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Research Article

Formulation and Characterization of Cefixime Phytosomes for Oral Drug Delivery

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ABSTRACT

Novel drug delivery systems (NDDS) are one of the most strategies which enable to overcome the problems related to drug bioavailability. It is the rate and extent to which a drug becomes available to the target tissue after its administration. Over the last century, phyto-chemical science and phyto-pharmacological science established numerous plant compounds with various biological activities and health promoting benefits such as anti-mutagenicity, anti-carcinogenicity and anti-oxidative activity, for age-related diseases namely memory loss, osteoporosis, diabetic wounds, immune and liver disorders, etc. Herbal medicines have been known since eons for their safety, efficacy, folk acceptability and fewer side effects.

Key Word:- Anti-mutagenicity, osteoporosis, anti-carcinogenicity,

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INTRODUCTION

Since ancient times the therapeutic uses of traditional medicines and phyto-medicines have proved very popular for health maintenance by various means. The advancement in the field of herbal drug delivery started recently with the aim to manage human diseases efficiently [3]. Every nation is seeking health care beyond the traditional boundaries of modern medicine; turning to self medication in the form of herbal remedies. Most of bioactive constituents of phyto-medicines are water soluble molecules (e.g. Phenolics, glycosides, flavonoids etc.). However, water soluble phytoconstituents are limited in their effectiveness because they are poorly absorbed when taken orally or when applied topically. Many approaches have been developed to improve the oral bioavailability, such as inclusion of solubility and bio availability enhancer, structural modification and entrapment with the lipophilic carriers and thus extensive research in the field of herbal drug delivery systems as a means of improving the therapeutic indices of drugs is inevitable. The use of formulation technology to deliver herbal products and drugs by improved absorption and, as a consequence, produce better results than those obtained

by conventional herbal extracts. Phytosome are not liposome; structurally the two are distinctly different. The phytosome is a unit of a few molecules bonded together, while liposome is an aggregate of many phospholipid molecules and encloses other phyto-active molecules but without specially bonding to them [4]. Phytosome technology is a breakthrough model for marked enhancement of bioavailability, significantly greater clinical benefit, assured delivery to the tissues, without compromising nutrient safety [5].

Therapeutic benefits of novel drug delivery systems

- Increase efficacy of the drug.
- Site specific delivery.
- Decrease toxicity/side effects.
- Viable treatments for previously incurable diseases.
- Potential for prophylactic applications.
- Lower health care costs both short and long term.
- Better patient compliance

METHODOLOGY:-

Experimental Work

Preparations of cefixime-phospholipid Complex Phytosome

The cefixime-phospholipid Complex was prepared by refluxing cefixime and phospholipid S100 in different millimolar ratios of (1:1, 1:2, 1:3, 1:4 1:5, 1:6 and

1:7).Briefly, accurately weighed amounts of cefixime and phospholipid S100 were placed into a 100 mL round bottom flask and dissolved in 20 mL of methanol. The reaction temperature of the reflux was controlled at 60 °C using a water bath for 5 h. The resultant clear solution was dried at 60°C under vacuum to remove traces of solvents in order to obtain the cefixime-phospholipid complex. The prepared thin layer had been kept overnight in room temperature prior to hydration. This dried film was hydrated with 10ml distilled water in a rotary at 60°C. The phytosome was finally sonicated for 4 minutes in a probe sonicator, with 60% amplitude and 5 seconds on-off interval. All phytosome was stored in the refrigerator.

Table 1: Composition of different Phytosome formulations containing millimolar ratio of cefixime and phosphatidylcholine S100 (PC).

S. No.	Formulation Code	Drug Ratio: Phosphatidylcholine S100 Ratio(milimolar)	Methanol (ml)
1	F1	1:1	20
2	F2	1:2	20
3	F3	1:3	20
4	F4	1:4	20
5	F5	1:5	20
6	F6	1:6	20
7	F7	1:7	20

Evaluation of Phytosome

Visual Appearance: Phytosome can range from translucent to milky, depending on the composition and particle size.

Optical microscopy

Optical Microscopy of drug loaded phytosome formulation was determined by optical microscopy at 100x magnification.

Particle size and zeta potential determinations

Vesicle properties, particle size diameter and zeta potential, were determined at room temperature by Zeta Potential/ Particle Sizer analyzer. Phytosome formulations were diluted with phosphate buffered saline, pH 7.4, for Zeta potential and particle size determination, respectively] .

Solubility Study of drug Phospholipid complex

Solubility determination of Pure cefixime and cefixime-phospholipids complex was carried out by adding excess of cefixime or phospholipids complex to 2 ml of water or n-octanol in sealed glass containers at 25°C. The liquids were agitated for 24 h, and then centrifuged to remove excessive cefixime (15 min, 15,000 rpm). The supernatant was collected & the concentration of cefixime was determined spectrophotometrically.

Drug Content

Drug Content of phytosome loaded can be determined by dissolving accurately weighed 100mg of phytosome loaded in 10ml methanol. After appropriate dilution absorbance may be determined by UV-Spectrophotometer (ʎmax= 288 nm). The drug content was calculated.

Determination of Entrapment efficiency

The entrapment efficiency of phytosome was determined by calculating the amount of entrapped cefixime in the phytosomes. To determine the entrapment efficiency of cefixime in phytosome, an appropriate amount of dispersion was transferred in culture tube. The dispersion was centrifuge for 15 min at 15000 rpm. After centrifugation the supernatant was collected and Percentage Drug Entrapment amount of free cefixime was determined spectrophotometrically (ʎmax= 288 nm). The entrapment efficiency has been determined according to the following equation:

$$EE\ \% = \frac{W_{(Added\ drug)} - W_{(free\ drug)}}{W_{(Added\ drug)}} \times 100$$

Where, W (added drug) is the amount of drug added during the preparation of phytosomes, W (free drug) is the amount of free drug measured in the lower chamber of the culture tube after centrifugation.

In-Vitro Drug Release Study

In vitro release kinetics of phytosome was determined in this work using dialysis method. In brief, phytosome (10mL) or drug solution with the equivalent drug concentration was enclosed in a dialysis bag and then placed in 100 mL of phosphate buffer saline (PBS) pH 6.8 used as release media. The entire system was kept at 37°C ± 0.5°C with continuous magnetic stirring. At selected time intervals (0.25,0.5,1,1.5,2,3,4,5,6,8,10,12 and 24 hour), 3 mL of solution was withdrawn from the release medium and replenished with the same volume of release medium. The collected samples were suitably diluted and analyzed by UV–visible spectrophotometer at 288nm. [24]

RESULTS AND DISCUSSIONS

Result of Preformulation study of drug

Table 2: Organoleptic Properties of Cefixime

Sr. no.	Properties	Inferences
1.	Colour	White to light yellow
2.	Odour	Odourless
3.	Form	Crystalline
4.	Taste	Bitter

Table 3: Melting Point of Cefixime

Drug	Reference M.P.	Observed M.P.
Cefixime	218-225°C	221.667±0.755°C

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UV Spectroscopy Determination of absorption maxima

Absorption maxima of Cefixime were found to be at 288 nm similar to literature as shown in Figure 1

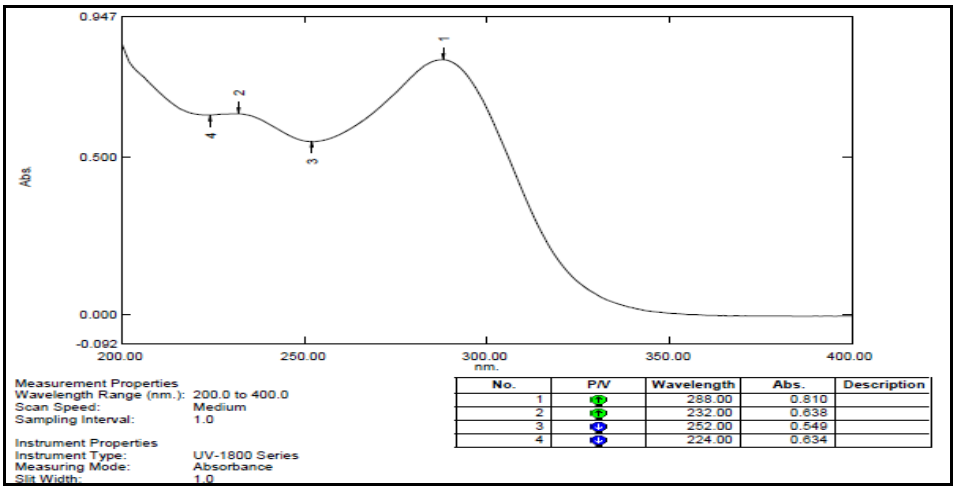

Figure 1: UV Spectrum of Cefixime

Preparation of standard curve of Cefixime

Table 4: Calibration curve of Cefixime (λ_{max} = 288 nm)

Sr. No.	Concentration µg/ml	Absorbance
1	2	0.102±0.002
2	4	0.197±0.001
3	6	0.290±0.002
4	8	0.373±0.002
5	10	0.474±0.001
6	12	0.573±0.004
7	14	0.650±0.001
8	16	0.741±0.001
9	18	0.811±0.001
10	20	0.892±0.001

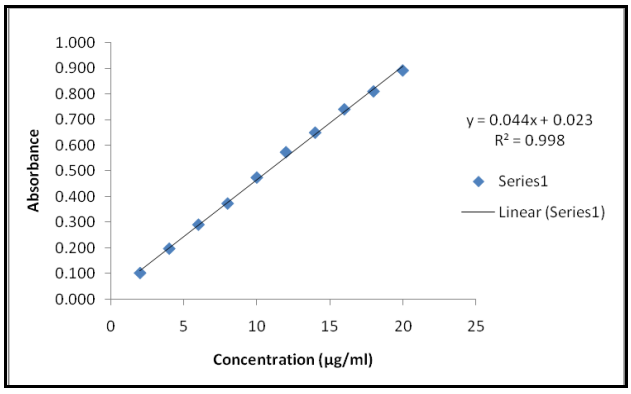

Figure 2: Graph of standard calibration curve of Cefixime

Table 5: Result of regression analysis of UV method for estimation of Cefixime

Statistical parameters	Results
λ max	288 nm
Regression equation: y=mx+C	Y=0.044x+0.023
Slope (m)	0.044
Intercept (C)	0.023
Correlation coefficient (r^2)	0.998

Table 6: Solubility studies of Cefixime for different solvents

Sr. No	Solvent	Solubility In (Mg/Ml) (Mean ± SD) *
1	Methanol	117.348±0.694
2	Ethanol	16.614±0.099
3	PBS 7.4	13.682±0.039
4	Acetone	11.894± 0.057
5	PBS 6.8	5.826±0.047
6	.1nhcl	1.530±0.002
7	Water	1.414±0.007
8	Chloroform	0.021±0.0003
9	DCM	0.009±0.0003

* Each value is average of three independent determination

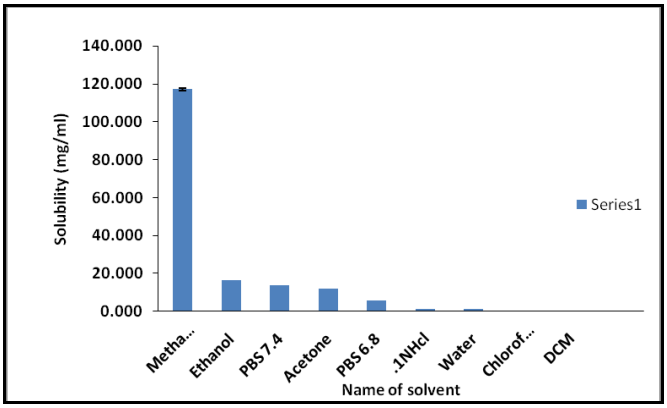

Figure 3: Solubility study of drug in different solvents

Partition coefficient determination

Table 7: Partition coefficient determination of Cefixime

Partition coefficient of drug	Solvent system	Log P Values
Cefixime	n- octanol:water	-0.442± 0.005

Discussion: The partition coefficient of Cefixime in n-Octanol: Water was found to be -0.442± 0.005 this indicates that the drug is Hydrophilic in nature.

FTIR of Cefixime and Excipients

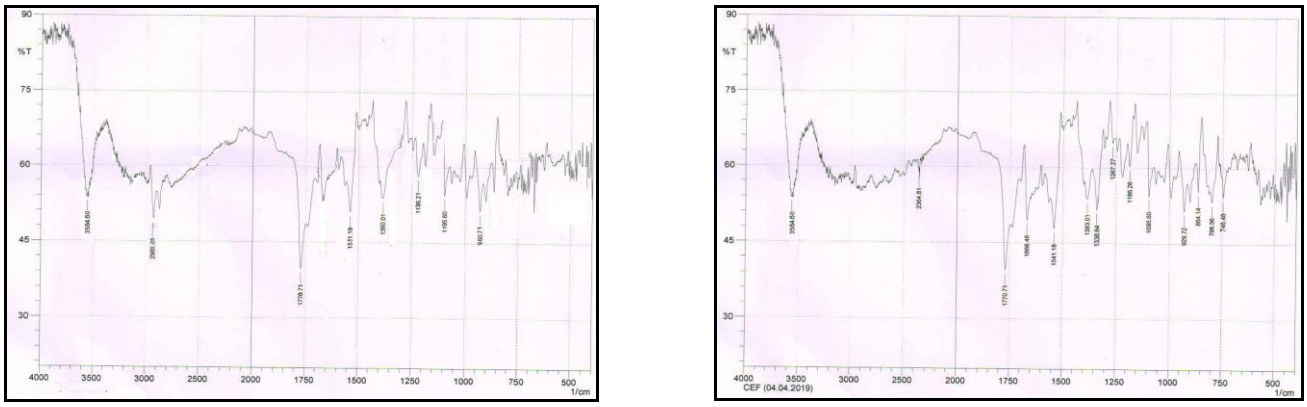

Figure 4: FTIR spectrum of Cefixime

Table 8: FTIR interpretation of Cefixime

Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
C-H stretch	2942.02	2364.81
OH, stretch, COOH	3563.91	3564.60
C O stretch CONH	1669.09	1668.48
C N stretching, aromatic	1337.88	1338.64
C O, stretch, COOH	1771.79	1770.71
C H,bending	746.16	746.48
C C, stretch	1542.09	1541.18

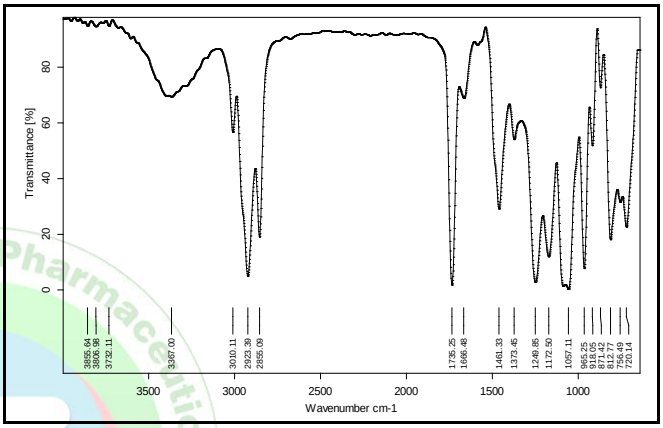

Figure 5: FTIR spectrum of Phosphatidylcholine S100

Table 9: FTIR interpretation of Phosphatidylcholine S100

Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
C–H stretching band of long fatty acid chain	2918.3 and 2854.96	2923.39 and 2856.09
Carbonyl stretching band in the fatty acid ester	1728.22	1735.25
C=O stretch α,β–unsaturated aldehydes, ketones	1710–1665	1666.48
P=O stretching band	1236.37	1249.85
P–O–C stretching band	1093.65	1057.11
N+(CH3)3 stretching	966.34	985.25

FTIR of Pure drug and physical mixtures:

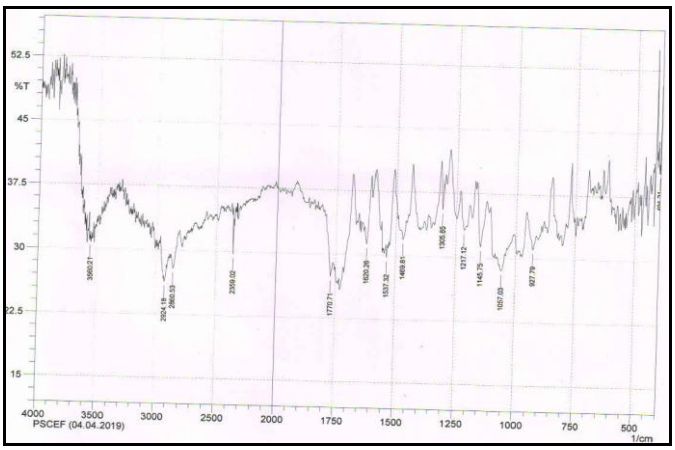

Figure 6: FTIR spectra of Cefixime and phosphatidylcholine S100

Table 10: FTIR interpretation of Cefixime and phosphatidylcholine S100

Characteristics Peaks	Reported (cm^{-1})	Observed (cm^{-1})
C-H stretch	2364.81	2359.02
OH, stretch, COOH	3564.60	3560.21
C O stretch CONH	1668.48	1620.26
C N stretching, aromatic	1338.64	1305.85
C O, stretch, COOH	1770.71	1770.71
C C, stretch	1541.18	1537.32
C–H stretching band of long fatty acid chain	2923.39 and 2856.09	2924.18 and 2860.53
P=O stretching band	1249.85	1217.12
P–O–C stretching band	1057.11	1057.03
N+(CH3)3 stretching	985.25	927.79

Preparation of Cefixime -phospholipid Complex Phytosome

The method of preparation of phytosome was found to be simple and reproducible.

Evaluation of Phytosome

Appearance of Phytosome

Figure 7: Cefixime-phospholipid Complex Phytosome.

Discussion: From the above **Figure 7**, we observe the milky white appearance.

Optical microscopy

Optical Microscopy of drug loaded phytosome formulation was determined by optical microscopy at 100x magnification and result was shown in **Figure 8 [**7]

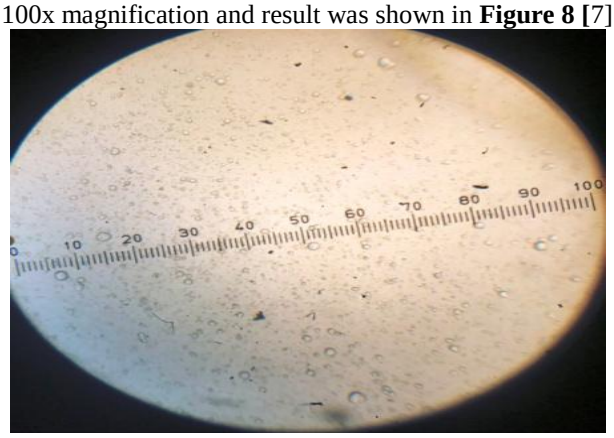

Figure 8: Optical Microscopy of Phytosome

Discussion: Uniform, regular and rigid vesicles were observed in optical microscopic view.

Particle size and zeta potential determinations

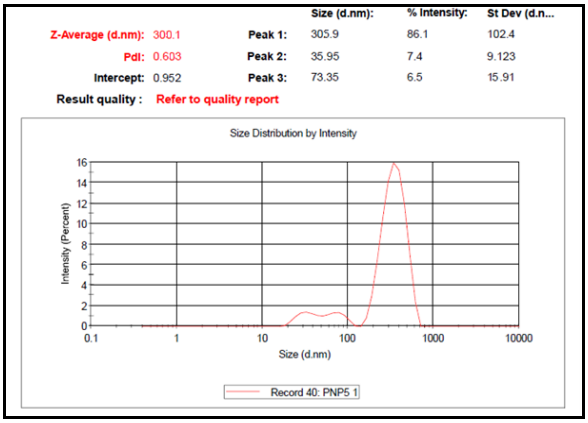

Figure 9: Particle size peak of phytosomal formulation

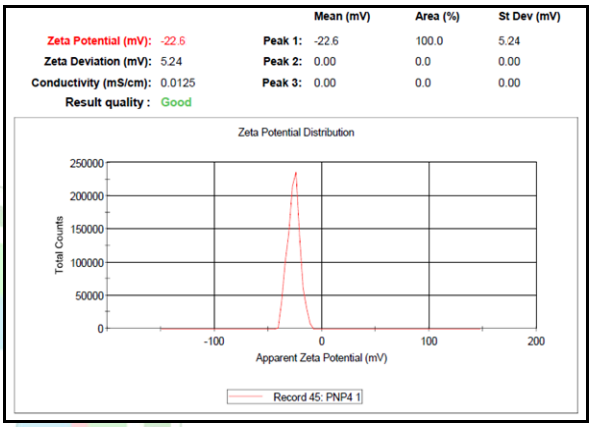

Figure 10: Zeta potential graph of phytosomal formulation

Table 11: n-Octanol Solubility of Pure drug & Cefixime-phospholipid Complex.

Drug: Phospholipid Ratio ,m(mm)	Solubility in n-octanol (mg/ml)
Pure drug	0.593±0.010
1:1 Complex	0.623±0.005
1:2 Complex	0.756±0.011
1:3 Complex	0.892±0.009
1:4 Complex	1.033±0.003
1:5 Complex	0.499±0.011
1:6 Complex	0.386±0.010
1:7 Complex	0.220±0.005

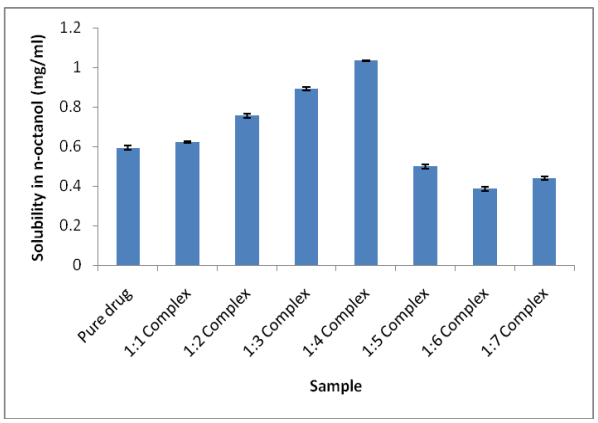

Figure 11: n-Octanol Solubility of Pure drug & Cefixime - phospholipid Complex

Percentage drug content

Table 12: Percentage drug content of different Phytosome formulation containing Cefixime-phospholipid Complex.

S. No.	Formulation Code	Percentage drug Content
1	F1	97.273±0.455
2	F2	88.181±0.909
3	F3	94.106±0.932
4	F4	89.848±0.694
5	F5	91.515±0.525
6	F6	94.879±0.735
7	F7	92.197±0.347

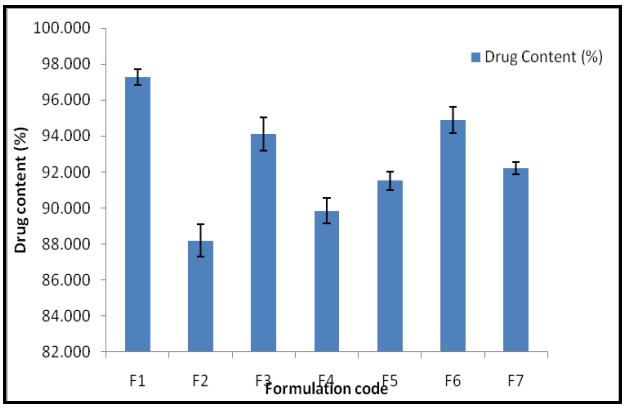

Figure 12: Percentage drug content of Phytosomal formulations containing Cefixime-phospholipid Complex

Discussion: The drug content of phytosome was found to be 88.848±0.694 and 97.273±0.455 %, respectively. The percentage drug content of all formulations was found to be satisfactory. Hence, the method adopted for phytosome formulations was found to be suitable.

Entrapment efficiency

Table 13: Percentage Entrapment efficiency of different Phytosome formulation containing Cefixime-phospholipid Complex.

S. No.	Formulation Code	Entrapment efficiency (%)
1	F1	77.591±0.045
2	F2	79.894±0.160
3	F3	83.864±0.079
4	F4	88.909±0.091
5	F5	73.970±0.069
6	F6	72.727±0.164
7	F7	69.803±0.095

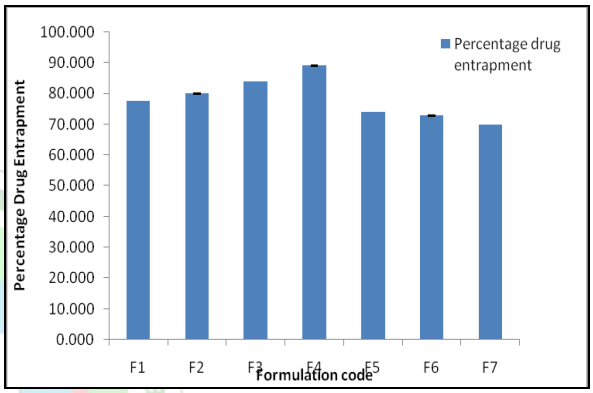

Figure 13: Percentage entrapment efficency of Phytosomal formulations containing Cefixime-phospholipid Complex

FTIR spectral analysis

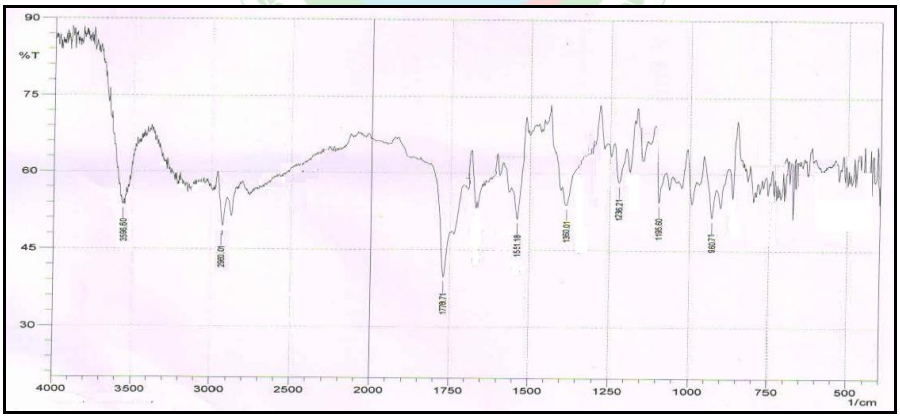

Figure 14: FTIR spectra of Formulation F4

Table 14: FTIR interpretation of FTIR spectra of Formulation F4

Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
OH, stretch, COOH	3564.60	3596.60
C N stretching, aromatic	1338.64	1360.01
C O, stretch, COOH	1770.71	1778.71
C C, stretch	1541.18	1551.18
C–H stretching band of long fatty acid chain	2923.39 and 2856.09	2960.01
P=O stretching band	1249.85	1236.21
P–O–C stretching band	1057.11	1195.60
N+(CH3)3 stretching	985.25	960.71

In-vitro Drug release study

Table 15: Percentage drug release of Formulation F4 and Pure drug

Time (Hr)	Drug Release of Pure drug(%)	Drug Release of F4 Formulation (%)
0.00	0.000	0.000
0.25	18.121±0.100	4.900±0.331
0.50	34.667±0.410	14.155±0.146
1.00	56.727±0.090	22.909±0.091
1.50	80.939±0.860	29.091±0.182
2.00	99.394±0.520	34.758±0.212
3.00	-	42.009±0.307
4.00	-	47.303±0.139
5.00	-	51.839±0.231
6.00	-	56.485±0.344
8.00	-	63.182±0.182
10.00	-	69.464±0.168
12.00	-	73.758±0.319
24.00	-	82.455±0.182

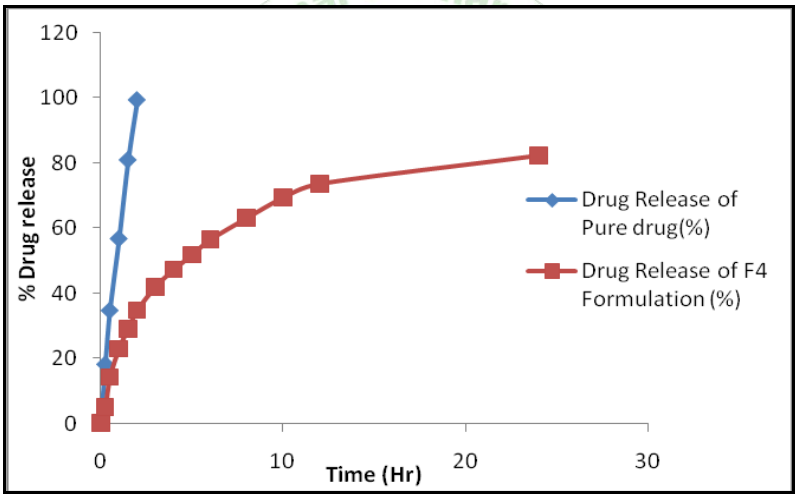

Figure 15: In-Vitro Drug release of F4 Formulation and pure drug

In-vitro drug release kinetic

In-vitro drug release kinetic study data of formulation F4 was given below.

Zero order

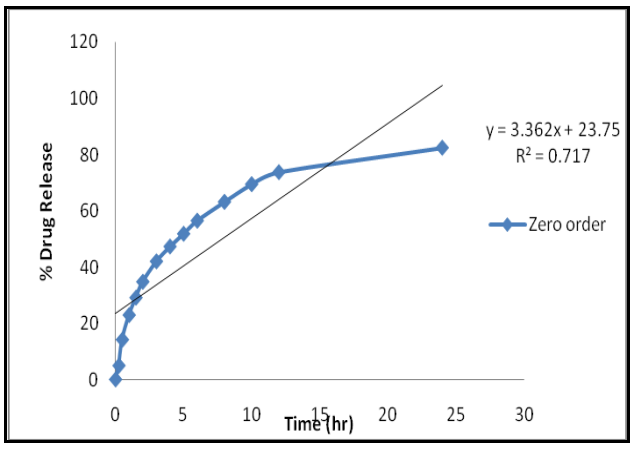

Figure 21: Zero order graph of formulation F4

First Order

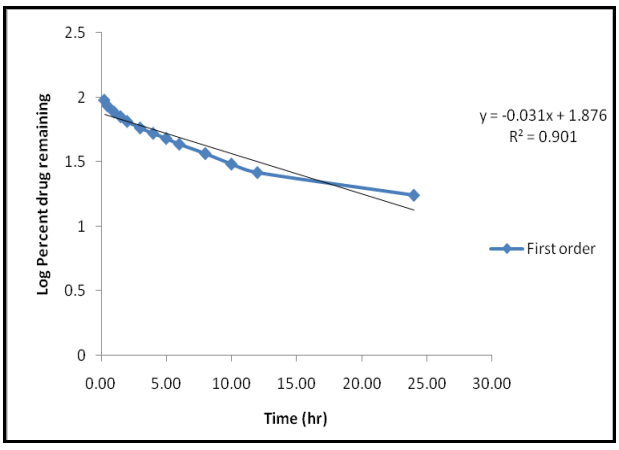

Figure 16: First order graph of formulation F4

Higuchi model

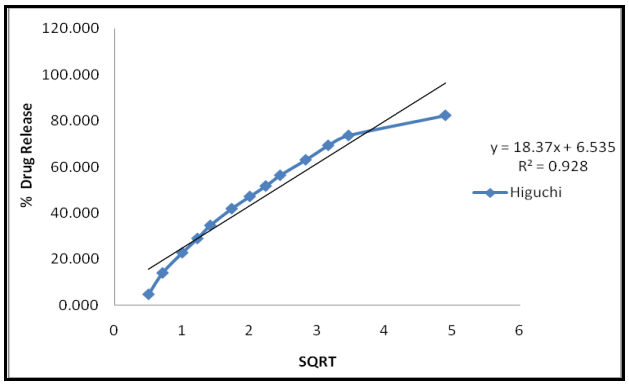

Figure 23: Higuchi order graph of formulation F4

Korsmeyer peppas model

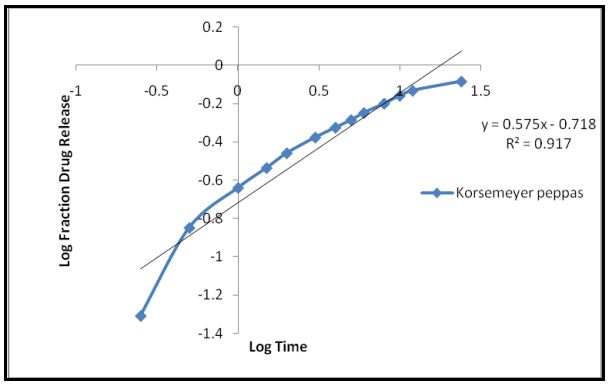

Figure 17: Korsmeyer peppas order graph of formulation F4

Table 16: Kinetic equation parameter of formulation F4

Formulation	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F3	0.717	3.362	0.901	-0.031	0.928	18.37	0.917	0.575

Summary and Conclusion:-

The goal of any drug delivery system is to provide therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired plasma concentration of drug for a particular period of time. However, incomplete release of drug, shorter residence time of dosage form in the gastrointestional tract and high hepatic first pass effect leads to lower bioavailability. Such limitations of the conventional dosages forms have paved to an era of controlled and novel drug delivery systems.

Cefixime is a broad-spectrum, third-generation cephalosporin antibiotic derived semisynthetically from the marine fungus Cephalosporium acremonium with antibacterial activity. Cefixime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases, may be susceptible to cefixime. The antibacterial effect of cefixime results from inhibition of mucopeptide synthesis in the bacterial cell wall. Cefixime can be administered by different routes: oral and intravenous. The convenience of oral administration is attractive. However, orally delivered cefixime is rapidly cleared by first-pass hepatic metabolism (50%) and this result in poor bioavailability. Consequently, evidence has indicated that orally administered cefixime has lesser efficacy for the treatment of urinary tract infections.

By incorporation of cefixime in phytosme, the drug delivery system was successfully developed that showed sustained release and could be potentially useful to overcome poor bioavailability problems associated with cefixime.

Drug-phospholipid complexes improve the bioavailability of drugs which have either very low lipid solubility or very poor water solubility. Therefore, drug can be complexed for improving biopharmaceutical properties. In addition to improving the drug absorption, drug-phospholipid complexes also have the following advantages: 1) increasing the stability of drugs, 2) prolonging the duration of action of drugs.

Before phytosome development, preformulation studies were carried out to characterize the chemical and physical properties of drug substance. The FT-IR spectrum of drug samples was found to be in concordant with the reference chemical groups present in the structure of the cefixime. The UV spectrum of cefixime exhibited a broad band at 288nm. The melting point was determined by capillary method which complies with the melting point given in reference. The solubility results showed that cefixime highly soluble in methanol. The solubility profile of drug in different solvents shows that drug is hydrophilic in nature which is further confirmed by the partition coefficient study.

The standard curves of cefixime were prepared methanol: water and the absorbance data obtained subjected to linear regression. The correlation coefficients were found to be 0.998 for cefixime which is closed to one indicated for good linearity.

The preformulation study (FT-IR spectrum, UV spectrum and melting point) results suggested that cefixime was pure and good in quality and the estimation procedure was found to be quite reliable, accurate and suitable for formulation development.

Phytosomal formulation of cefixime was prepared by using the reflux technique method.

For optimization of Phytosome, different formulations (F1 to F7) were prepared using the various quantities of lipid. Formulation (F4) with maximum n-octanol solubility, entrapment efficiency and optimum size considered as optimized formulation.

The shape and size of the optimized F4 formulation was confirmed through microscope and particle size and found that most of the particles were well identified.

Optimized formulation *in vitro* drug release was studied in phosphate buffer saline (PBS) pH 6.8 using dialysis method. To know precisely, the rate and mechanism of

drug release, the *in vitro* data was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas model. The results showed that the drug release of F4 formulation followed Higuchi order which describes that the cefixime follows a sustain mechanism for release from phytosome.

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