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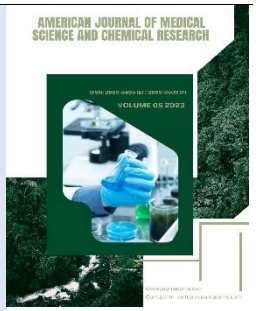

FORMULATION AND EVALUATION OF PHYTOSOMAL GEL OF *MORINDA CITRIFOLIA* EXTRACT FOR ENHANCED TOPICAL DELIVERY

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ABSTRACT

The study aimed to enhance the solubility, bioavailability, and skin permeation of *Morinda citrifolia* extract by formulating it into phytosomes using the antisolvent precipitation technique and incorporating these into topical gels. The plant extract was initially prepared via Soxhlet extraction using ethanol, followed by rotary evaporation. Phytosomes were formed at varying molar ratios of drug to phospholipid (1:1 to 1:7) and characterized by optical microscopy, entrapment efficiency, drug content, solubility, and in-vitro drug diffusion studies. Among all formulations, F1 (1:1 ratio) exhibited optimal characteristics, including the highest drug entrapment efficiency (89.87%), drug content (88.43%), and cumulative drug release (91.23% in 10 hours). This optimized phytosomal complex was then incorporated into Carbopol 934-based gels, evaluated for pH, homogeneity, viscosity, spreadability, extrudability, and in-vitro release. The F1 gel formulation showed excellent drug content (90.29%), spreadability (4.1 cm), and cumulative drug release (89.35% in 12 hours), with sustained release following Higuchi kinetics and a non-Fickian diffusion mechanism. Stability studies confirmed the formulation's physical and chemical stability over 45 days. Overall, the phytosomal gel of Morinda citrifolia demonstrates promising potential for enhanced dermal drug delivery.

KEYWORD: *Spread ability, F1 Formulation, Morinda Citrifolia, Phytosomes, Drug.*

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1. INTRODUCTION

Herbal medicines have been widely used for centuries due to their natural origin, therapeutic benefits, and relatively low side effects. However, despite their potential, many herbal drugs face challenges such as poor solubility, low bioavailability, instability, and limited absorption, especially when administered orally or topically **(Yadav et al., 2014).** These limitations often result from the hydrophilic nature and large molecular size of active phytoconstituents like flavonoids and glycosides, which cannot easily cross lipid-rich biological membranes.To overcome these issues, Novel Herbal Drug Delivery Systems (NHDDs) have emerged as a promising strategy. These systems utilize advanced pharmaceutical technologies to deliver herbal drugs more effectively by enhancing their solubility, stability, and targeted delivery. NHDDs aim to release the drug at a controlled rate, at the desired site of action, and for an optimal duration, thereby increasing therapeutic efficacy while minimizing side effects. Formulations such as liposomes, phytosomes, nanoparticles, microspheres, and transdermal patches are being explored for their ability to improve herbal drug delivery **(Bhokare et al., 2016).**

Among these, phytosome technology has gained significant attention. Phytosomes are complexes formed by binding water-soluble phytoconstituents with phospholipids, enhancing their lipid compatibility and enabling better absorption across biological membranes. This method improves the pharmacokinetic profile and bioavailability of herbal extracts without compromising safety **(Anju et al., 2012).**

Morinda citrifolia (Noni) is a medicinal plant traditionally used for its antioxidant, anti-inflammatory, and immune-boosting properties. However, like many herbal extracts, its therapeutic efficacy is limited by poor absorption. By formulating *Morinda citrifolia* extract into a phytosome delivery system, it is possible to enhance its drug loading capacity, improve release profiles, and ultimately increase its clinical effectiveness. This study focuses on the development and evaluation of phytosomes of *Morinda citrifolia* to overcome conventional formulation challenges and maximize its medicinal benefits **(Ravi et al., 2015**

2. MATERIALS AND METHODS

2.1 Preparation of plant extract (Keerthi et al., 2014)

The leaves of plant was air-dried until dryness at room temperature and under shade. The dried leaves was then powdered to a fine grade by using laboratory scale mill. Further it was sequentially extracted successively with ethanol using soxhlet apparatus. The solvent was removed and concentrated in a rotary evaporator and water bath. The dried extracts were stored in refrigerator for further studies.

2.2 Formulation of phytosomes of *morinda citrifolia* extract by antisolvent precipitation technique

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(Singh et al., 2015)

To prepare the phytosomes of *Morinda citrifolia* extract , drug extract and soya lecithin at molar ratio of 1:1, 1:2 ,1:3 , 1:4 , 1:5 , 1:6 and 1:7 were taken in the flask of vacuum rotary evaporator. Dichloromethane were added in the flask. The mixture was shaken at a temperature not exceeding 40˚C for 2 hours. The resultant solution was evaporated by increasing temperature up to 60˚C and by using vacuum pump in vacuum rotary evaporator. Ethanol was added to the flask with continuous stirring. The phytosomes was precipitated and ethanol was evaporated under vacuum to remove the traces of solvent. The dried residues were gathered and placed desiccators over night, than crushed in the mortar and sieved through 80 mesh then subjected to further characterization **(Manisha Yadav et al., 2014)**

2.3 Evaluation of phytosomal complex

1 . Microscopic view (Keerthi et al., 2014)

Optical microscopy was used for characterization of the complex. Microscopic view of the complex was observed at a magnification of 45X.

2. Percentage Practical Yield (Thani et al., 2010).

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production.

3. Entrapment efficiency (Thani et al., 2010).

To separate the phytosomes from the unentrapped medication, 100 mg of *Morandacitrifoli*a phytosomal complex were centrifuged at 2000 rpm for 30 minutes using a Remi centrifuge. By utilizing a UV-visible spectrophotometer to measure absorbance at 279 nm, the concentration of the free medicine as the supernatant was ascertained. The following formula was used to determine the percentage of drug entrapment:

$$\text{Entrapment efficiency (\%)} = \frac{(\text{Total amount of drug}) - (\text{amount of free drug})}{(\text{Total amount of drug})} \times 100 \quad \textbf{(2)}$$

3. Drug content (Rajashekar et al., 2015)

Phytosomes of 10 mg of drug were weighed, dissolved in ethanol, sonicated, adjusted volume, filtered, and spectrophotometrically determined using a UV spectrophotometer after appropriate dilutions

4. Solubility Determination (Rajashekar et al., 2015)

The solubility of drug extract and phytosomal complex was determined by adding excess drug and

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phytosomes to distilled water, phosphate buffer, and n-octanolin vials, shaking, centrifuging, filtering, and analyzing spectrophotometrically at 279 nm.

5. In-vitro Drug Diffusion study through Egg Membrane (Matias et al., 2015)

The study prepared an egg membrane for drug diffusion using a Franz Diffusion Cell, washed with pH 7.4 phosphate buffer, and placed phytosomes on the membrane for analysis.

6. Ex-vivo Skin Permeation Study (Matias et al., 2015) (optimized batch)

The permeation of Morinda citrifolia extract from phytosomal complex was studied using an in-vitro Franz Diffusion Cell and samples were withdrawn and analyzed spectrophotometrically at 279nm.

7. Scanning Electron Microcopy (SEM) Analysis (Matias et al., 2015)

SEM of phytosome complex was performed using ScanningElectronMicroscopeJSM6390 at STIC, Cochin University, Ernakulam, observing surface morphology using secondary electron detector attached to the microscope.

2.4 Formulation of gels of phytosome complex (Sangeeta et al., 2012).

Gel formulations were prepared by dispersing Carbopol 934 in distilled water with continuous mechanical stirring. The pH was adjusted to 5.5–6.5 using triethanolamine. A phytosomal complex solution, prepared in 0.1 ml ethanol, was incorporated into the gel base. Various formulations were developed using different concentrations of the gelling agent, and the resulting gels were stored in appropriate containers at room temperature for further evaluation.

Table 1: Formulation of Gels of Phytosome Complex

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Carbopol 934	1%	1.5%	2%	2.5%	3%	3.5%
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s
Propyl paraben	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Ethanol	1%	1%	1%	1%	1%	1%
Distilled Water	q.s	q.s	q.s	q.s	q.s	q.s

2.5 EVALUATION OF GELS OF PHYTOSOMECOMPLEX

1. Homogeneity (Thani et al., 2010).

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container.

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2. Measurement of pH (Pingali et al., 2015)

The pH of phytosome gels was measured using a digital pH meter after dissolving 0.5g in distilled water and storing it for two hours.

3. Drug content (Allam et al., 2015).

The gel was mixed with 100ml of solvent, aliquots of varying concentrations were prepared, and absorbance was measured at 279 nm after filtering the stock solution.

4. Rheological study (Pingali et al., 2015)

The measurements of viscosity of prepared gels were carried out with Brookfield Viscometer (spindle type S–96). The readings of each formulation were taken.

5. Spreadability (Pingali et al., 2015)

On a glass plate of 10×5cm, 350mg emulgel was taken and another plate of same sized was dropped from a distance of5cm. After 1 minute the diameter ofthe circle spread was measured.

6. Extrudability

The study assessed extrudability by measuring the weight needed to extrude a 0.5cm gel from a lacquered aluminum tube in 10 seconds, and calculated using an equation.

$$\text{Extrudability} = \frac{\text{Applied weight to extrude gel from tube (in gram)}}{\text{Area}(\text{incm}^2)} \quad \textbf{……3)}$$

7. *In-vitro* drug release study (Allam et al., 2015).

In-vitro rug release studies were conducted using a modified Franz diffusion cell, with a formulation applied on an egg membrane. Phosphate buffer was used as diffusion media, and samples were analyzed spectrophotometrically at 279 nm to calculate cumulative drug release. The cell was maintained at 37˚C.

2.5 Drug Release Kinetics

To know the release kinetics, the data obtained from the in-vitro release profile was fitted into various models like :

a. Zero order kinetics.

$$\mathbf{Qt=Q0+K0t} \quad \textbf{…(4)}$$

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b. First order kinetics

It describes the drug release from the systems in which the release rate is concentration dependent.

$$\text{Log } Qt = \log Q0 + kt/2.303 \quad \text{.....(5)}$$

c. Higuchi model

According to this model, the fraction of drug from the system is proportional to the square root of time.

$$Mt/M\alpha = kHt^{1/2} \quad \text{…(6)}$$

d. Korsmeyer–Peppas model(powerlaw)

The power law describes the drug release from the polymeric system in which the release deviates from Fickian diffusion. It is expressed using the following equations :

$$Mt/M\alpha = kt^n \quad \text{…(7)}$$

$$\text{Log } [Mt/M\alpha] = \log k + n \log t \quad (8)$$

Table 2: Release Mechanisms

'n'value	**Drug Release**
<0.5	Fickian
0.5<n<1	Non–Fickian
>1	Case2transport

2.6 STABILITY STUDIES

Stability of a drug in a dosage formulation was studied under different environmental conditions, determining its expiry date. Samples were analyzed for physical characteristics, drug content, and cumulative release **(Allam et al., 2015)**

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3.RESULTS AND DISCUSSION

3.1 Calibration Curve of *Morinda citrifolia* Extract

The λ of *Morinda citrifolia* Extract was determined by scanning the prepared solution in the max wavelength range of 200-400 nm. The maximum wavelength was found to be 279nm. The calibration curve of *Morinda citrifolia* extract was constructed by dissolving the drug in pH 7.4 phosphate buffer. The linearity of the curve was found in the concentration range of 2-10µg/ml. A regression coefficient (R2) value of 0.9989 was obtained.

Table 3: Calibration curve data of *Morinda citrifolia* extract

Concentration(µg/ml)	Absorbance
2	0.172
4	0.314
6	0.491
8	0.657
10	0.793

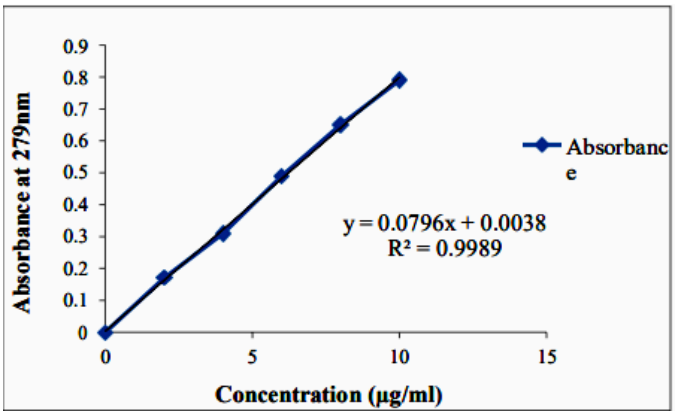

Figure 1: calibration curve of *Morinda citrifolia* extract

3.2 Evaluation of phytosomal complex

1. Optical Microscopy

Optical microscopy was performed by viewing the formulations under microscope. It was observed that the preparations showed vesicle formation. The vesicles formed were found to be of uniform size and shape.

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2. Percentage Practical Yield

Table 4: Results of Percentage Practical Yield

Formulation	Percentage Practical Yield
F1	91.34
F2	88.51
F3	86.87
F4	86.04
F5	85.42
F6	83.87
F7	81.09

% Practical Yield of different formulations was shown in table No:2. F1 have higher % Practical yield of 91.34% than other formulations.

3. Entrapment Efficiency

Table 5: Results of Entrapment Efficiency

Formulation	Percentage Entrapment Efficiency
F1	89.87
F2	86.94
F3	84.71
F4	79.09
F5	75.08
F6	71.58
F7	67.47

Formulation F1 demonstrated the highest entrapment efficiency of 89.87%, indicating optimal lipid concentration for phytosome formation, but increased lipid concentration decreased efficiency.

4. Drug Content

Table 6: Results of Drug Content

Formulation	Drug Content(%W/W)

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F1	88.43
F2	86.84
F3	86.22
F4	84.19
F5	83.49
F6	80.76
F7	78.08

The drug content of *Morinda citrifolia* extract in the complexes was found to be in the range of 88.43% - 78.08% indicating the presence of an acceptable amount of drug in the formulations. The percentage of drug loading decreased with an increase in the concentration of lipid. The formulation F_1 showed the maximum drug content of 88.43%.

5. Solubility Determination

Table 7: Solubility profile in different media

Formulation	Solubilityin Water (mg/ml)	Solubility in pH7.4Phosphate Buffer (mg/ml)	Solubilityin n-Octanol (mg/ml)
Drug Extract	0.143	0.197	0.231
F1	0.789	5.273	5.976
F2	0.781	5.151	5.640
F3	0.652	4.837	5.284
F4	0.694	3.950	4.569
F5	0.528	3.752	4.191
F6	0.573	3.864	4.237
F7	0.617	4.356	4.587

6. *In-vitro* Drug Diffusion Study of Phytosomes

Table 8: Results of *In-vitro* Drug Diffusion Study

Time in hrs	Pure drug extract	F1	F2	F3	F4	F5	F6	F7
0.25	2.51	4.6	3.61	3.22	2.85	3.26	3.95	3.07
0.5	8.66	11.58	10.37	9.88	8.64	9.54	7.85	7.33

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1	12.33	21.29	20.07	18.96	15.37	16.73	14.26	13.42
2	15.06	33.16	27.68	25.65	23.03	23.46	20.11	16.66
3	20.49	40.64	38.42	36.19	29.31	31.51	26.33	25.13
4	27.86	51.36	44.74	42.34	37.77	39.22	35.21	31.05
5	31.15	58.61	50.32	49.25	42.08	45.58	40.29	39.11
6	36.4	65.77	57.35	53.64	48.2	50.96	48.07	45.28
7	39.22	75.31	66.32	62.31	57.54	55.18	52.14	51.11
8	46.78	84.33	74.62	69.23	62.03	64.41	60.17	58.19
9	50.22	89.17	82.79	77.01	68.56	72.33	65.23	61.13
10	54.16	91.23	86.34	81.26	72.48	76.23	70.03	65.31

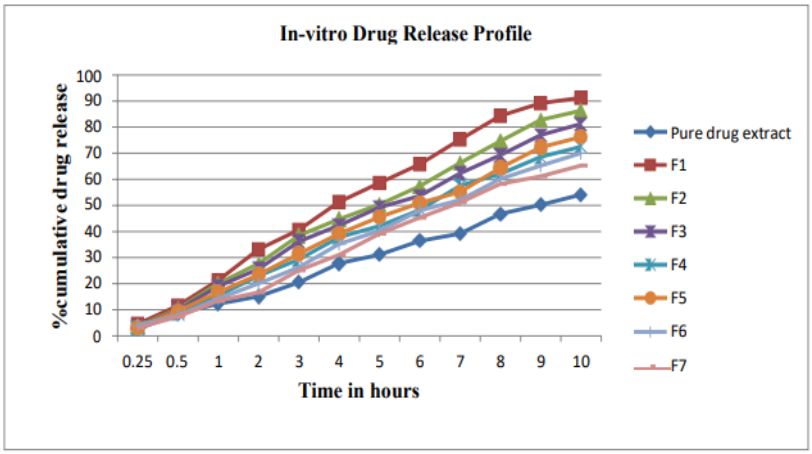

Figure 2: In-vitro Drug Diffusion Profile

The phytosomes of *Morinda citrifolia* demonstrated better diffusion profiles than pure drug extract, with formulations ranging from 65.31 to 91.23% cumulative drug release, with phospholipids improving solubility and diffusion profile

7. *Ex-vivo* Skin Permeation Study

Table 9: Results of *Ex-vivo* Skin Permeation Study

Time in hours	Cumulative % permeation
0.25	5.36
0.5	13.08
1	21.76
2	27.43
3	34.22
4	40.24
5	46.03

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6	51.07
7	59.35
8	66.1
9	73.46
10	83.51
11	90.23
12	92.57

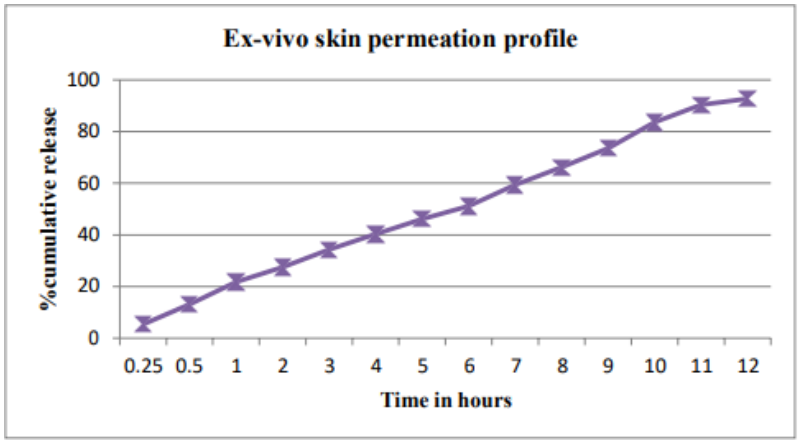

Figure 3: Drug Permeation Profile of F1

The drug permeation of the formulation F1 through the abdominal skin of chicken was carried using Franz diffusion cell and the results are reported in table no:12.The permeation profile was plotted between% cumulative drug permeated v/s time. It was observed that the formulation showed an optimum release of92.57% over a period of12 hours.

8. Scanning Electron Microcopy (SEM) Analysis

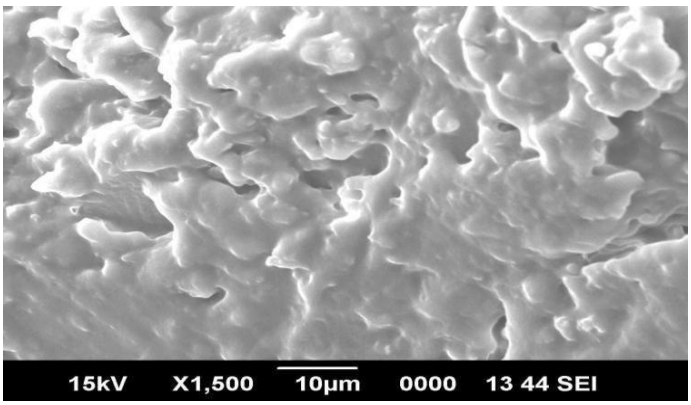

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Figure 4: SEM image of *Morinda citrifolia* Phytosome (F1)

The surface morphology of the formulated phytosome (optimized formulation)were confirmed by scanning electron microscopy. The vesicles are spherical in shape and smooth in nature.

3.3 EVALUATION OF GELS OF PHYTOSOME COMPLEX

1. Homogeneity

Table 10: Results of Homogeneity of Different Gel Formulations

Formulation	Homogeneity
F1	Good
F2	Good
F3	Good
F4	Good
F5	Good
F6	Good

The visual inspection of all the prepared gel formulations were carried out and it was concluded that all the gel formulations showed good appearance and homogeneity.

2. Measurement of pH

Table 11: Results of pH of different gel formulations

Formulation	pH
F1	5.4
F2	5.2
F3	5.3
F4	5.7
F5	5.1
F6	5.6

The pH of the gel formulations was in the range of5.4 to5.7, which lies in the normal pH range of the skin and would not produce any skin irritation.

3. Drug Content

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Table 12: Results of Drug Content of different gel Formulation

Formulation	Drug Content(%)
F1	90.29
F2	89.17
F3	87.79
F4	87.42
F5	85.21
F6	82.37

The drug content of the formulated gels was estimated spectrophotometrically at 279nm. The drug content ofall the formulation was found to be in the range of82.37 % to 90.29% in which the best formulation F1 contained 90.29% of the drug.

4. Rheological study

Table 11: Results of Viscosity of Different Gel Formulations

Formulation	Viscosity(Centipoise)
F1	9564
F2	10672
F3	11296
F4	12420
F5	12717
F6	13619

The gel was rotated at 50 rpm for 10 minutes with spindle 64. The corresponding reading was noted. The viscosity of the formulations increases as concentration of polymer increases. The viscosity of the best formulation was found to be 9564 centipoise

5. Spreadability

Table 12: Results of Spredability of Different Gel Formulations

Formulation	Spreadability(cm)
F1	4.1
F2	3.8

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F3	3.3
F4	3.6
F5	3.5
F6	2.9

The spreadability of the gel formulations was tested, with the best formulation having a spreadability coefficient of 4.1cm, indicating easy spreadability with minimal shear.

6. Extrudability

Table 13: Results of Extrudability of Different Gel Formulations

Formulation	Extrudability(gm/cm^2)
F1	9.3
F2	11.2
F3	13.1
F4	13.7
F5	14.3
F6	14.7

The gel formulation's extrudability is influenced by the concentration of gelling agents, with the best formulation F1 having the highest extrudability of 9.3 gm/cm2.

7. *In-vitro* drug release study

The in-vitro permeation studies used Franz diffusion cell with egg membrane for formulations. Comparative data showed cumulative drug permeation and cumulative drug release ranged from 66.32% to 89.95% after 12 hours.

Table 14: Results of *In-vitro* drug release study of Gel Formulations

Time in hours	F1	F2	F3	F4	F5	F6
0.5	10.36	9.11	8.47	7.23	5.92	5.92
1.5	12.63	11.06	10.34	9.24	8.03	7.34

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1	18.07	15.07	13.36	11.65	10.56	9.18
2	24.1	20.15	17.54	14.87	13.76	10.94
3	30.17	24.65	20.54	18.65	17.45	14.23
4	35.17	27.67	22.45	20.87	20.12	17.65
5	38.14	30.65	27.34	26.56	25.43	23.01
6	43.58	35.65	33.44	30.67	29.54	26.25
7	52.07	39.78	36.55	35.42	34.76	31.11
8	59.34	48.19	44.13	40.63	38.95	35.78
9	67.46	58.74	52.85	48.63	45.65	40.67
10	74.02	66.13	59.65	57.57	53.23	49.63
11	84.27	74.16	68.13	65.13	61.76	60.54
12	89.35	80.56	73.48	69.03	68.49	66.32

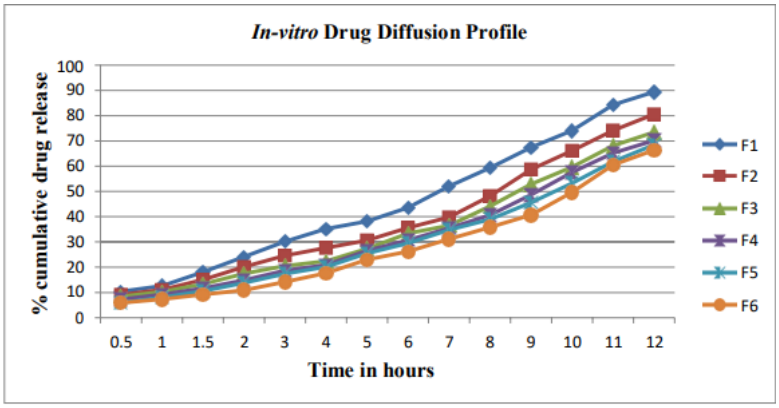

Figure 5: *In-vitro* Drug Diffusion Profile of Gel Formulation

8. Drug Release Kinetics

The study analyzed in-vitro drug release data to determine the best formulation F1 for release kinetic studies. The cumulative drug release was fitted into various models, with the model selected based on regression coefficient values.

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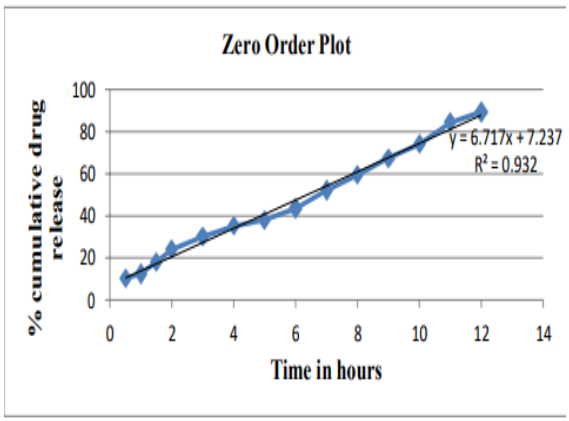

Figure 6: Zero Order Plot

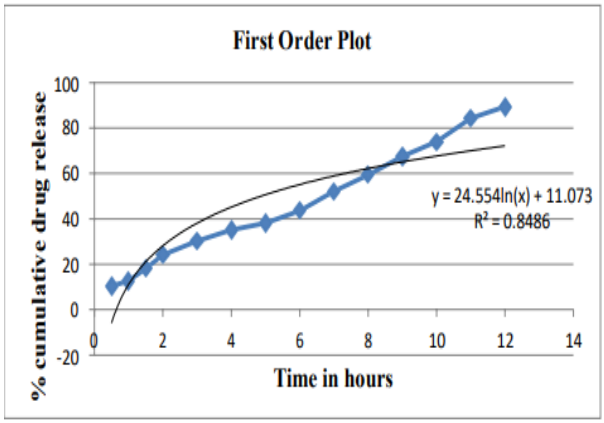

Figure 7: Zero Order Plot

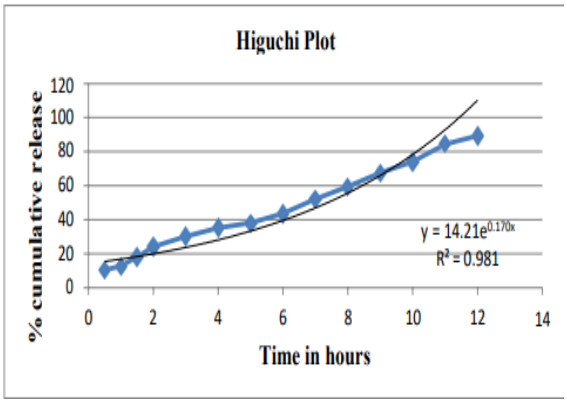

Figure 8: Higuchi Plot

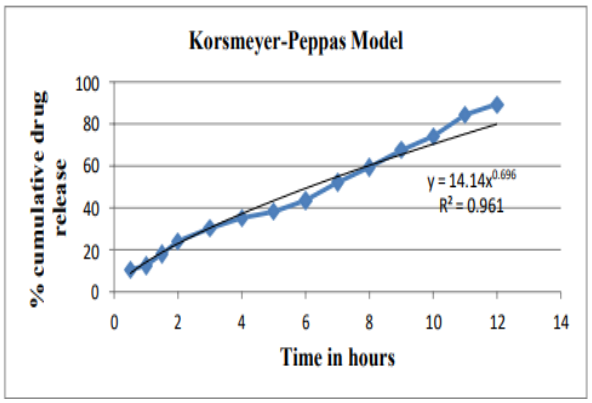

Figure 9: Korsmeyer-Peppas Plot

Table 15: Results of kinetic analysis

Formulation	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	
	R^2	R^2	R^2	n	R^2
F_1	0.932	0.848	0.981	0.696	0.961

The formulation follows the Higuchi model kinetics, with a slope value of 0.696 from the Peppas plot, indicating a Non-Fickian diffusion mechanism of drug release.

9. Stability Studies

Table 16: Stability Studies For F1 Formulation

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Sl. No	Parameters	Initial	th 30 Day	th 45 Day
1	Homogeneity	Good	Good	Good
2	Drug Content(%)	90.29	90.23	90.23
3	pH	5.4	5.4	5.4
4	Spreadability(cm)	4.1	4.1	4
5	2 Extrudability(gm/cm)	9.3	9.3	9.3
6	Viscosity(cps)	9564	9561	9555
7	% cumulative release	89.35	89.30	88.83

4. CONCLUSION

The study successfully demonstrated that the phytosome formulation of *Morinda citrifolia* extract enhances its solubility, stability, and permeability. Among the various formulations, the 1:1 ratio of extract to soya lecithin (F1) showed the most favorable characteristics in terms of entrapment efficiency, drug content, solubility, and release profile. Incorporation into a Carbopol gel base further facilitated its topical application with desirable properties like good spreadability, pH compatibility, and sustained release. Overall, the phytosomal gel formulation of *Morinda citrifolia* holds promising potential as an effective and stable herbal delivery system for transdermal therapeutic applications.

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