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Formulation and evaluation of paroxetine phytosome for oral drug delivery

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Abstract: "Phyto" implies plant while "some" means cell-like. Phytosomes are greater absorbed and improve bioavailability of bio ingredients Phytosomes presented good pharmacokinetic and pharmacodynamics feedback than standard natural extracts. Many types of products available in the market in which contain Ginkgo biloba, Silybum marianum, and Camellia sinensis. The property of Phytosomes generally depends on the method of formulation and drug polymer complex formation. The phytoconstituents of various plants which provide the hepatoprotective property i.e Ginkgo biloba, Mangiferin, Andrographis paniculata Linn, were extracted and formulated as phytosome drug delivery system. Phytosome represents the antioxidant property, hepatoprotective activity, and it is used for the wound healing.

keywords: Phytosomes, phospholipid, phosphatidylcholine, phytoconstituent, bioavailability, drug, therapeutic uses.

I. INTRODUCTION

Phytosomes are lipid compatible molecular complex which are composed of “phyto” which means plant and “some” meaning cell-like[1]. Phytosomes are advanced forms for herbal products that are better absorbed and utilized to produce better results. Than produced by conventional herbal extracts. Phytosomes show better pharmacokinetic and therapeutic profiles than conventional herbal extracts [2].

Advantages of phytosomes:-

1. Phytosome increases the absorption of active constituents, so its dose size required is small.
2. There is appreciable drug entrapment and improvement in the solubility of bile to herbal constituents, and it can target the liver.
3. In Phytosome, chemical bonds are formed between phosphotidylcholine molecules, so it shows good stability [3].
4. Phytosome improves the percutaneous absorption of herbal phytoconstituent [4].

Disadvantages of Phytosomes:-

1. Regardless of all advantages phytosome may rapidly exclude the phytoconstituent.[5]
2. Phytosomes drawback is leaching of the phytoconstituent off the ‘some’ which decrease

The anticipated drug concentration. [6]

Marketed formulation of phytosomes

S.No.	Phytosome product	Phytoconstituent complexed with phosphatidylcholine	Dose	Indications
1.	Green Tea Phytosome	Epigallocatechin from *Thea sinensis*	50 to 100 mg	Nutraceutical, Systemic antioxidant. Best choice for protection against cancer and damage to cholesterol.
2.	Silybin PhytosomeTM	Silybin from *Silybum marianum* .	120 mg	Hepatoprotective, antioxidant for liver and skin.
3.	Super Milk thistle ExtractTM	Silybin from *Silymarin* Food product	150 mg	Antioxidant for liver and skin
4.	Ginkgo Biloba PhytosomeTM	24 % Ginkgoflavonglycosides from *Ginkgo biloba*	120 mg	Protects brain and vascular lining; Anti-skin ageing agent. Best choice for most people over the age of 50.
5.	Grape Seed PhytosomeTM	Procyanidins from *Vitis vinifera*	50-100 mg	Nutraceutical, systemic antioxidant. Best choice for most people under age of fifty. Also specific for the eyes, lungs, diabetes, varicose veins, and protects against heart disease[7].
6.	Curcumin (Merinoselect) Phytosomes	Polyphenol from Curcuma Longa	200-300 mg	Cancer Chemo preventive Agent Improved the oral bioavailability of curcuminoids, and that the plasma.
7.	Ginkgo select phytosome	Flavonoids from ginkgo biloba	120 mg	Anti aging, Protects Brain & Vascular Liling[8].

Table 1: Marketed formulation of phytosomes

2. EXPERIMENTAL WORK

2.1. Pre-formulation studies

The obtained drug sample was identified by various analytical techniques such as IR spectroscopy, UV spectroscopy, melting point etc. In which we have studied following properties Organoleptic and melting point,

2.1.1 Organoleptic Characteristics:

The drug sample was characterized for the physical characterization like appearance, colour and odour.

2.1.2 Melting point

The melting point of the solid is defined as the temperature at which solid and liquid are at sequilibrium at a total pressure. Melting point apparatus is used for the determination of melting point of the drug.

2.1.3 UV spectrum of Paroxetine

Double beam UV-visible spectrophotometer (Shimadzu, UV-1800, Japan) was used to know the λ_{max} of drug. A 10-90 µg/ml solution of Paroxetine in distilled water was scanned in the range of 200-400 nm.

2.1.4 Estimation of paroxetine

2.1.4.1 Estimation of paroxetine by UV-visible spectrophotometer

Absorbance of these solutions was recorded at 292 nm against distilled water. UV-visible spectrophotometer and standard curve was plotted against concentration.

2.1.5 Solubility Studies

Solubility study was found in different solvent i.e Ethanol, Methanol, Distilled water, DMF (dimethyl formide), Buffer1.2 ph, Buffer 6.8.

2.1.6 Partition Coefficient of Drug

Partition coefficient (oil/water) is a measure of a drug's lipophilicity/hydrophilicity and an indication of drug's ability to cross cell membranes.

Shake flask method

The partition coefficient determination study was performed by using shake flask method. Excess amounts of the drug (paroxetine 50mg) dissolved in 10 ml of two solvents (n-octanol: Water) together (1:1) and placed for 24 h.

2.1.7 FTIR of paroxetine and Excipients

FT-IR Spectroscopy was used for structure analysis An FT-IR spectrum of Paroxetine and drug plus excipients mixture was recorded for the determination of drug interaction with excipients. Infrared spectrum was recorded in the 4000 - 400 cm^{-1} region.

2.1.8 FTIR of Pure drug and physical mixtures

Drug and various excipients were mixed thoroughly in ratio of 1:1. Samples were scanned by FTIR under the range of 400-4000 cm^{-1}. The spectra of pure drug and drug with excipients were compared to check any incompatibility and physical changes.

2.2 Preparation, optimization and characterization of paroxetine phytosomes

Paroxetine phytosomes were prepared by conventional rotary evaporation sonication method.

Formulation	Ratio
F1	1:05
F2	1:1
F3	1:1.5
F4	1:2
F5	1:2.5
F6	1:3

Table 2: Composition of phytosomes as prepared follow.

2.3 Evaluation of phytosomes:

2.3.1. Photomicroscope study

A selected phytosome formulation was chosen for microscopic investigation due to its optimum relative deformability.

2.3.2 pH of phytosomes formulation

Quantitative measure of the acidity or basicity of aqueous or other liquid solutions.

2.3.3 Drug Entrapment Efficiency

Paroxetine phytosomes entrapped was estimated by centrifugation method Encapsulation efficiency is expressed as the percent of drug trapped. The %EE was calculated as:

$$\%EE = \frac{\text{Amount of drug added} - \text{Amount of drug unentraped}}{\text{Amount of drug added}} X100$$

2.3.4 FT-IR spectroscopy of formulation

The formation of the phytosomal complex was confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the single components and their mechanical mixtures. The stability of the complex was confirmed by comparing the spectrum of the complex in solid state (phytosomes) with the spectrum of micro-dispersion in water after lyophilization process, at different times.

2.3.5 Transmission Electron Microscopy (TEM) Analysis

The TEM analysis of Phytosomes was performed for morphological characterization and visualization of emulsion droplets.

2.4 In-vitro drug release study

The permeation of paroxetine -bearing phytosomes through an artificial cell phase membrane was performed in Franz-type diffusion cells. All samples were analyzed for paroxetine content spectrophotometrically at λmax of drug.

2.5 in vitro Drug release kinetic studies.

In the present study, raw data obtained from in vitro release studies was analyzed, where in data was fitted to different equations and kinetics model to calculate the percent drug release and release kinetics of optimized formulation from floating beads. The kinetic models used were a Zero-order equation, First-order, Higuchi's model and Korsmeyer-Peppas equation.

3.0 RESULTS AND DISCUSSIONS

3.1 Result of Preformulation study of drug

The aim of preformulation studies is to investigate the physical and chemical properties of a drug substance. The selected drug Nandrolone decanoate was subjected for investigation of physical characterization parameters such as:

1. **Organoleptic properties**
2. **Melting point**
3. **UV-visible spectra**
4. **Solubility Study**
5. **Partition coefficient**
6. **FT-IR spectra**

3.1.1 Organoleptic properties

Organoleptic properties of drug Paroxetine found to be as per USP monograph. The Organoleptic properties of Paroxetine were found to the given **Table 3**.

Sr. No.	Properties	Inferences
1.	Colour	White
2.	Odour	Characteristics
3.	Form	Powder

Table 3: Organoleptic Properties of Paroxetine

3.1.2 Melting Point

The melting point of a substance is the temperature at which the solid phase gets converted to liquid phase under the one atmosphere of pressure. The melting point determination implies the purity of drug. Melting point of Paroxetine was determined by capillary tube method and was found to be quite similar to the reported melting point as shown in **Table 4**.

Drug	Observed melting point	Reference melting point
Paroxetine	145ºC – 155ºC	147ºC -155ºC

Table 4: Melting Point of Paroxetine

Discussion: The melting point of Paroxetine was found to be in range 145°C – 155ºC which is of the pure drug. Hence drug sample was free from any type of impurities.

3.1.3 UV Spectroscopy

3.1.3.1 Determination of absorption maxima of paroxetine in distilled water

Absorption maxima of Paroxetine were found to be at 292 nm similar to literature as shown in **Figure 1**.

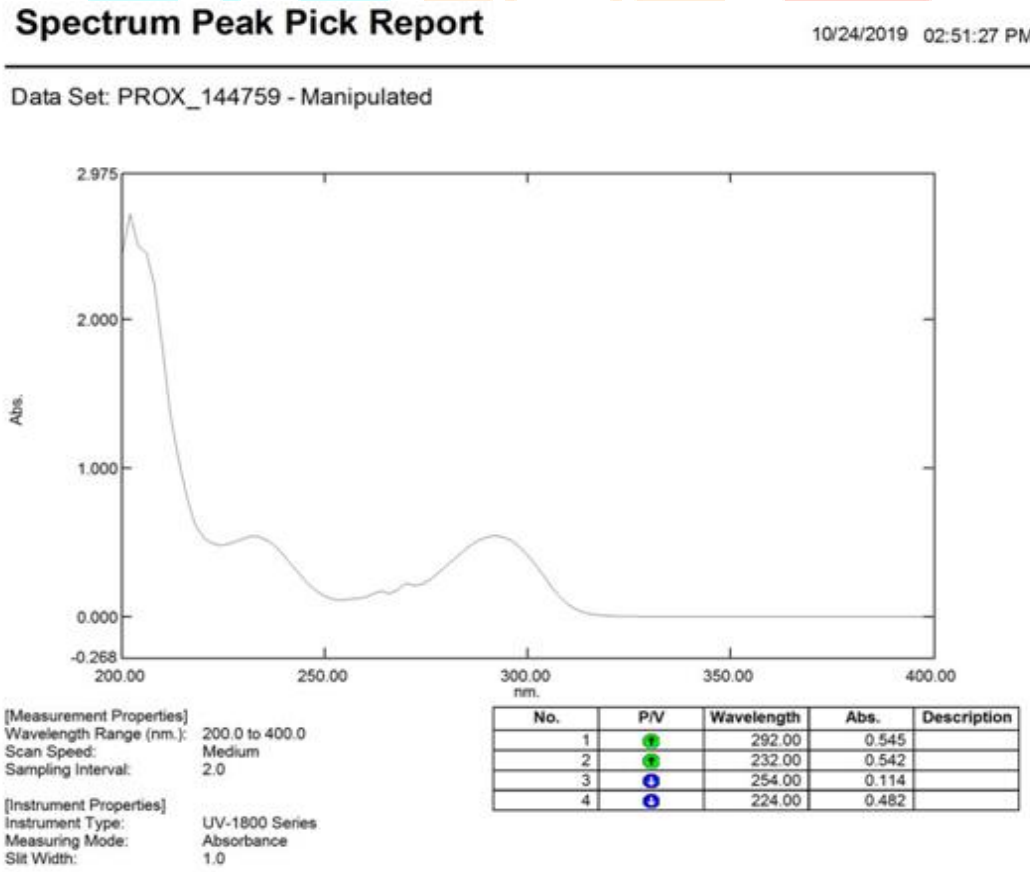


Figure 1: UV spectrum of Paroxetine in distilled water

3.1.3.2 Preparation of standard curve of Paroxetine in distilled water

Sr. no.	Concentration µg/ml	Absorbance
1	10	0.096
2	20	0.223
3	30	0.337
4	40	0.482
5	50	0.602
6	60	0.766
7	70	0.874
8	80	0.984

Table 5: Calibration curve of Paroxetine in distilled water (λ_{max} = 292nm)

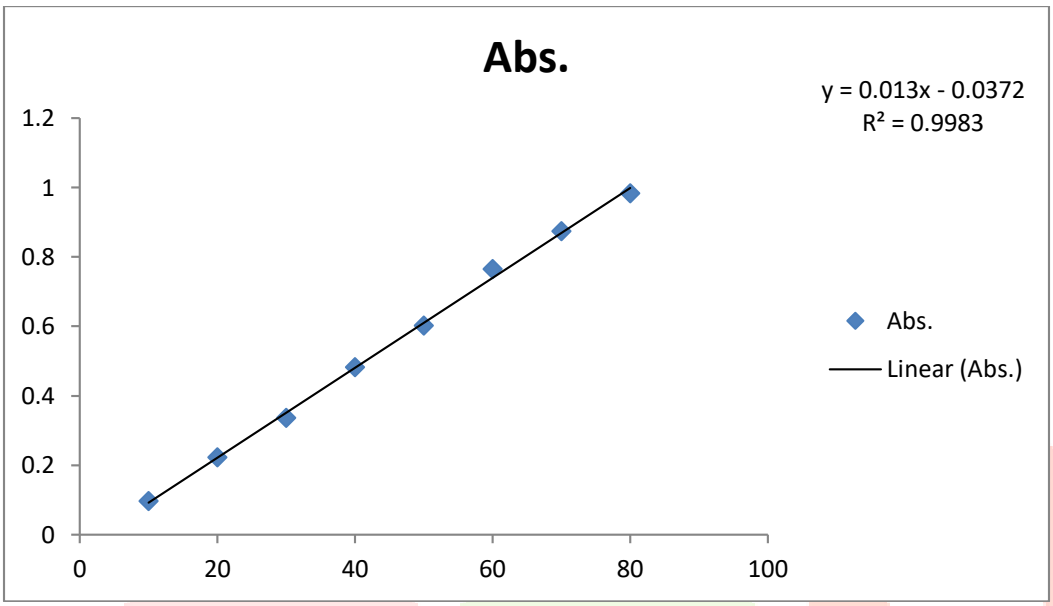


Figure 2: Graph of standard calibration curve of paroxetine in distilled water

Statistical parameters	Results
λ max	292nm
Regression equation (Y=mx+C)	Y= 0.013x-0.0373
Slope (b)	0.013
Intercept (C)	0.0373
Correlation coefficient (r^2)	0.9983

Table 6: Result of regression analysis of UV method for estimation of paroxetine

Discussion: - The calibration curve for Paroxetine was obtained by using the 10-90 µg/ml concentration of Paroxetine in distilled water. The absorbance was measured at 292 nm. The calibration curve of Paroxetine as shows in graph indicated the regression equation Y=0.013x - 0.0373 and R^2 value 0.9983, which shows good linearity as shown in **Table 6** and **Figure 2**.

3.1.4 Solubility studies

Solubility of drug in solvents was carried out in order to screen for the components to be used for formulation development. Analysis of the drug was carried out on UV Spectrophotometer at 292nm.

3.1.4.1 Solubility Studies of Paroxetine in various Solvents:

S. No	Solvent	Solubility in (mg/ml) (mean±SD) *
1	Ethanol	239.4615385
2	Methanol	61.79230769
3	DMF (dimehyl formide)	30.48461538
4	Distilled water	7.025384615
5	Buffer 1.2 PH (HCL)	1.902307692
6	Buffer (6.8)	2.463846154

Table 7: Solubility studies of Paroxetine for different solvents

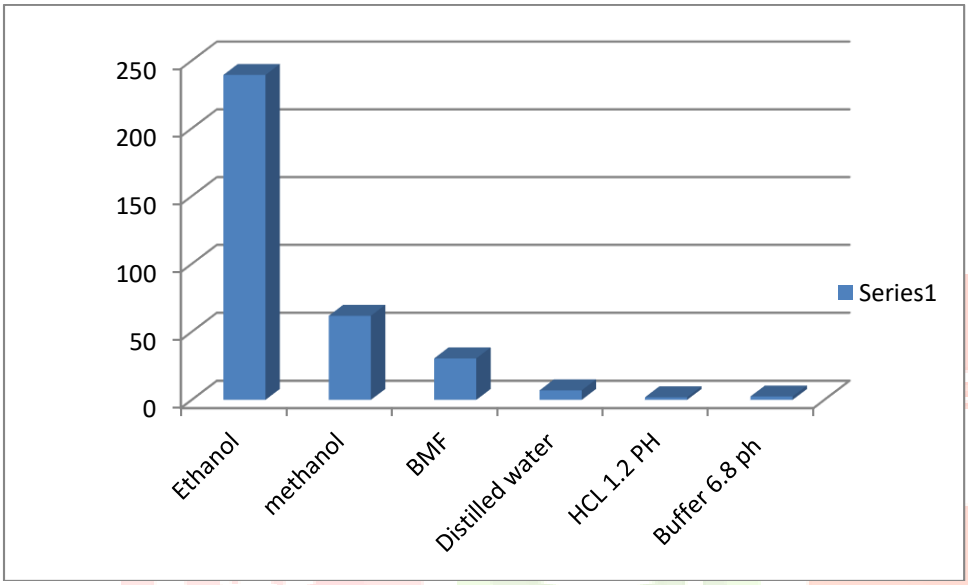


Figure 3: Solubility study of drug in different solvents

Discussion: From the above data, it was clearly seen that Paroxetine is highly soluble in ethanol. (**Figure 3 and Table 7**).

3.1.5 Partition coefficient determination

Partition coefficient of the Paroxetine was determined using n-octanol and water. Log P greater than one indicates that the drug is lipophilic in nature, whereas those with partition coefficients less than one are indicative of a hydrophilic drug. This indicated the lipophilicity and purity of drug.

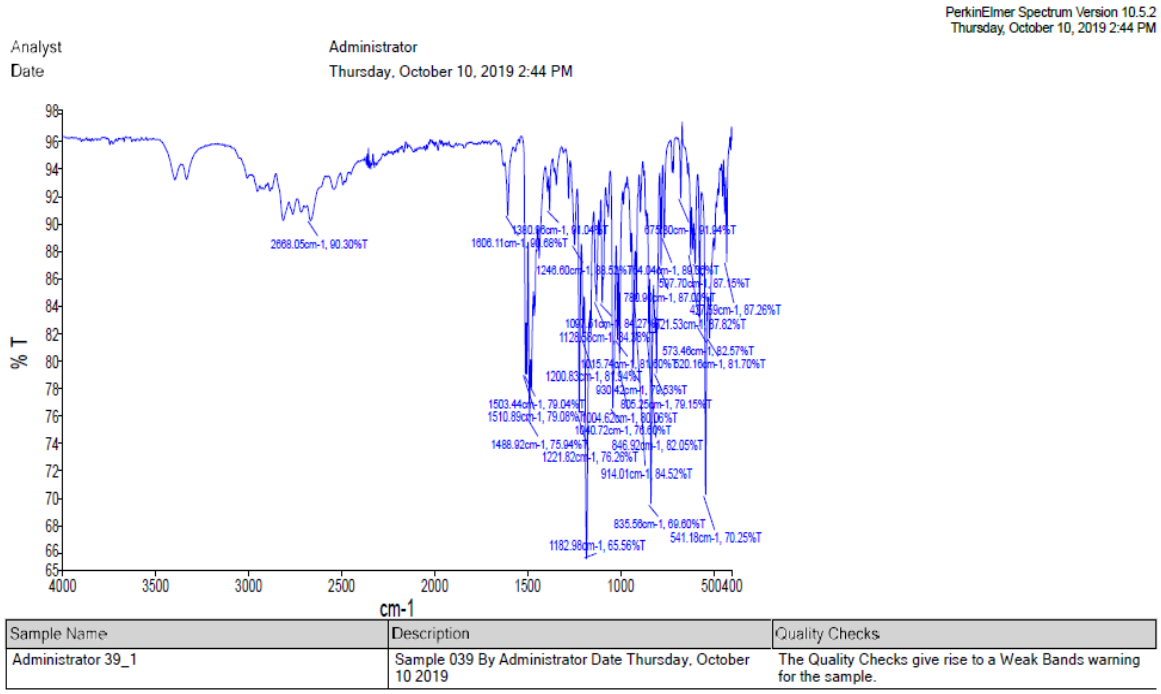
Partition coefficient of Drug	Solvent System	Log P Value
Paroxetine	Water:n-octanol	0.97296

Table 8: Partition coefficient determination of Paroxetine

Value is expressed as mean ± SD; n = 3

Discussion: The partition coefficient of Paroxetine in n- Octanol: Water was found to be 0.97296.

3.1.6. FTIR Interpretation of Paroxetine.



Sample Name	Description	Quality Checks
Administrator 39_1	Sample 039 By Administrator Date Thursday, October 10 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

Figure 4: FTIR Interpretation of Paroxetine

S.No.	Functional Group	Reported (cm^{-1})	Observed (cm^{-1})
1.	Aromatic (CKC) stretch	1606	1606.11
2.	Aromatic (CKC) stretch	1512	1510.89
3.	Ether (CJOJC) asymmetric stretch,	1222	1221.82
4.	fluoro aromatic (CJF) stretch	1185	1182.98
5.	Ether (CJOJC) symmetric stretch	1041	1097.61
6.	Acetal (CJOJC)	930	930.42
7.	Aromatic (CJH) out of plane bend	836	835.56

Table 9: FTIR Interpretation of Paroxetine.

The FTIR spectra of Paroxetine were shown in the **Figure 6** and **table 9.** These are all observed principal peaks. This observation of Paroxetine confirmed the purity and integrity below in IR spectra.

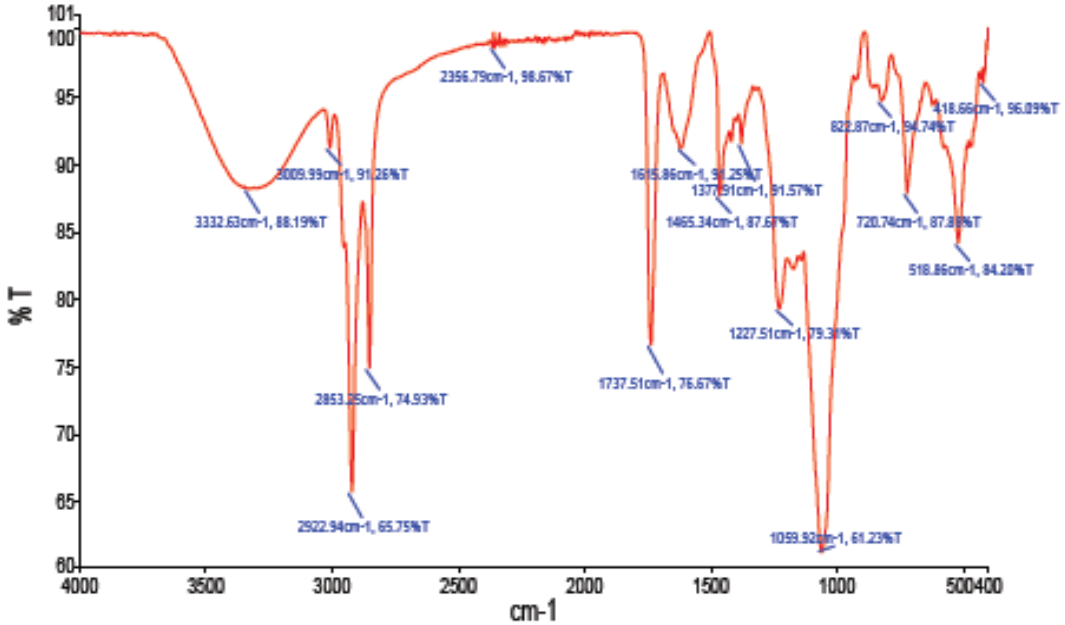


Figure 5: FTIR spectrum of Soya lecithin

Table 10: FTIR interpretation of Soya lecithin

Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
C–H stretching band of long fatty acid chain	3421.92	3332.63
Carbonyl stretching band in the fatty acid ester	2923.84	2922.94 and 2853.25
C=O stretch α,β–unsaturated aldehydes, ketones	1745.09	1737.51
P=O stretching band	1459.17	1465.34
P–O–C stretching band	1098.87	1059.92
N+(CH3)3 stretching	721.22	720.74

Table 11: FTIR interpretation of Soya lecithin

The FTIR spectra of soya lecithin were shown in the **Figure 7 and Table 11**. The IR absorption peaks of soya lecithin at 3332.63cm^{-1} (C–H stretching band of long fatty acid chain), 2922.94 and 2853.25cm^{-1} (Carbonyl stretching band in the fatty acid ester), 1737.51cm^{-1} (P=O stretching band), 1465.34cm^{-1} (P–O–C stretching band) and 1059.92cm^{-1} (N+(CH3)3 stretching) were all observed in the spectra of lecithin. All these observed principal peaks. This observation confirmed the purity and integrity of the lecithin.

3.1.7. FTIR of Pure drug and physical mixtures:

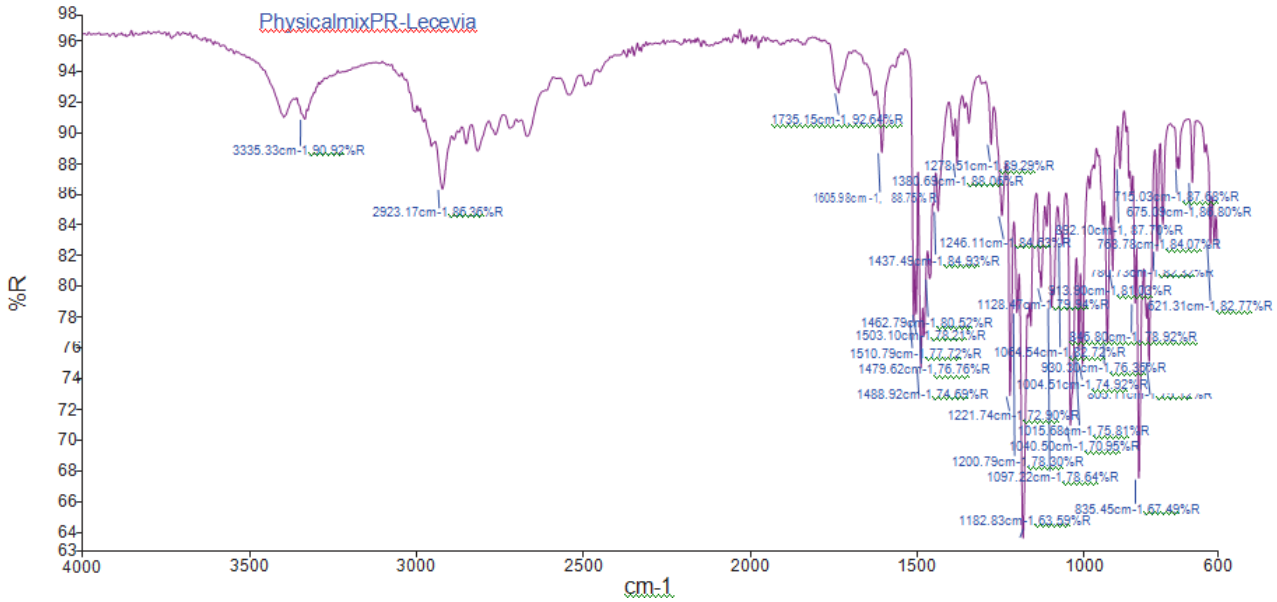


Figure 6: FTIR spectra of Paroxetine and Soya lecithin. Paroxetine

Functional group	Reported (cm^{-1})	Observed (cm^{-1})
Aromatic (CKC) stretch	1606.11	1605.98
Aromatic (CKC) stretch	1510.89	1510.79
Ether (CJOJC) asymmetric stretch	1221.82	1246.11
fluoro aromatic (CJF) stretch	1182.98	1128.47
Ether (CJOJC) symmetric stretch	1097.61	1064.54
Acetal (CJOJC)	930.42	913.80
Aromatic (CJH) out of plane bend	835.56	846.80

Table 12 Soya Lecithin

Functional group	Reported (cm^{-1})	Observed (cm^{-1})
C–H stretching band of long fatty acid chain	3332.63	3335.33
Carbonyl stretching band in the fatty acid ester	2922.94 & 2853.25	2923
C=O stretch α,β–unsaturated aldehydes, ketones	1737.51	1735.15
P=O stretching band	1465.34	1462.79
P–O–C stretching band	1059.98	1064.54
N+(CH3)3 stretching	720.74	768.78

Table 12: FTIR interpretation of Paroxetine and Soya lecithin

FTIR studies of Pure drug and physical mixture is depicted above **(Figure 8 and Table 12)** were carried out to remove the possibility interaction between drug and excipients. All the spectrum peaks revealed that corresponding peaks of drugs are present in the above spectra along with excipients peaks. Hence no interactions were observed in this mixture.

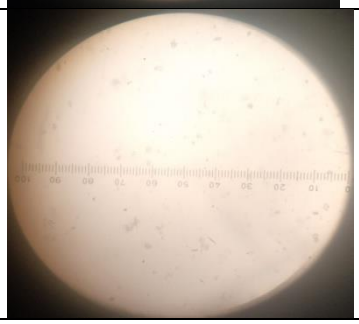
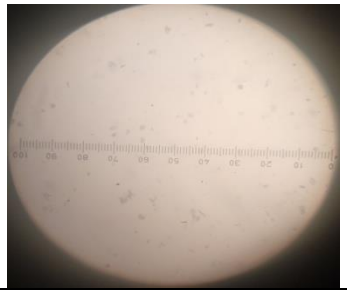
3.2 Preparation, optimization and characterization and evaluation of phytosomes

The various character of phytosomes in both physical and biological systems is determined by factors such as the physical size, membrane permeability, percentage of entrapped , and chemical Nature as well as the quantity and accuracy of the selected materials.Thus, phytosomes can be characterized by several mechanism and their physical properties i.e. shape, size, distribution, percentage drug captured, entrapped volume, percentage drug release and chemical composition, solubility etc.

3.3 Evaluation of Phytosomes

3.3.1 Photomicroscopic study

The photomicrograph of Paroxetine Phytosomes formulation manifested that particles present in uniform shape without any aggregation.

Formulation	Microscopic study
F1	
F2	
F3	

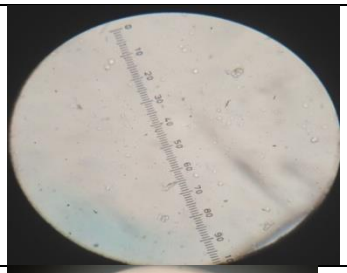
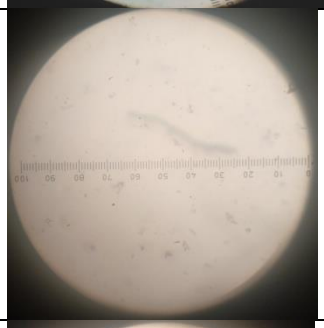
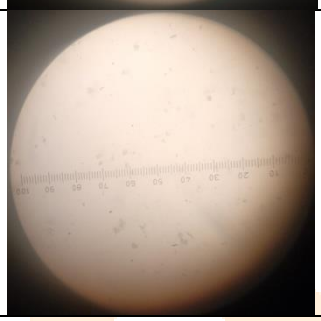
F4	
F5	
F6	

Table 13: The photomicrograph of Paroxetine loaded phytosomes

3.3.2 pH of phytosomes formulation

Formulation	**Ph range**
F1	3.90
F2	4.10
F3	4.41
F4	4.54
F5	4.33
F6	4.26

Table 14 : pH range of different phytosomes formulation.

3.3.3 Drug Entrapment efficiency

Formulation Code	Drug : soya lecithin (Molar ration)	%EE
F1	1:0.5	60.73%
F2	1:1	63.28%
F3	1:1.5	70.74%
F4	1:2	85.36%
F5	1:2.5	67.43%
F6	1:3	62.82%

Table 15: Different Ratio of drug and phospholipid for phytosomes formulation

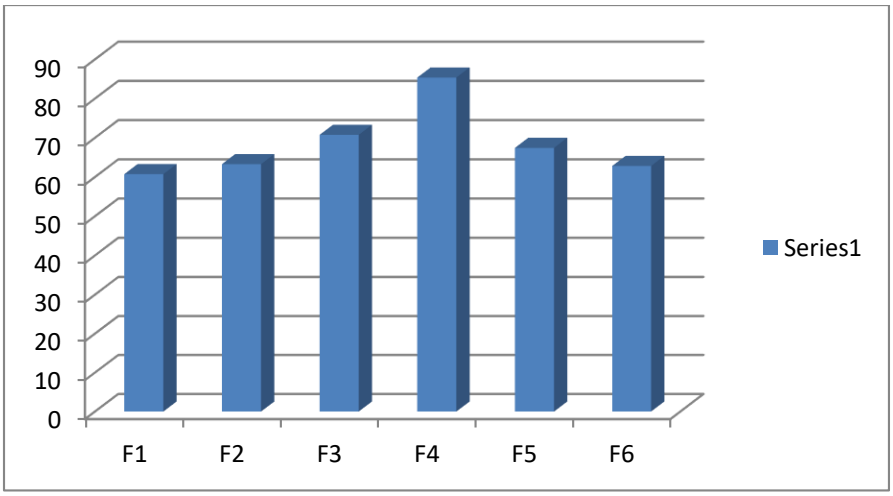


Figure 7: Percentage entrapment efficiency of phytosomes formulation

3.3.4 FT-IR spectroscopy of final formulation

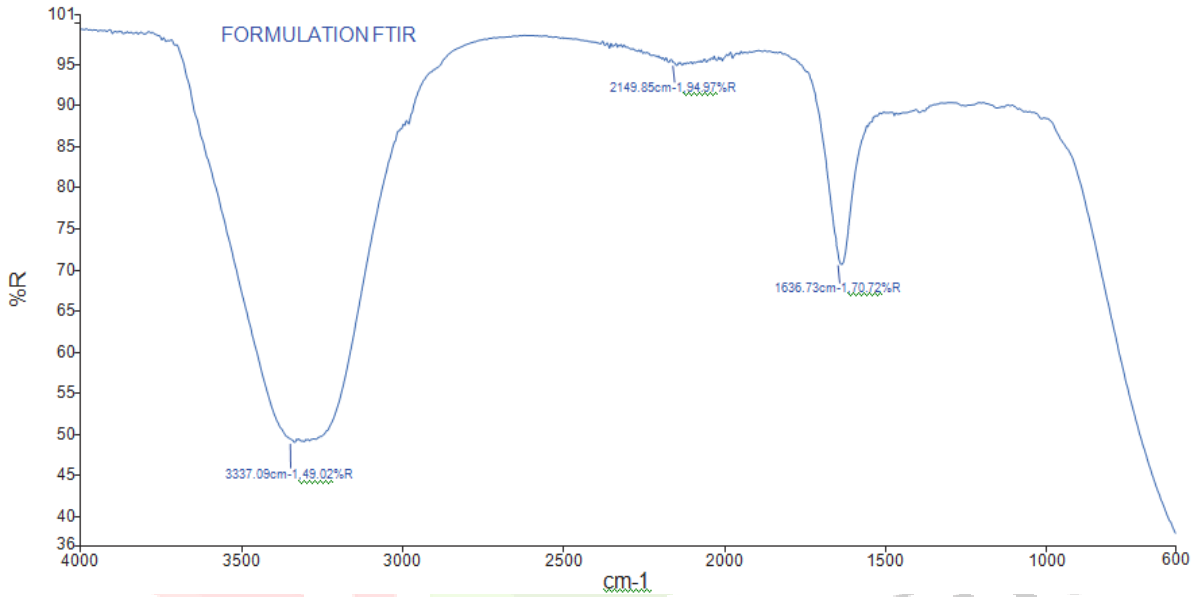


Figure 8: FT-IR spectroscopy of final formulation

Discussion: The FT-IR spectra of final formulation (F4) represent that characteristic peak of Paroxetin was not apperead in the phytosome spectra that which indicates that drug was completely encapsulate in the phytosome.

3.3.5 Transmission electron microscopy.

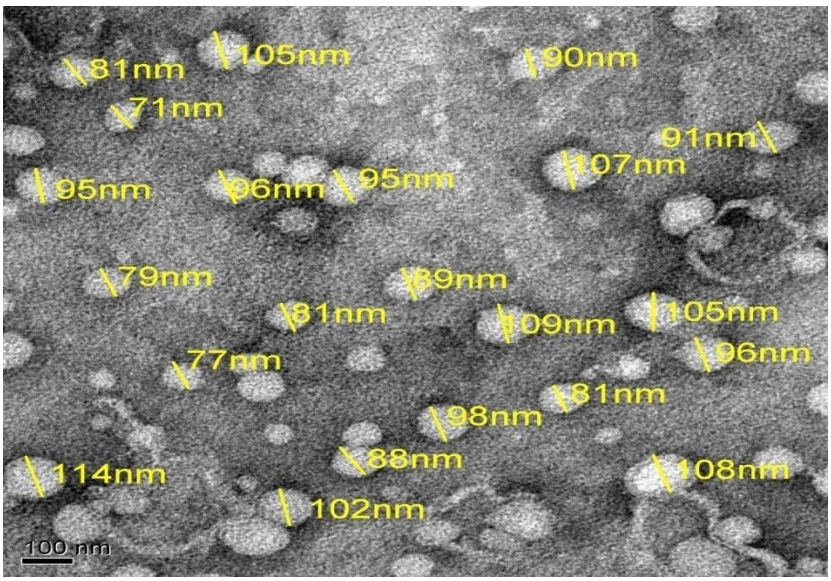


Figure 9: Transmission electron microscopy

3.4 In-vitro drug release study

Time (Hr)	Drug Release of Pure drug(%)	Drug Release of Formulation (F4) (%)
0	0	0
0.25	4.17623	6.17692
0.5	9.023077	13.63846
1	16.63846	21.40769
2	27.25385	32.79231
3	33.48462	40.25385
4	38.48462	47.40769
6	42.79231	64.71538
8	45.63846	71.71538
10	47.02308	79.40769
12	48.17692	84.07692
24	64.71538	91.76923

Table 16: In vitro drug release study

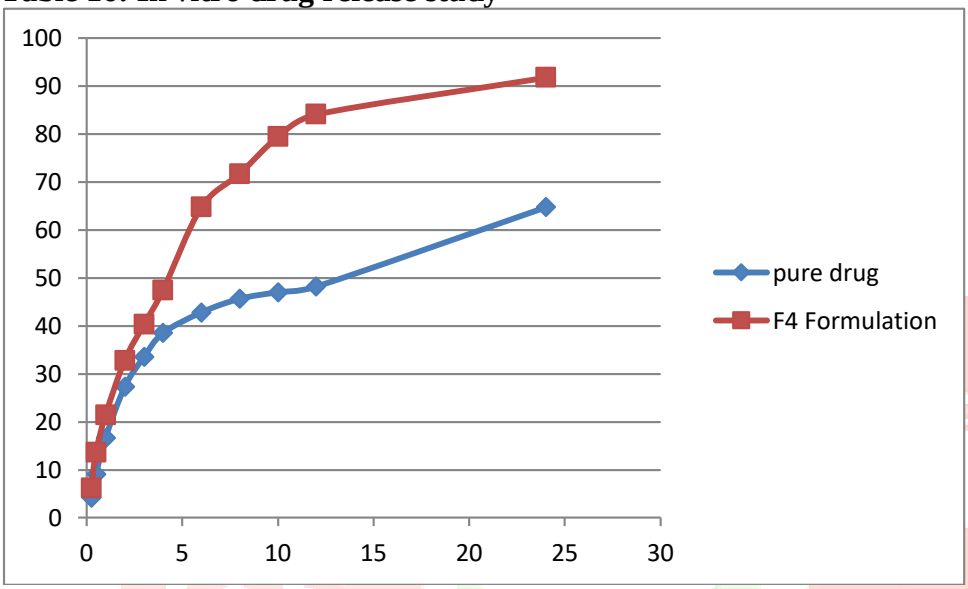


Figure 10: In-vitro drug release study

3.5 In-vitro drug release kinetic

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

3.5.1 Zero order kinetics

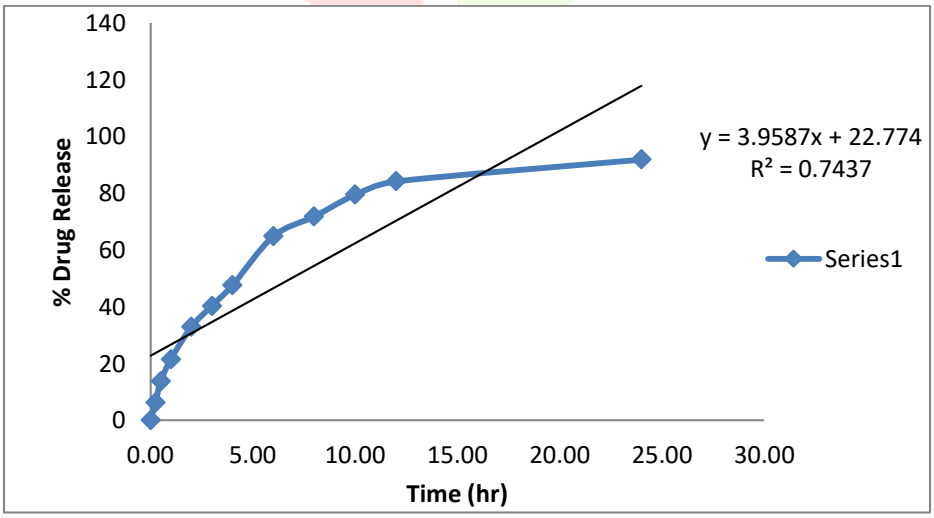


Figure 11: Zero order graph of formulation F4

3.5.2 First Order kinetics

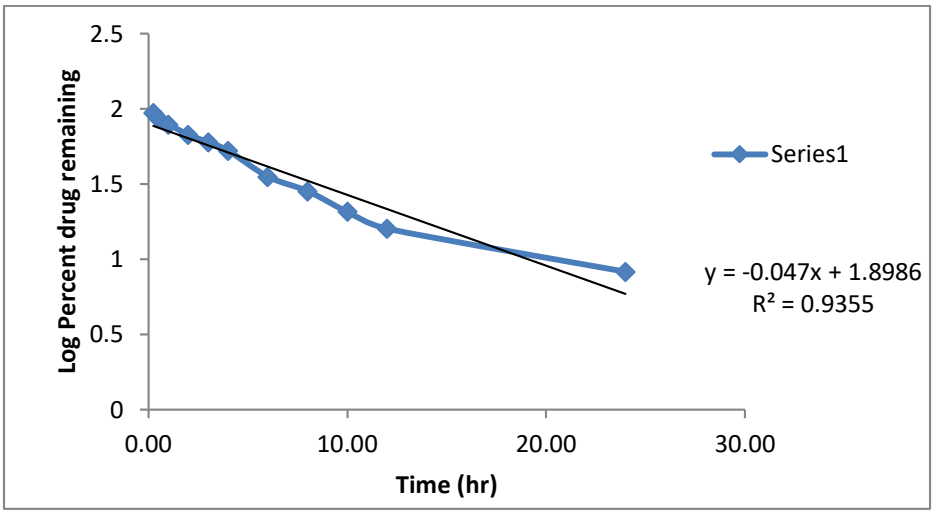


Figure 12: First order graph of formulation F4

3.5.3 Higuchi model

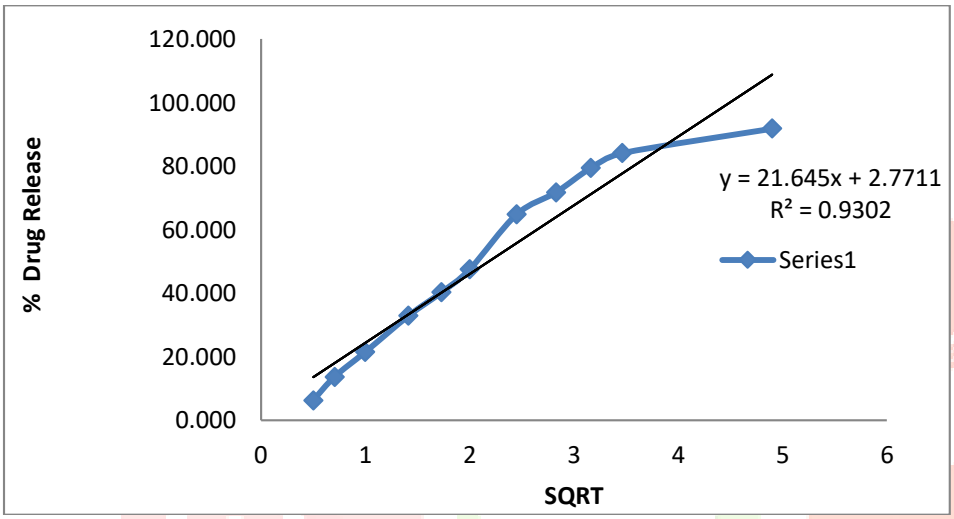


Figure 13: Higuchi order graph of formulation F4

3.5.4 Peppas Korsmeyer model

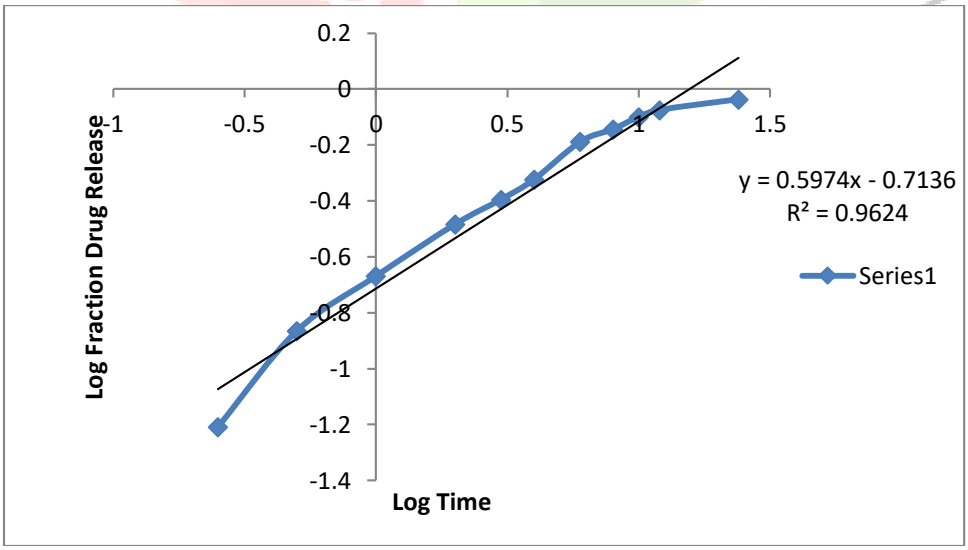


Figure 14: Korsmeyer peppas order graph of formulation F4

Formulation Name	Zero order		First order		Higuchi		Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
	0.7437	3.9587	0.9355	0.047	0.9302	21.645	0.9624	0.5974

Table 17: Kinetic equation parameter of F4 Formulation

Mathematical models of kinetic release are commonly used to predict the release process of the prepare formulation and compare the release profile. For the optimized formulation, the % drug release vs time (zero order), log percent drug remaining vs time (first order), log per cent drug release vs square root of time (Higuchi plot), and log of log % drug release vs. log time (Korsmeyer and Peppas Exponential Equation) were plotted. In each case, R^2 value was calculated from the graph and reported in **Table 17** and **Figure 14**. Considering the determination coefficients, Korsmeyer peppas order was found (R^2=0.9624) to fit the release data best. Hence, that the drug was released from Paroxetine phytosome by a controlled mechanism.

CONCLUSIONS

Phytosomes play an important role in novel drug delivery system and can be prepared by numerous methods. By utilising various medicinal aspects of herbal drugs, they can be formulated into phytosomes for a better drug delivery at predetermined rate in a controlled manner. The effective use of phytosomes has proved very efficient and useful for formulations as well as in therapies. These have provided many advantages over other drug delivery systems since the time being used. Many marketed formulations of different herbal drugs as phytosomes shows the diverse benefit of physomes in the field of pharmacy. There are still many fields in which phytosomes can be further utilised. With all advantages phytosomes have proven to be relevant in modern day drug targeting methods.

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