drug loaded into the liposome is protected against physiologically occurring events, such as enzymatic degradation, chemical and immunologic inactivation and fast plasma clearance, contributing to

improving and extending its action. Since the drug is inside the liposome, there is a minimization of its exposure to healthy tissue, reducing the undesirable side effects compared with the free drug form [1].

Design of liposomes. A suitable liposomal formulation can be achieved by choosing an adequate liposome composition, functionalization and even a targeting strategy, as developed further in the following sections. The selection of phospholipids, head group and chain length, and the ratio of liposome components are crucial features to determine liposome safety, stability, and efficiency. Moreover, the ability of liposomes as a drug delivery system can be affected by the number and rigidity of lipid bilayers, size, surface charge, lipid organization and surface modification [3,4].

There is a wide variety of techniques for producing liposomes, including liposomal formulation methods and size reduction methods. The different techniques can influence the final properties of liposomes, such as size, lamellarity, and encapsulation efficiency (EE) [5].

The Characterisation of liposomes after production and before application, liposomes need to be extensively characterized for evaluation of their physical and chemical properties to guarantee their in vitro and in vivo performance [6]. Cefuroxime is a second-generation cephalosporin antibiotic widely used in the treatment of bacterial infections. It exhibits a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, making it a valuable option for respiratory tract infections, urinary tract infections, skin and soft tissue infections, and other bacterial diseases [7]. Cefuroxime functions by inhibiting bacterial cell wall synthesis through its high affinity for penicillin-binding proteins (PBPs), leading to bacterial lysis and cell death [10]. One of the challenges associated with cefuroxime therapy is its susceptibility to enzymatic degradation by β-lactamases, which can reduce its effectiveness [9]. To overcome this, advanced drug delivery systems such as liposomes have been explored to enhance their stability, prolong their half-life, and improve their therapeutic efficacy [12]. Liposomal encapsulation of cefuroxime can protect it from degradation, reduce toxicity, and enable targeted drug delivery, minimizing side effects while maximizing antimicrobial activity [8].

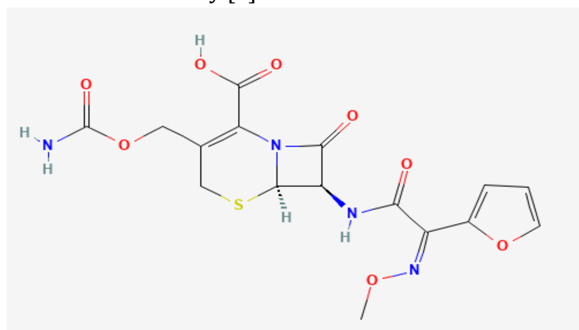

Fig. 1 Structure of cefuroxime

The development of liposomal cefuroxime formulations has gained attention due to their ability to enhance drug bioavailability and controlled release profiles, providing a promising alternative to conventional cefuroxime administration [11]. This study aims to investigate the formulation and characterization of cefuroxime-loaded liposomes to optimize drug entrapment, stability, and release kinetics, ultimately improving its clinical efficacy.

Materials and Methods

Standard calibration curve of cefuroxime

Potassium dihydrogen phosphate, 0.2M: Dissolved 27.218g of potassium dihydrogen phosphate in water and diluted with water to 1000 mL.

Sodium hydroxide 0.2M: 8g of sodium hydroxide in 1000 mL of water.

Preparation of pH 7.4 buffer: 50ml of 0.2M potassium dihydrogen phosphate was placed in a 200ml volumetric flask, and 39.1ml of 0.2M Sodium hydroxide was added and made up to water.

Construction of calibration curve of cefuroxime in phosphate buffer pH

Standard solution of cefuroxime

100mg of cefuroxime was accurately weighed and transferred to a 100 mL phosphate buffer in a 100 mL volumetric flask.

Preparation of primary stock solution

10 ml of standard solution is transferred to a 100 ml phosphate buffer.

Preparation of secondary stock solution

1 ml of primary stock solution is transferred to 100 ml phosphate buffer.

Preparation of working standard solution

A series of dilute solutions from the secondary stock solution was prepared, such as 2,4,6,8,10µg/ml in 10ml volumetric flask. The absorbance of the solutions was measured at 281 nm using a pH 6.8 phosphate buffer solution as a blank. A graph was plotted by taking concentration(µ/ml) on the X-axis and absorbance on the Y-axis. The coefficient (r2) value, slope(m) and the intercept(c) were determined.

Compatibility Studies

Drug-Excipient Compatibility Studies

DSC analysis was performed to ascertain the lack of potential interactions between the formulation components and confirm the formation of liposomes. The instrument was calibrated with an indium standard. Accurately weighed samples were placed in open, flat-bottom Aluminum sample pans. Thermograms were obtained by heating the sample at a constant rate of 100/minute. A dry purge of nitrogen gas (20ml/min) was used for all runs. Samples were heated in the presence and absence of endotherm peaks observed in the DSC graphs.

Method of Preparation of Liposomes

Nine formulations were prepared by using lipid components, soya lecithin and cholesterol by the thin lipid evaporation method. The drug solution was prepared by dissolving 100mg of cefuroxime in 1 ml of distilled water. Respective quantities of Soya lecithin were dissolved in 5

mL chloroform. 50mg of Cholesterol was dissolved in 5 ml of ethanol. All the solutions were mixed, and the organic solvents were allowed to evaporate at room temperature for 2 hrs. Then, the mixture was evaporated in a rotary evaporator. The thin film was formed in a round-bottom flask and then hydrated with phosphate buffer pH 7.4. The formulation was agitated by vortex for 10 to 20 minutes. Then, it was allowed to reside at room temperature for 2 – 3 hrs to achieve the complete swelling of the lipid film and, hence, to obtain the vesicular suspension.

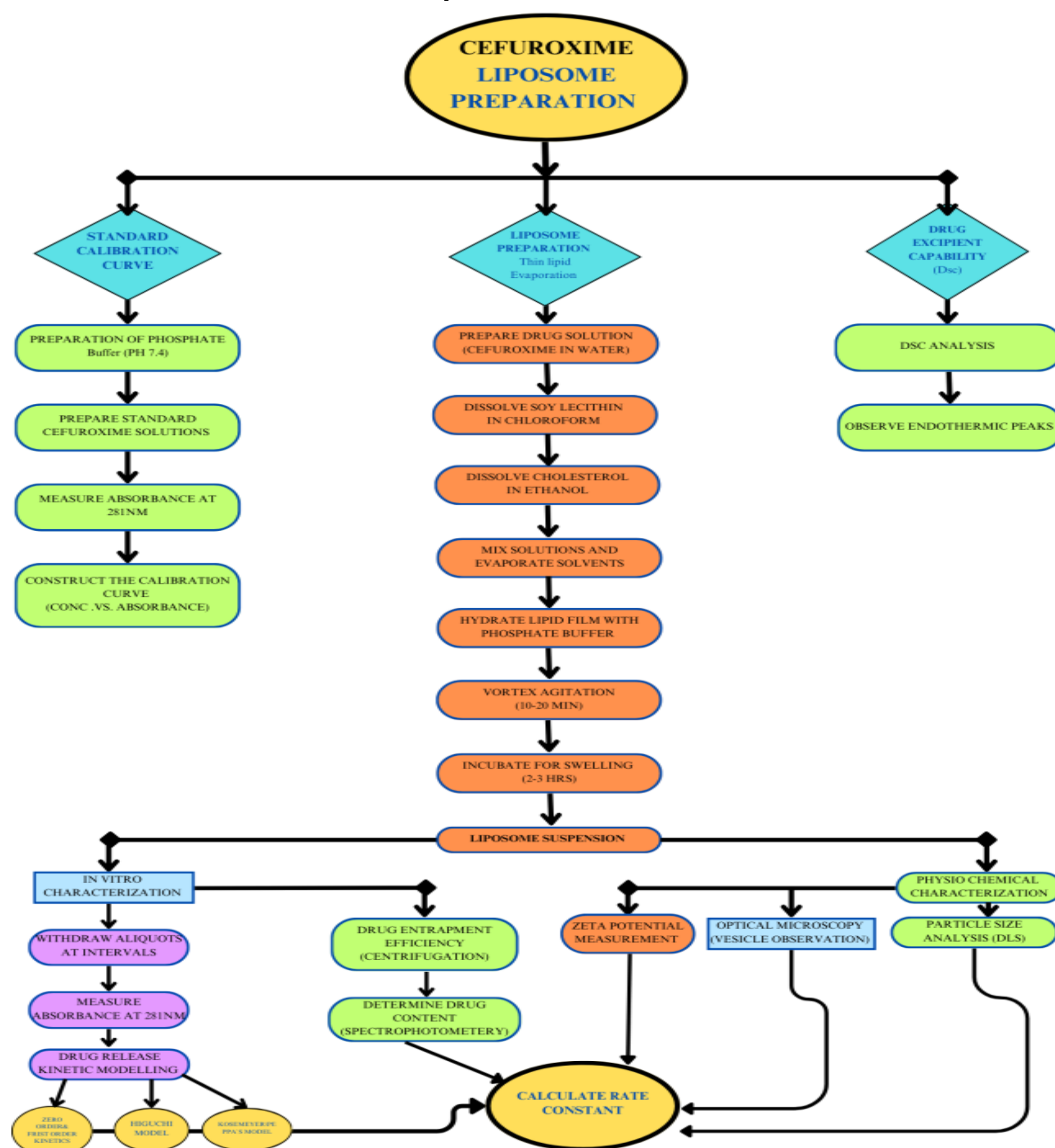

Fig 2: Cefuroxime liposome preparation

Table 1: Liposome Formulations

S.no	Drug	Cholesterol	soya lecithin	Vortex time (min)	Aqueous volume	Ethanol
F1	100mg	50mg	400mg	10	5ml	5ml
F2	100mg	50mg	400mg	15	5ml	5ml
F3	100mg	50mg	400mg	20	5ml	5ml
F4	100mg	50mg	500mg	10	5ml	5ml
F5	100mg	50mg	500mg	15	5ml	5ml
F6	100mg	50mg	500mg	20	5ml	5ml
F7	100mg	50mg	600mg	10	5ml	5ml
F8	100mg	50mg	600mg	15	5ml	5ml
F9	100mg	50mg	600mg	20	5ml	5ml

Results and Discussion

Standard Calibration Curve for Cefuroxime

The standard plot is done at pH 7.4. A spectrum of working standards was obtained by scanning from 180-400 nm against the blank reagent at λmax281 nm. The linear equation was y = 0.0415x + 0.0094. A regression value of 0.9936 supported the goodness of fit of the regression equation. Different standard concentrations and their absorbance values are shown below.

Table 2: Standard calibration curve of cefuroxime at pH 7.4

Concentration(µg/ml)	Absorbance(nm)
0	0
2	0.097
4	0.194
6	0.253
8	0.326
10	0.432

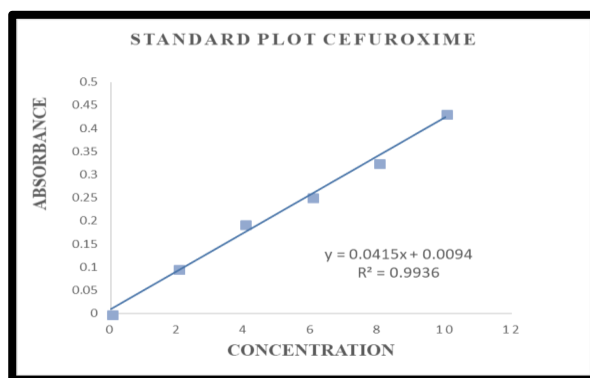

Fig 3: Standard plot of cefuroxime

Drug-Excipient Interaction Studies

DSC measurements were performed to study closely the physicochemical properties of liposomal membranes and their interactions with encapsulated cefuroxime. DSC thermograms of pure drug, phosphatidylcholine and cholesterol as liposome constituents and DSC thermograms of loaded liposome formulation are given below.

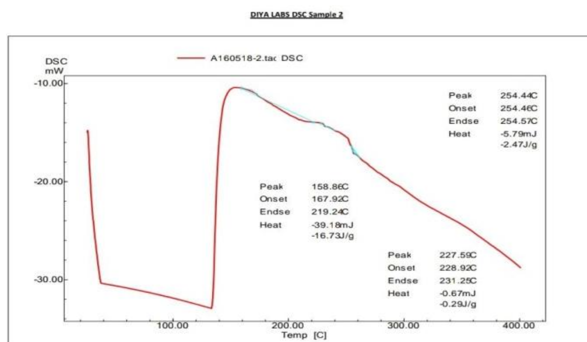

Fig 4: DSC thermogram of Drug, PC and Cholesterol

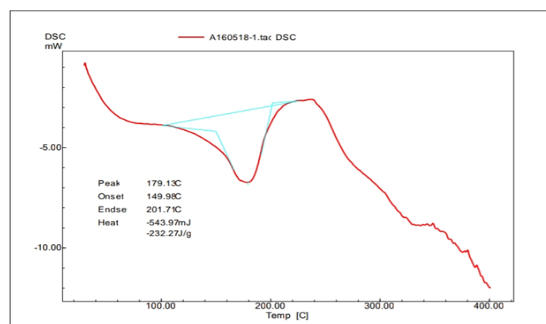

Fig 5: DSC thermogram of liposomal formulation F9

Cefuroxime shows a sharp endothermic peak, corresponding probably to the melting of its crystalline structure at 158.86 °C. CH exhibited a sharp melting peak at 227.59 °C. DSC of PC showed no characteristic melting peak and a degradation endotherm of PC at 254.44 °C. Phospholipids do not undergo a simple melting process on heating, passing from solid to liquid state instead, depending on the amount of water present, they exist in one or more liquid crystalline forms.

Physico-Chemical Characterization

Optical Microscopy

The prepared liposomal formulation was viewed under an optical microscope. The globules are almost spherical, and images were made.

Fig 6: Microscopic image of liposomal formulation

Particle Size Analysis

The particle size distribution was performed by using a particle size analyser, and the results showed that the mean particle size z-average of the liposome vesicle in F9 was 1246.4nm. The results indicated that vesicle size is in the nanoparticulate range and the size distribution is uniform. Histograms were made between diameter and frequency. Therefore, particle size decreased with an increase in the amount of lipids.

Scattering Angle : 90
Temperature of the holder : 25.0 deg. C
T% before meas. : 15
Viscosity of the dispersion medium : 0.552 mPa.s
Form Of Distribution : |Standard|
Representation of result : Scattering Light Intensity
Count rate : 2351 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	1246.4 nm	400.0 nm	1132.6 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	1246.4 nm	400.0 nm	1132.6 nm

Fig 7: Particle size analysis

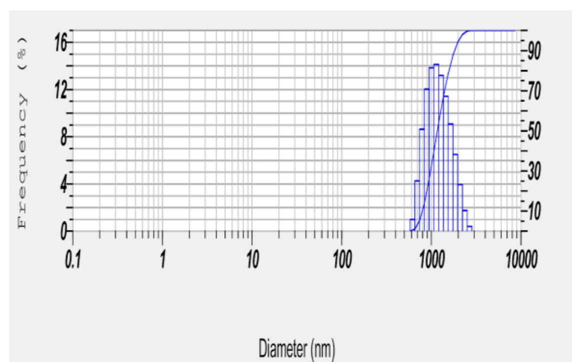

Figure 8: Histogram of particle distribution

Zeta Potential

The zeta potential of optimized formulation (F9) was selected based on entrapment efficiency. The value was -47.2 mV, which indicates that the surface of liposomes was dominated by the anions and proves that the prepared liposomes have sufficient charge to avoid the aggregation of vesicles. Zeta potentials more positive than +30 mV and more negative than -30 mV are normally considered stable for colloidal dispersion. The optimized liposomal formulation zeta potential value was more than -40mV, which suggests that the formulation was a stable suspension.

Measurement Type : Zeta Potential
Sample Name : C160518-M-ZETA
Temperature of the holder : 25.0 deg. C
Viscosity of the dispersion medium : 0.896 mPa.s
Conductivity : 2.772 mS/cm
Electrode Voltage : 2.8 V

Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	-55.1 mV	-0.000427 cm2/Vs
2	50.5 mV	0.000391 cm2/Vs
3	-- mV	-- cm2/Vs

Zeta Potential (Mean) : -47.2 mV
Electrophoretic Mobility mean : -0.000365 cm²/Vs

Fig 9: Zeta potential measurements

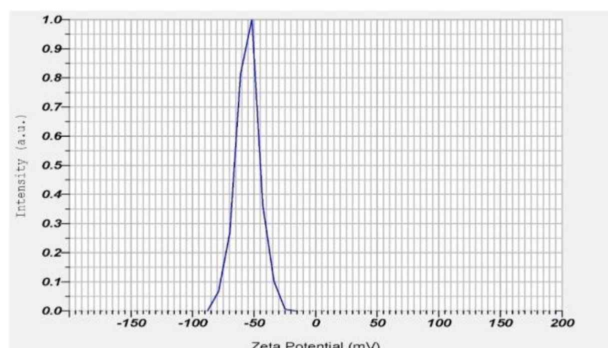

Fig 10: Zeta potential measurements

Drug Entrapment Efficiency

The encapsulation efficiency of liposomes is governed by the ability of the formulation to retain drug molecules in the aqueous core or the bilayer membrane of the vesicles. The percentage of drug entrapped showed that a decrease in lipid concentration decreases entrapment efficiency. The percent drug entrapment efficiency of the nine formulations ranges from 62.25% to 87.36 %, where formulation F9 showed a maximum drug entrapment of 87.36 %. The result of the drug entrapment efficiency of liposomes indicates that as the concentration of soya lecithin decreases, the drug entrapment efficiency of liposomes decreases, which was due to the saturation of the lipid bilayer with the drug, where low soya lecithin content provides limited entrapment capacity.

Table 3: Drug entrapment efficiency

S.no	Formulation	Drug entrapped (%)
1	F1	62.25
2	F2	65.08
3	F3	67.19
4	F4	72.35
5	F5	76.51
6	F6	79.41
7	F7	82.57
8	F8	84.15
9	F9	87.36

Drug Content

The drug content of the prepared cefuroxime-containing formulations was determined by using a UV spectrophotometer at 277nm. The % drug content of all liposomal formulations is listed in the table below. The percentage drug content of all formulations was found to be within the acceptable limits of the drug content test.

Table 4: Percent drug content

S.no	Formulation	Drug content (%)
1	F1	97.61
2	F2	98.29
3	F3	97.42
4	F4	96.52
5	F5	95.67
6	F6	98.13
7	F7	95.78
8	F8	96.61
9	F9	98.93

In Vitro Drug Release Studies

Table 5: In vitro drug release studies of various formulations of liposomes

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	3.95	3.34	2.55	5.21	4.57	5.39	5.81	5.27	4.55
1	7.56	6.18	7.32	7.504	7.32	9.01	7.38	11.06	7.56
2	12.3	14.82	12.34	14.19	14.82	15.39	13.34	17.26	14.73
3	20.8	22.22	20.65	27.56	25.04	22.2	25.03	21.6	22.74
4	33.4	33.71	33.48	33.4	32.26	38.83	32.26	34.31	33.4
5	42.48	41.06	44.78	46.72	44.35	47.5	44.31	45.09	45.33
6	53.78	52.08	53.34	51.54	53.34	57.56	53.34	59.43	57.44
7	72.65	67.26	73.13	67.2	66.87	65.81	68.22	65.75	66.6
8	81.24	81.66	82.26	78.71	78.26	79.37	72.86	73.46	73.77

Among formulations F1 to F3, F4 to F6, and F7 to F9, there is no significant increase in drug release, which may be because the difference between the formulations of those batches is only vortex timing. There was a slight increase in drug release as the vortex time increased. As the concentration of soya lecithin increased from F1-F9, the drug release decreased. F9 shows entrapment efficiency increased due to an increase in lipid concentration, and the percentage of drug release (73.77%) decreased.

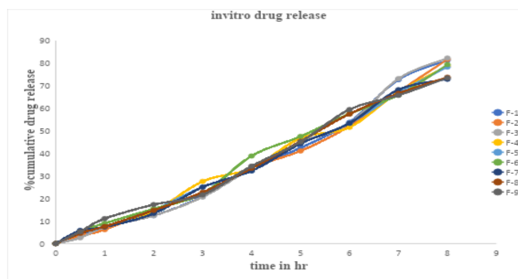

Fig 11: In vitro drug release plot of all formulations

Table 6: Comparison of Drug entrapment efficiency & In-vitro drug release

S.No	Drug entrapment efficiency	In-vitro drug release
1	62.25	81.24
2	65.08	81.66
3	67.19	82.26
4	72.35	78.71
5	75.51	78.26
6	78.9	79.37
7	82.57	72.86
8	84.15	73.46
9	87.36	73.77

In Vitro Drug Release Kinetic Models

Invitro drug release kinetic models are zero order, first order, Higuchi and kosmeyer-peppa models. Drug release from all the prepared formulations followed zero-order kinetics r2=0.9933, showing the drug release is independent of drug concentration in the formulation. The release kinetics showed that the diffusion mechanism is followed by Korsemeyer-Peppa with exponent(n = 1.0491) showing super case 2 transport. The respective plots of zero order, first order, Higuchi and Peppa are given in the tables and figures below.

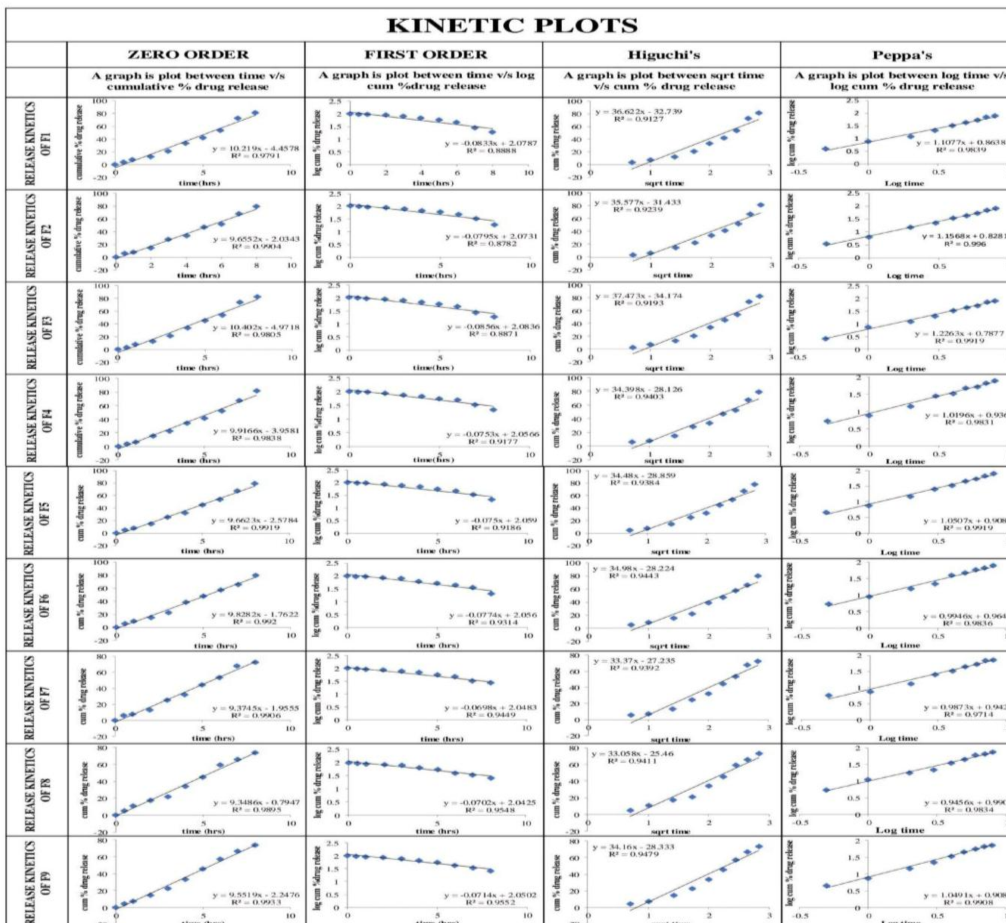

Fig. 12: Kinetic plot graphs of release kinetics from F1-F9

Table 7: Zero-Order Drug Release Kinetics

% CUMULATIVE DRUG RELEASE									
TIME (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.5	3.95	3.34	2.56	5.21	4.55	5.39	5.81	5.27	4.55
1	7.56	6.18	7.38	7.50	7.38	9.01	7.38	11.06	7.56
2	12.38	14.85	12.38	14.19	14.85	15.39	13.34	17.26	14.73
3	20.87	22.20	20.63	27.56	25.03	22.20	25.03	21.60	22.74
4	33.46	33.71	33.46	33.40	32.26	38.83	32.26	34.31	33.40
5	42.44	41.06	44.79	46.72	44.31	47.50	44.31	45.09	45.33
6	53.77	52.08	53.34	51.54	53.34	57.56	53.34	59.43	57.44
7	72.68	67.26	73.10	67.20	66.84	65.81	68.22	65.75	66.60
8	81.24	81.66	82.26	78.71	78.28	79.37	72.86	73.46	73.77

Table 8: First-Order Release Kinetics

LOG CUMULATIVE % DRUG RELEASE									
TIME (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	2	2	2	2	2	2	2	2	2
0.5	1.98	1.98	1.98	1.97	1.97	1.97	1.97	1.97	1.97
1	1.96	1.97	1.96	1.96	1.96	1.95	1.96	1.94	1.96
2	1.94	1.93	1.942	1.933	1.930	1.927	1.93	1.91	1.93
3	1.89	1.89	1.899	1.859	1.874	1.890	1.87	1.89	1.88
4	1.82	1.82	1.823	1.823	1.830	1.786	1.83	1.81	1.82
5	1.76	1.77	1.741	1.726	1.745	1.720	1.74	1.73	1.73
6	1.66	1.68	1.66	1.685	1.668	1.627	1.66	1.60	1.62
7	1.43	1.51	1.42	1.515	1.520	1.533	1.50	1.53	1.52
8	1.27	1.26	1.24	1.328	1.336	1.314	1.43	1.42	1.41

Table 9: Higuchi Kinetic Release

% CUMULATIVE DRUG RELEASE									
Sqrt time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.707	3.95	3.349	2.566	5.216	4.554	5.397	5.81	5.27	4.55
1	7.566	6.180	7.385	7.506	7.385	9.012	7.38	11.06	7.56
1.414	12.38	14.855	12.385	14.192	14.855	15.39	13.34	17.26	14.73
1.732	20.87	22.204	20.638	27.566	25.036	22.20	25.03	21.60	22.74
2	33.46	33.7108	33.469	33.409	32.265	38.83	32.26	34.31	33.40
2.236	42.44	41.060	44.795	46.722	44.313	47.50	44.31	45.09	45.33
2.449	53.77	52.0843	53.349	51.5421	53.349	57.56	53.34	59.43	57.44
2.645	72.68	67.265	73.108	67.204	66.843	65.81	68.22	65.75	66.60
2.828	81.2	81.662	82.26	78.710	78.289	79.37	72.86	73.46	73.77

Table 10: Peppa's Kinetic Release

LOG % CUMULATIVE DRUG RELEASE									
Log time	F1	F2	F3	F4	F5	F6	F7	F8	F9
-0.301	0.596	0.524	0.409	0.717	0.658	0.732	0.764	0.722	0.658
0	0.878	0.791	0.868	0.875	0.868	0.954	0.868	1.043	0.878
0.301	1.092	1.171	1.092	1.152	1.171	1.187	1.125	1.237	1.168
0.477	1.319	1.346	1.314	1.440	1.398	1.346	1.398	1.334	1.356
0.602	1.524	1.527	1.524	1.523	1.508	1.589	1.508	1.535	1.523
0.698	1.627	1.613	1.651	1.669	1.646	1.676	1.646	1.654	1.656
0.778	1.730	1.716	1.727	1.712	1.727	1.760	1.727	1.774	1.759
0.845	1.861	1.827	1.863	1.827	1.825	1.818	1.833	1.817	1.823
0.903	1.905	1.912	1.915	1.896	1.893	1.892	1.862	1.866	1.867

Table 11: Regression Coefficient Values of F1-F9 Formulations

S.NO	Zero-order	First order	Higuchi	Korse-Meyer Peppa's	
	R^2	R^2	R^2	Slope(n)	R^2
F1	0.9791	0.8888	0.9127	1.1077	0.9839
F2	0.9838	0.8782	0.9239	1.1568	0.996
F3	0.9805	0.8871	0.9193	1.2263	0.9919
F4	0.9904	0.9177	0.9403	1.0196	0.9831
F5	0.9919	0.9186	0.9384	1.0507	0.9919
F6	0.992	0.9314	0.9443	0.9946	0.9836
F7	0.9906	0.9446	0.9392	0.9873	0.9714
F8	0.9895	0.9548	0.9411	0.9456	0.9834
F9	0.9933	0.9552	0.9479	1.0491	0.9908

Conclusion

The formulated cefuroxime liposomes gave satisfactory results in various parameters, including the formulation of cefuroxime-containing liposomes, which shows a delayed release pattern. In vitro drug release rate studies showed that the F9, the highest lipid concentration,

showed the least drug release (73.77%), which showed maximum entrapment efficiency (87.36%). Kinetic models of drug release were plotted, and based on the regression values, which are closest to 1, the formulation F9 of Cefuroxime containing liposomes was known to follow zero order (r^2=0.9933) and Peppa's model (r^2=0.9919).

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Conflict of interest:

The authors declare no conflicts of interest.

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Authors contribution

Conceptualization, M.V, A.G; Methodology, M.V, S.N.S.R; Validation and investigation, M.V, D.V.K, S.D.P.R; Writing-original draft preparation, M.V, A.G, S.N.S.R, B.E; Writing-review and editing, A.G, D.V.K; Supervision, D.N; All authors have read and agreed to the published version of the manuscript.

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