Quest Journals
Journal of Research in Pharmaceutical Science
Volume 11 ~ Issue 5 (Sep.- Oct.2025) pp: 90-99
ISSN(Online): 2347-2995
www.questjournals.org

Research Paper

Formulation and evaluation of indomethacin loaded pharma cosomal gel for the management of rheumatoid arthritis

Reema Mujeeb[1*], Preetha Mathew[2], Nevlin Maria Sam[3], Elessy Abraham
[1*]*M Pharm Delegate, Nazareth College of Pharmacy, Othera, P.O Thiruvalla*
[2]*Assistant Professor, Nazareth College of Pharmacy, Othera, P.O Thiruvalla*
[3]*M pharm Delegate, Nazareth College of Pharmacy, Othera, P.O Thiruvalla*
*Corresponding Author**

ABSTRACT
The current study focuses on the development of a pharmacosomal gel containing indomethacin to enhance its therapeutic efficiency in a sustained-release manner. The formulation aims to improve the solubility and bioavailability of the drug while minimizing potential side effects. Preformulation studies and analytical validation confirmed drug-excipient compatibility using FTIR and DSC analyses. Pharmacosomes were prepared using the thin-film hydration method and optimized through a Central Composite Design (CCD), varying the concentrations of soya lecithin and the rotation speed of the evaporator. Among thirteen formulations, batch F9 was found to be optimal with a particle size of 188.4 nm and an entrapment efficiency of 97.8%. This optimized batch was incorporated into a 0.4% Carbopol 934-P gel and was subjected to various evaluations, including in vitro drug release, stability, and anti-inflammatory studies. The findings indicate that the gel provides prolonged drug release and may serve as an effective transdermal delivery system for managing rheumatoid arthritis.

Keywords: *Indomethacin, Pharmacosomal gel, Sustained release, Vesicular drug delivery, Rheumatoid arthritis.*

*Received 14 Sep., 2025; **R**evised 25 Sep., 2025; **A**ccepted 27 Sep., 2025 © The author(s) 2025.*
P**ublished with open access at **www.questjournas.org

I. INTRODUCTION

Vesicular systems that are used to improve drug stability, solubility, and delivery. A special kind of pharmacosome is formed by the covalent linkage of drugs with phospholipids which also aids in improving these factors. These supports increase bioavailability while controlling release as well enhancing therapeutic efficiency. Traditional semi solid dosage forms have aged gels, which provide better patient and user compliance than more traditional semi solids, this improved spreadability and enhanced stability is very helpful when it comes to aiding transdermal applications. Indomethacin is another NSAID that is orally used widely to manage pain and inflammation, it does have gastrointestinal side effects or serving too much so maintaining oral intake helps avoiding too much side effects. The idea behind pharmacosomal gels can deliver indomethacin through gels aims enhanced skin permeability combined with controlled release of the drugs promises bypassing some of these issues. This study focuses on formulating advanced technology for undifferentiated indomethacin gel loaded with pharmacosomes specifically looking at dealing with rheumatoid arthritis focusing on increasing targeted solubility relative to effect while reducing systemic side effect damage through acute transdermal dosing sustained over time translucent layers. [1-16]

II. METHODOLOGY

Preformulation Studies of Indomethacin:
For indomethacin, preformulation tests include color, appearance, odor, melting point by capillary method, and solubility in different solvents. Compatibility of the excipients with drug substance was confirmed using FTIR and DSC techniques.

The efficiency of entrapment was evaluated with centrifugation technique. Thin film hydrating phosphate buffer pH 7.4 has also been reported. After centrifugation lasting twenty minutes at seventy-five thousand RPM (75K RPMS), the supernatant underwent analysis to measure unentrapped drug quantitatively through UV spectroscopy at wavelength 316 nanometers (55,56). The remaining portion containing the pellet underwent extraction with methanol to assess total drug content determination of balance portion post-extraction quantification alongside supernatant volume termed as residue fraction calculation technique.

Formulation of Indomethacin Pharmacosomes:

It is prepared by solvent evaporation followed by thin film hydration methods. A solution containing drug (20mg) and soya lecithin was made in dichloromethane (12 ml). That mixture was put in a rotary evaporator set at 43 ± 2 °C for 25 min resulting in a thin film. This thin film was then hydrated with phosphate buffer pH 6.8 forming a vesicular suspension of pharmacosomes .[30,54]

Table: 1: Formulation Design of Indomethacin Pharmacosomes generated by the DoE software in Central Composite Design

		Factor 1	Factor 2
Std	**Run**	**A: lecithin (mg)**	**B: rotation (rpm)**
1	1	30	75
9	2	40	112
11	3	40	112
2	4	50	75
12	5	40	112
7	6	40	59
3	7	30	150
6	8	54.14	112
4	9	50	150
10	10	40	112
5	11	25.85	112
13	12	40	112
8	13	40	165

Evaluation of Pharmacosomes

Particle Size and Shape

The shape and size of pharmacosomes were evaluated using optical microscopy coupled with dynamic light scattering (DLS) methods

Entrapment Efficiency and Drug Content

The efficiency of entrapment was evaluated with centrifugation technique. Thin-film hydrating phosphate buffer pH 7.4 has also been reported. After centrifugation lasting twenty minutes at seventy-five thousand RPM (75K RPMS), the supernatant underwent analysis to measure unentrapped drug quantitatively through UV spectroscopy at wavelength 316 nanometers [55,56]. The remaining portion containing the pellet underwent extraction with methanol to assess total drug content determination of balance portion post-extraction quantification alongside supernatant volume termed as residue fraction calculation technique.[55,56]

- Drug Content (%) = (Amount of drug in residue / Total drug taken) × 100
- Entrapment Efficiency (%) = [(Total drug added – Drug in supernatant) / Total drug added] × 100

In-vitro Drug Release

In the release assessment, 5 ml of pharmacosomal suspension was placed in the donorcompartment of a diffusion tube equipped with an eggshell membrane. The membrane was submerged in 50 ml phosphate buffer (pH 7.4) at 37°C under magnetic stirring. At specific time points, 2 ml aliquots were taken and drug-free buffer equivalent to the removed volume was added. The concentration of drug was determined by UV spectrometry at 316 nm.

Solubility Enhancement

The solubility of indomethacin and its pharmacosomal complex was determined in distilled water as well as in phosphate buffer (pH 6.8). After 24 hours, samples were taken, filtered through 0.45 µ membranes, diluted appropriately and analysed via UV spectroscopy at 316nm.

Zeta Potential and PDI

Surface charge and PDI were assessed by DLS for Zeta potential. These are colloidal systems parameters that determine suspension system stability, e.g., pharmacosomes stability.

III. RESULT AND DISCUSSION

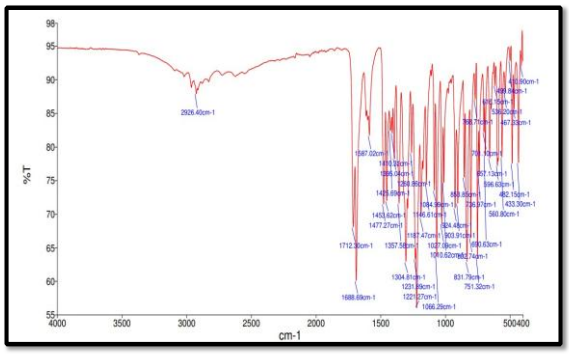


Fig No1: Spectrum of Indomethacin

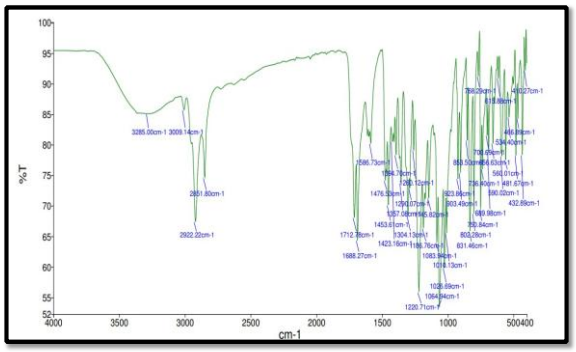


Fig No2: FTIR Spectrum of Indomethacin+Soyalecithin

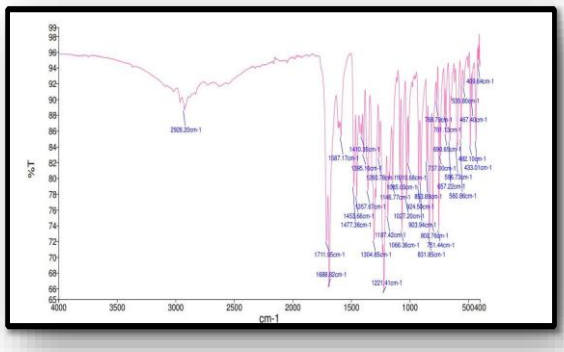
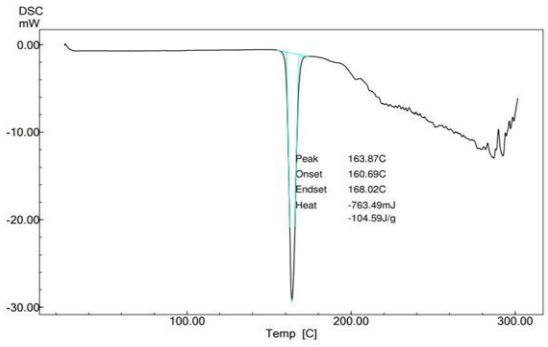


Fig No3: FTIR Spectrum of Indomethacin + Soya lecithin+ Carbopol 934-P+Methyl paraben+Propyl paraben

No significant shifts showing loss or gain of absorption peaks associated with the functional groups were observed, so the drug was determined to be compatible with the excipients.

DSC STUDIES



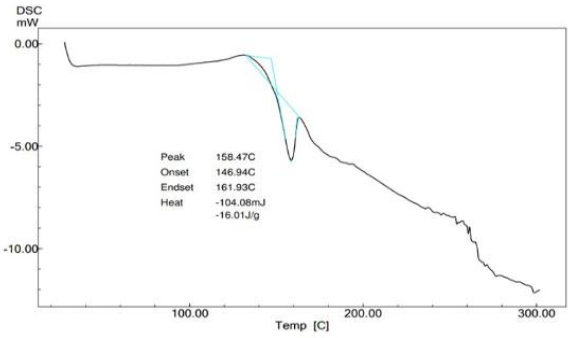


Fig No4: DSC Curve of Indomethacin Fig No5: DSC Curve of Indomethacin +Soya lecithin + Carbopol 934-P+Methyl paraben+Propyl paraben

DSC Studies were performed for the samples containing excipient and separately for drug alone. DSC Curve of indomethacin showed melting point of 163.87°C while one obtained from blend with excipients showed a curve with peak at 158.47°C. The converging values indicate that both components exhibit relatively close melting points hence are compatible.

Optimization ofindomethacin pharmacosomes by Central Composite Design (CCD)

Table.20: Composition & Characterization of Indomethacin Pharmacosomes using CCD

			Factor 1	Factor 2	Response 1	Response 2
Std	**Run**	**Formulation code**	**A: lecithin (mg)**	**B: rotation (rpm)**	**Size (nm)**	**EE (%)**
1	1	F1	30	75	1395.5	52.5
9	2	F2	40	112.5	251.2	67.12
11	3	F3	40	112.5	550	68
2	4	F4	50	75	2791.1	83.62
12	5	F5	40	112.5	628	62.8
7	6	F6	40	59.467	2791.1	71.4
3	7	F7	30	150	189	47
6	8	F8	54.1421	112.5	480	97.5
4	9	F9	50	150	188.4	97.8
10	10	F10	40	112.5	314	62.8
5	11	F11	25.8579	112.5	697.7	39.8
13	12	F12	40	112.5	251.2	64.2
8	13	F13	40	165.533	314	70.68

EVALUATION OF INDOMETHACIN PHARMACOSOMESS

Particle size

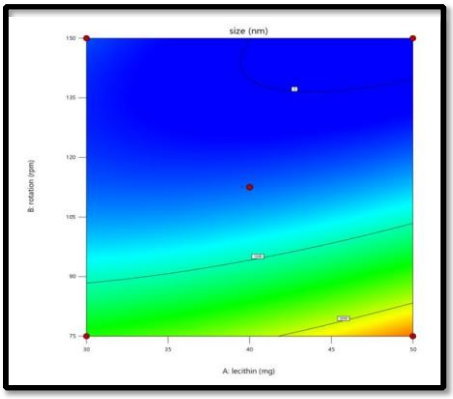


Fig No6: 2D Contour plot for particle size

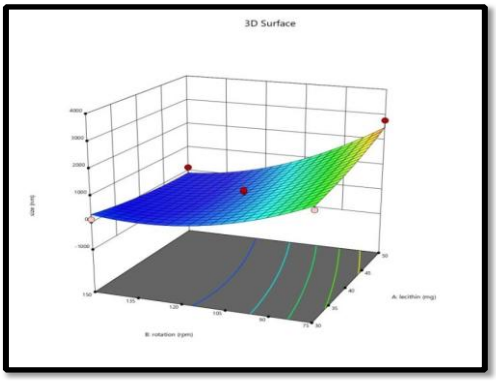


Fig No7: 3D-Surface plot for Particle size

The sample and its excipient underwent DSC studies. The DSC curve for indomethacin revealed a melting point of 163.87°C, while the DSC curve for the drug containing excipients revealed a melting point of 158. 47°C.These findings imply that the Aside is compatible with the excipients because both melt at nearly the same temperature.

$Y1 = 100.107 + -1.10772*A + -0.989141*B + 0.01312*AB + 0.0211675*A^2 + 0.00217724*B^2$

Y1 = Particle size, A= Amount of lecithin, B= rpm of rotary evaporator

Percentage Entrapment Efficiency

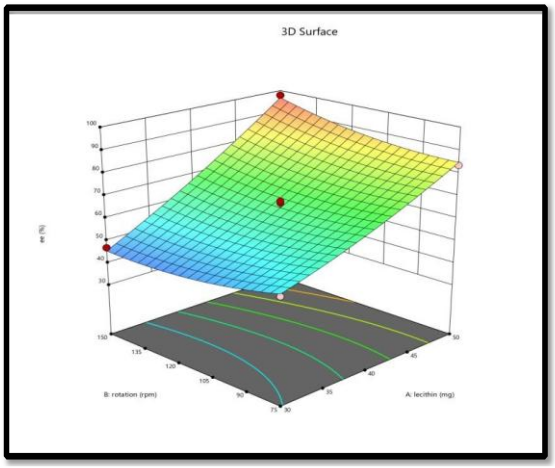


Fig No8: 3D Response surface plot showing the effect of the amount of lecithin and rpm on percentage entrapment efficiency.

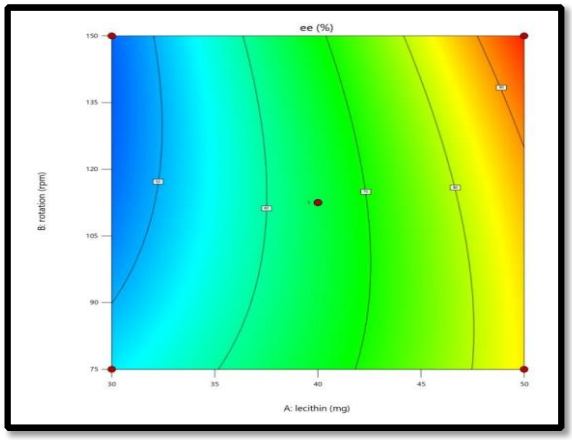


Fig No.9: 2D Contour Plot showing the effect of the amount of lecithin and rpm on percentage entrapment efficiency

In these samples, DSC studies were conducted alongside formulations to assess compatibility for the final formulation. Thermograms of indomethacin indicated melting peaks at 163.87°C, and his combination with excipients showed a peak at 158.47°C., confirming partial degradation corroborated by reduced diastolic temperatures suggesting some form of interaction during blending Estos supresores sugieren que sustancia puede ser algo metabolizable o modificable dependiendo de otros factores. It is apparent from both 3D and 2D surface plots that the concentration of lecithin has considerable effect on entrapment efficiency (%EE). The EE values showed a proportional increase with regard to the increased amounts of lecithin. A further observation noted increases in EE with increase in rotation speed as well. The correlation between formulation parameters and EE (Y2) is defined by this equation:

Y2 = 5.417.28 + 25.3148*A + -77.591*B + -0.929667*AB +1.16104*A2 + 0.396945*B2

Y2 = Entrapment efficiency, A = Amount of lecithin, B= rpm of rotary evaporator

Using Design Expert Software, we optimized the formulation F9 which has a desirability score of 0.994.

From the 3D and 2D surface plots, it is evident that the concentration of lecithin greatly impacts the entrapment efficiency (%EE). With increasing concentrations of lecithin, both EE values and to a lesser extent higher rotational speeds increased EE. The relationships between factors of formulation and Y2 – EE are given this equation:

Table No:24 Percentage Drug Content

Formulation code	***Percentage Drug Content (%)**
F1	46.4% ± 0.11
F2	63.7 ± 0.16
F3	65.13 ± 0.22
F4	78.60 ± 0.33
F5	58.20 ± 1.1
F6	67.60 ± 0.21
F7	43.95 ± 0.72
F8	94.17 ± 1.33
F9	94.80 ± 76
F10	61.4 ± 0.40
F11	39.06 ± 0.32
F12	64.15 ± 0.57
F13	69.37 ± 0.86

In Vitro Drug Release Study

In vitro drug release study of the optimized formulation, F9 was done. The formulation showed a drug release of 94.3068% for 20 hours. Thus, proving that the indomethacin pharmacosomes have a sustained drug release.

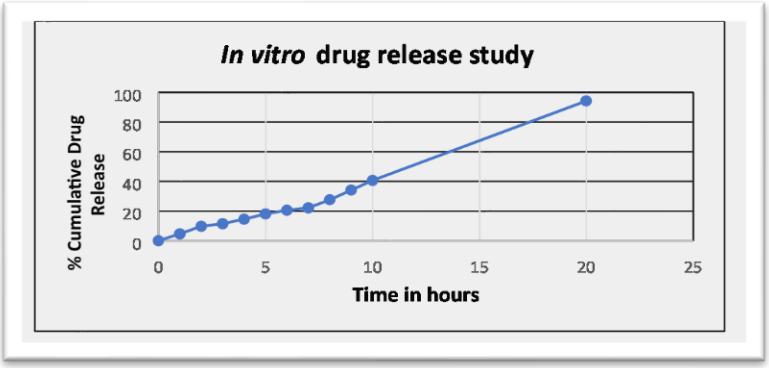


Fig No10: Graph of in vitro drug release of F9 formulation

Solubility Enhancement

Table No:28Solubility Enhancement

Drug / Formulation	**Solubility in water**	**Solubility in pH 6.8**
Indomethacin	**24.58 mcg/ml**	**24.54 mcg/ml**
Indomethacin pharmacosomes (F9)	**147.48 mcg/ml**	**56.17 mcg/ml**

Pharmaceutical formulation of indomethacin though pharmacosomal improved its solubility significantly. The drug demonstrated low soluble data in terms of water and phosphate buffer (pH 6.8) with 24.58 mcg/ml and 24.54 mcg/ml respectively. On the other hand, F9 pharmacosome refined formulation

revealed better solubility giving out 147.48 mcg/ml in water while 56.17 mcg/ml in the buffer solution. Such increase in the documented value is closely associated to amphiphilic structural constituents of lipids involved in the formulation to aid solubilization sixfold better than before. These solubilizing factors work by improving wetting, dispersion, and formation of micelles among others. The phospholipid-drug complex defined as "pharmacosomes" due to their simultaneous hydrophilic and lipophilic features enhances indomethacin's dissolution rate thus increasing bioavailability when applied trans dermally.

Zeta Potential and Polydispersity Index

The indomethacin pharmacosome formulation (F9) was found to have an excellent stability with a zeta potential value of -70.2mV. We can conclude that the prepared pharmacosomes are sufficiently charged to prevent particle aggregation. The formulation's PDI was determined to be 0.416, indicating that the system was monodispersed and that the particle size was homogeneous.

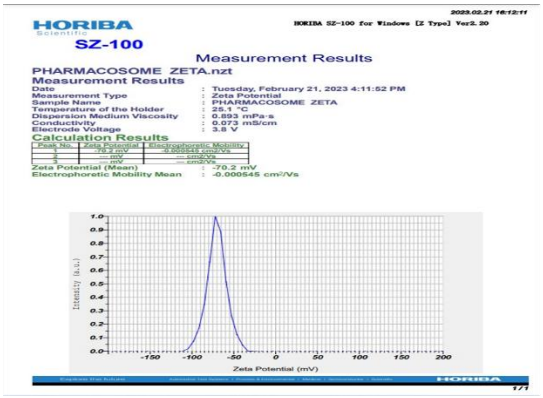


Fig No11: Zeta Potential

SEM Analysis

The crystalline drug's attachment to the phospholipids is visible. In SEM, pharmacosomes appear clumped together. Because the complexes were made with high-purity phospholipids, their surfaces were rough, free-flowing, and non-stick; in contrast, complexes made with low-purity phospholipids had sticky surfaces.

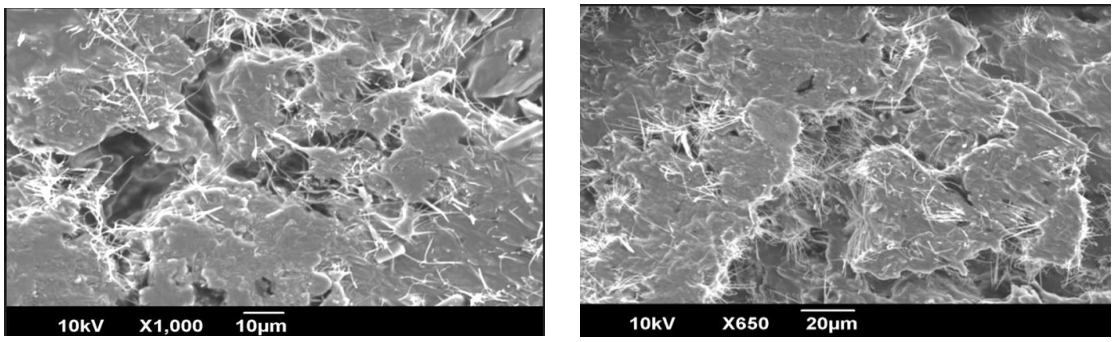


Fig No.12: SEM Images of Pharmacosmes

KINETIC STUDY OF OPTIMIZED INDOMETHACIN

Several kinetic models, including Zero-order, First-order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas, were used to perform in vitro drug release studies of the pharmacosome formulation. The best fit model was determined to be the one with an R2 value that was closest to unity. A release mechanism independent of drug concentration was suggested by the release kinetics data, which showed that drug release from the pharmacosomes followed zero-order kinetics. A diffusion-controlled release mechanism was also suggested by the high R^2 value obtained when fitting the data to the Higuchi model. An "n" value of 1.1856 was obtained through analysis using the Korsmeyer-Peppas model, indicating super case II transport, which combines diffusion and polymer relaxation mechanisms.

These findings suggest that drug release from the pharmacosomes is governed by a diffusion mechanism following zero-order kinetics**.**

Physical evaluation of pharmacosomal gel

PH Determination

The pharmacosomal gel's pH was measured and found to be 5.61±0.01.

Spreadability

The pharmacosomal gel's spreadability was assessed, and it was discovered to be good. A good spreading aids in the gel's even skin application.

Extrudability

The pharmacosomal gel was found to have good extrudability after the gel's extrudability was assessed.

Viscosity

The pharmacosomal gel's viscosity was measured and found to be 9199 cps.

Percentage drug content

The pharmacosomal gel's indomethacin content was 90.56±0.47%.

Table No.36: *In vitro* drug release &*ex vivo* skin permeation study data

***In vitro* Drug Release Study**			***Ex vivo* skin permeation study**
Time in Hours	**%CDR of IND plain Gel**	**% CDR of IND-PC Gel**	**% CDR of IND-PC Gel**
0	0	0	0
1	31.79 %	4.54 %	4.15%
2	49.76 %	9.81 %	7.89%
3	61.57 %	13.07 %	12.01%
4	74.62 %	17.48 %	17.56%
5	81.35 %	22.65 %	22.09%
6	94.21 %	26.81 %	24.62%
7	-	32.53 %	29.07%
8	-	38.62 %	34.51%
9	-	43.86	38.64%
10	-	48.73	43.32%
20	-	88.42	79.02%
24	-	-	83.58%

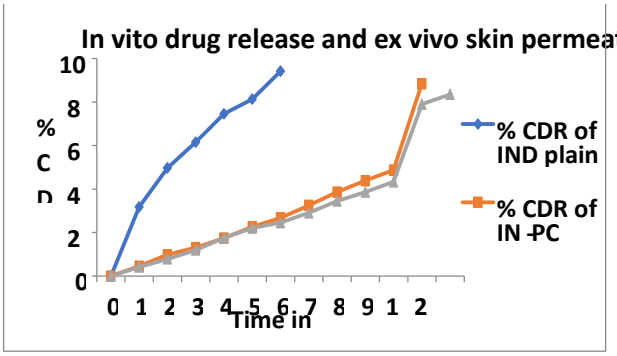


Fig No13: *In vitro* drug release and *Ex vivo* skin permeation study

According to the in vitro study, the IND-PC Gel exhibits 88.42% drug release over 20 hours, while the IND plain gel exhibits 94.21% drug release in 6 hours. As a result, it demonstrates the IND-PC Gel's prolonged drug release. 83.58% of the drug is released in a 24-hour period in the ex vivo skin penetration study. Accordingly, the IND-PC Gel exhibits comparable drug release in in vitro, and ex vivo release studies.

Egg Albumin Denaturation Assay

The pharmacosomal gel's ability to reduce inflammation was assessed. It is possible to conclude from the current study's findings that the indomethacin pharmacosomal gel effectively prevents heat-induced albumin denaturation. It was determined that the percentage inhibition was 44.30 %.

Kinetic Study of Indomethacin Pharmacosomal Gel

Zero order R2	First order R2	Higuchi model R2	Hixson Crowell Model R^2	Korsmeyer Peppas Model	
				R2	N
0.859	0.022	0.859	0.007	0.848	1.2517

According to the release kinetics data, the drug's release from the pharmacosomal gel fits within the range of zero order release kinetics. This indicates that the drug concentration in the formulation had no bearing on the drug's release from the pharmacosomal gel. The Higuchi model, which was fitted to the in vitro data, produced a nearly linear plot with the highest R2 value, suggesting that diffusion was the mechanism of drug release. The indomethacin pharmacosomal gel exhibits super case II diffusion, as indicated by the "n" value of 1.2517 that was obtained from the Korsmeyer Peppas plot.

Stability Studies of Indomethacin Pharmacosomal

For three months, pharmacosomal gel was kept in a stability chamber at 40 ±2°C and 75 ± 5% relative humidity while undergoing accelerated stability studies. The formulated pharmacosomal gel is stable, as evidenced by the lack of discernible changes in physical characteristics, pH, drug content, and in vitro release.

IV. SUMMARY

Advanced vesicular carriers called pharmacosomes are created when medications are covalently bonded to phospholipids. Improved drug solubility, stability, and site-specific delivery are made possible by their membrane-like structure. The short half-life, frequent dosing, and gastrointestinal side effects of traditional delivery methods were addressed in this study by developing a pharmacosomal gel containing indomethacin. The compatibility of indomethacin with the chosen excipients was validated by preformulation studies. Using Central Composite Design, the pharmacosomes were optimized, yielding formulation F9 with the desired properties of a sixfold increase in solubility, a 98.8% entrapment efficiency, and a particle size of 188.4 nm. The pharmacosomes were added to a gel made of carbopol, which had good viscosity, spreadability, and pH. Studies on drug release revealed 83.58% skin penetration in 24 hours and sustained release of up to 88.42% over 20 hours.A zero-order model with super case II transport behaviour was used to describe the release kinetics. Additionally, the gel demonstrated significant stability and anti-inflammatory activity, indicating that it could be a successful transdermal treatment for rheumatoid arthritis.

V. CONCLUSION

A potent anti-inflammatory drug called indomethacin is commonly prescribed to treat the pain associated with rheumatoid arthritis (RA). However, topical formulations usually only provide temporary relief, and oral administration is frequently linked to gastrointestinal side effects. This study aims to develop a pharmacosomal gel that permits sustained transdermal delivery of indomethacin in order to overcome these constraints. The pharmacosomal system facilitates deeper skin penetration and serves as a depot for controlled drug release by improving the drug's solubility and bioavailability. This method reduces the need for frequent application, minimizes side effects, and may increase patient adherence, making it a promising therapeutic approach for skin-based RA treatment.

BIBLIOGRAPHY

[1]. B. Narasimha, K. Ravindra Reddy, B.Mounika, S. Rahath Fathima, A. Tejaswini. Vesicular Drug Delivery System.IJCRGG.2019; 12(5):39-53.
[2]. Irene Thomas, Beena P, Elessy Abraham. Formulation Development and Evaluation of Niosomal Gel of Combined Anti-Fungal Agents.Int J Pharm2018;8(3):3-20
[3]. Mohd. Gayoor Khan. The Novel Drug Delivery System. World J Pharm Sci.2017 May 13; 6(7):477-87.
[4]. Snehal Ashok Gavhane, Aditi Tukaram Gade. The Novel Drug Delivery
[5]. System.IJCRT.2021 Sep; 9(9): 373-85.
[6]. Kalpesh Chhotalal Ashara *et al*. Vesicular Drug Delivery System: A Novel Approach. Mintage j. pharm. med. sci.2014 Aug; 3(3):1-14.
[7]. Archana Pandita, Pooja Sharma. Pharmacosomes: An Emerging Novel Vesicular Drug
[8]. Delivery System for Poorly Soluble Synthetic and Herbal Drugs. ISRN Pharm.2013 Sep 9.
[9]. Bommala Supraja, Saritha Mullangi. An updated review on pharmacosomes, a vesicular drug delivery system. J. drug deliv. ther. 2019 Feb 15;9(1-s):393-402.
[10]. S.S. Biju, Sushama Talegaonkar, P. R. Mishra, R.K.Khar.Vesicular Systems: An overview. Indian J. Pharm. Sci.2006 Feb 2006;68 (2):141-153.
[11]. Sunil Kamboj, Vipin Saini, Nancy Magon, Suman Bala, Vikas Jhawat. Vesicular drug delivery systems: A novel approach for drug targeting.2013;5 (2):121-130.
[12]. Ujjwala Bhingare, Dr.S.S.Khadabadi, Nita Shinde. Pharmacosomes: A Novel Drug Delivery System.2014;3 (1):14-20.

[13]. Shikha Jain, Vikas Jain, S. C. Mahajan. Lipid Based Vesicular Drug Delivery Systems. Advances in Pharmaceutics.2014 Sep 02.
[14]. Shelke, S.J. and Shinkar, Dattatraya and Saudagar, Ravindranath. Topical gel: A novel approach for development of topical drug delivery system. Int. J. Pharm. Technol.2013 July;5(3):2739-63.
[15]. Loveleen Preet Kaur, Tarun Kumar Guleri. Topical Gel: A Recent Approach for Novel Drug delivery. Asian j.biomed.pharm.2013 March 15;3 (17):1-5.
[16]. Gerard J Tortora, Bryan Derrickson. Principles of Anatomy & Physiology.15th ed.2016;145-49.
[17]. Garg U, Jain K. Dermal and Transdermal Drug Delivery through Vesicles and Particles: Preparation and Applications. Adv Pharm Bull.2022;12(1):45-57.
[18]. Pierre, M.B.R., dos Santos Miranda Costa, I. Liposomal systems as drug deliveryvehicles for dermal and transdermal applications. Arch Dermatol Res 303;2011: 607–21.
[19]. Harsh Mohan. Textbook of PATHOLOGY.7th ed. JAYPEE Publishers. Chapter 26: TheMusculoskeletal System.843,844.
[20]. Zhang Y, Gao Z, Chao S, Lu W, Zhang P. Transdermal delivery of inflammatory factors regulated drugs for rheumatoid arthritis. Drug Deliv. 2022 Dec;29(1):1934-50.
[21]. Crofford JL. Use of NSAIDS in treating patients with arthritis. Arthritis Res Therapy.2013 July;15(3).
[22]. KD TRIPATHI. Essentials of Medical Pharmacology.8th ed. JAYPEE BROTHERS
[23]. MEDICAL PUBLISHERS. Chapter 16: Nonsteroidal Anti-inflammatory Drugs and Antipyretic-Analgesics.219,220.
[24]. Mungal A, Allam AE. Indomethacin. Stat Pearls Publishing;2023 Jan 31.
[25]. S. Naveen Taj, Y. Indira Muzib, R. Radha. Design And Optimization of FluconazoleLoaded Pharmacosome Gel for Enhancing Transdermal Permeation and Treating Fungal Infections Through Box-Behnken Design. Int J App Pharm.2023;15(1):131-40.
[26]. Meenu Soman, Prof. (Dr.). Shaiju S Dharan, Litto T Mathew. Formulation and Evaluation of Selective Cox-2 Inhibitor loaded Pharmacosomes for the treatment of Rheumatoid Arthritis. J. Pharm. Sci. Res.2020;12(12):1502-9.
[27]. Kolar Kusuma, D. Priyanka, Dr. J. Sundaraseelan. Formulation and Evaluation of Pharmacosomal Gel Loaded with NSAID. World J. Pharm. Res. 2018;4(7):81-8.
[28]. Vidya Viswanad, Sneha Letha, Shammika P. Formulation and evaluation of etodolac pharmacosomes: A novel approach towards Rheumatoid Arthritis. Int. J Pharm.Technol. 2017;9(2);29665-80.
[29]. Pintu Kumar De, Mitali Saha, Dibya Das, Himangshu Sekhar Maji. Formulation And Characterization of Atorvastatin Pharmacosomes as An Alternative Approach to Conventional Vesicular System. Int.Res.J.Pharm.2020;11(3):45-9.
[30]. Pal Tapas Kumar, Jayita Mishra, Abhishekh Podder. Design, Fabrication and Evaluation of Rosuvastatin Pharmacosome - A Novel Sustained Release Drug Delivery System. European j.pharm.med.2016 March 24;3(4):332-50.
[31]. M. Puroshotham, V. Viswanath, B. Narasimharoa, B. Sujitha, S. Sireesha. Formulation
[32]. And Evaluation ofPharmacosomes Containing Ornidazole.World J. Pharm.Res.2015;4(09):926-41.
[33]. Mona Semalty, Prateeksha Badoni, Devendra Singh, Ajay Semalty. Modulation of solubility and dissolution of furosemide by preparation of phospholipid complex. Drug Development and Therapeutics.2015 Aug; 5(2):172-76.
[34]. V.Chatap, P. Patil, S.D. Patil. In-Vitro, Ex-Vivo Characterization of Furosemide Bounded Pharmacosomes for Improvement of Solubility and Permeability.
[35]. Amandeep Kaur, Neha Sharma, S.L. Harikumar. Design And Development of Ketoprofen Pharmacosomes for Oral Delivery. Pharmacophore 2013;4(4):111-19.
[36]. Ajay Semalty, Yuveraj Singh Tanwar. Nimesulide-phosphatidylcholine Complex for Improvement of Solubility and Dissolution. Am. J. Drug Discov. Dev.2013;3(1):225-34.
[37]. Peg-Fei Yue et al. Process optimization by response surface design and characterization study on geniposide pharmacosomes. Pharm Dev Technol. 2012 ;17(1):94-102.
[38]. A. Semalty et al. Development and Evaluation of Pharmacosomes of Aceclofenac. Indian J Pharm Sci. 2010; 72(5): 576–81.
[39]. Ajay Semalty, Mona Semalty, Devendra Singh, M. S. M. Rawat. Development and physicochemical evaluation of pharmacosomes of diclofenac. Acta Pharm.2009; 59:335–44.
[40]. Ajay Semalty *et al.* Preparation and characterization of phospholipid complexes of naringenin for effective drug delivery. J Incl Phenom Macrocycl Chem. 2009 Nov 19; 67:253-60.
[41]. Nagalakshmi S, Teshini S, Shoba E, Madhavan S, Shilpa S, Sintinya S, Design, Development and Characterization of Hyaluronic Acid Based pH Sensitive Liposomal in Situ Gel for the Treatment of Keratoconjunctivitis Sicca. J. drugdeliv. ther.2023 Jan 15; 13(1):17-2.
[42]. Bhushan R Rane, Aishwarya K Patil, Prashant L Pingale, Ashish S Jain, Dilip O Morani, Rajan V Kalamkar. Development and in-vitro characterization of liposomal gel of bifonazole for topical use. Jour. of Med. P'ceutical & Allied. Sci. 2021 Nov 03; (1):134-42.
[43]. Gupta S, Bhairy S, Hirlekar R. Formulation development, characterization and assessment of In-Vitro antifungal efficacy against Candida albicans of diallyl disulphide liposomal gel using 32 factorial designs. J. drugdeliv. ther.2019 March 15;9(2):105-17.
[44]. Arun Raj R, Nikita Sara Abraham. Formulation, Optimization and Evaluation of Flurbiprofen Liposomal Gel. Research & Reviews: A Journal of Pharmaceutical Science. 2017;8(2): 33–42.
[45]. Deependra Singh, Rajendra Singh. Preparation and optimization of quercetin-loaded liposomes for wound healing, using response surface methodology. Artificial Cells, Nanomedicine, and Biotechnology.2016;44(2):635-41.
[46]. Carmelo Puglia, Domenico Trombetta, Vincenza Venuti, Antonella Saija, Francesco Bonina. Evaluation of in-vivo topical anti-inflammatory activity of indomethacin from liposomal vesicles. J Pharm Pharmacol.2004 Oct;56(10):1225-32.
[47]. Guadalupe Nava, Elizabeth Pinon, Luis Mendoza, Nestor Mendoza, David Quintanar, Adriana Ganem. Formulation and in Vitro, ex Vivo and in Vivo Evaluation of Elastic Liposomes for Transdermal Delivery of Ketorolac Tromethamine. Pharmaceutics.2011 Dec 15;3(4):954-70.
[48]. Ahlam Zaid Alkilani et al. Formulation and Evaluation of Azithromycin-Loaded Niosomal Gel: Optimization, In Vitro Studies, Rheological Characterization, and Cytotoxicity Study. ACS Omega.2022Oct 25;7(44):39782-93.
[49]. Sonia Tomar et al. Preformulation Studies of Niosomal Gel of Prednisolone & Azithromycin for Topical Drug Delivery System.JIPBS.2015Jan;2(3):312-21.
[50]. Amarachinta *et al*. Central composite design for the development of carvedilol-loaded transdermal ethosomal hydrogel for extended and enhanced anti-hypertensive effect. J Nanobiotechnol.2021 April;19(1).
[51]. Sundara Pandian Ramkanth et al. Box–Behnken Design: Optimization of Proanthocyanidin-Loaded Transferosomes as an Effective Therapeutic Approach for Osteoarthritis. Nanomaterials.2022 Sept;12(17):29-54.
[52]. Arvind Sharma, Sandeep Arora. Formulation and In Vitro Evaluation of Ufasomes for Dermal Administration of Methotrexate. International Scholarly Research Notices2012 Jun 12.
[53]. Akul Munjal, Abdallah E Allam. Indomethacin.StatPearls Publishing.2023 Jan 31.

[54]. PubChem Compound Summary for CID 57369748, Lecithin from Soybean. National Centre for Biotechnology Information.2023 May 6.
[55]. Raymond C R Raymond C Rowe, Paul J Sheskey, Sian C Owen. Handbook of pharmaceutical excipients. 4thedition. American Pharmacists association.Pg.409,10.
[56]. Raymond C R Raymond C Rowe, Paul J Sheskey, Sian C Owen. Handbook of pharmaceutical excipients. 4thedition. American Pharmacists association.Pg.111-14.
[57]. Dichloromethane. Byju's Chemistry.
[58]. Nihala Nazeer, Mathan S, Rajalekshmi VR, Bineesha KB. Development of Formulation and In Vitro Evaluation of Sterically Stabilized (Stealth) Liposomes Containing Selected Anti-Arthritic Drug. J. Pharm. Sci. & Res.2019;11(10):3526-35.
[59]. Irene Thomas, Beena P, Elessy Abraham. Formulation Development and Evaluation of Niosomal Gel of Combined Anti-Fungal Agents.Int J Pharm2018;8(3):3-20.
[60]. Darya A. Kuznetsova et al. Enhancement of the Transdermal Delivery of Nonsteroidal Anti-inflammatory Drugs Using Liposomes Containing Cationic Surfactants. ACS Omega
[61]. 2022; 7:25741−50.
[62]. Wasankar SR, Faizi SM, Deshmuk AD. Formulation and Development of Liposomal Gel for Topical Drug Delivery System. Int J Pharm Sci Res. 3(11); 4461-74.
[63]. Aswathy Bose et al. Formulation and evaluation of sitagliptin buccal patch. Research J.Pharm. and Tech. 2020; 13(10):4883-87.
[64]. Milla Gabriela Belarmino Dantas et al. Development and Evaluation of Stability of a Gel formulation containing the monoterpene borneol scientific World Journal.2016 April 19.
[65]. Sunil Kumar Dubey.Mahipal Reddy Donthi, Ranendra Narayan Saha, Gautam Singhvi.Dasatinib-Loaded Topical Nano-Emulgel for Rheumatoid Arthritis: Formulation Design and Optimization by QbD, In Vitro, Ex Vivo, and In Vivo Evaluation. Pharmaceutics.2023 Feb 22;15(3):736.