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Pharmacosomes encapsulated with Dapsone and Cloxacilline to Enhance Transdermal Penetration: In Vitro and Ex Vivo Study

Priyanka Maurya[1]*, Dr. Tapasvi Gupta[2], Dr. Ritu Gilhotra[3]

[1]Priyanka Maurya, PhD Research Scholer, Pharmacy Department, Suresh Gyan Vihar University, Jaipur, Rajasthan, India.

[2]Dr. Tapasvi Gupta, Associate Professor, Pharmacy Department, Suresh Gyan Vihar University, Jaipur, Rajasthan, India.

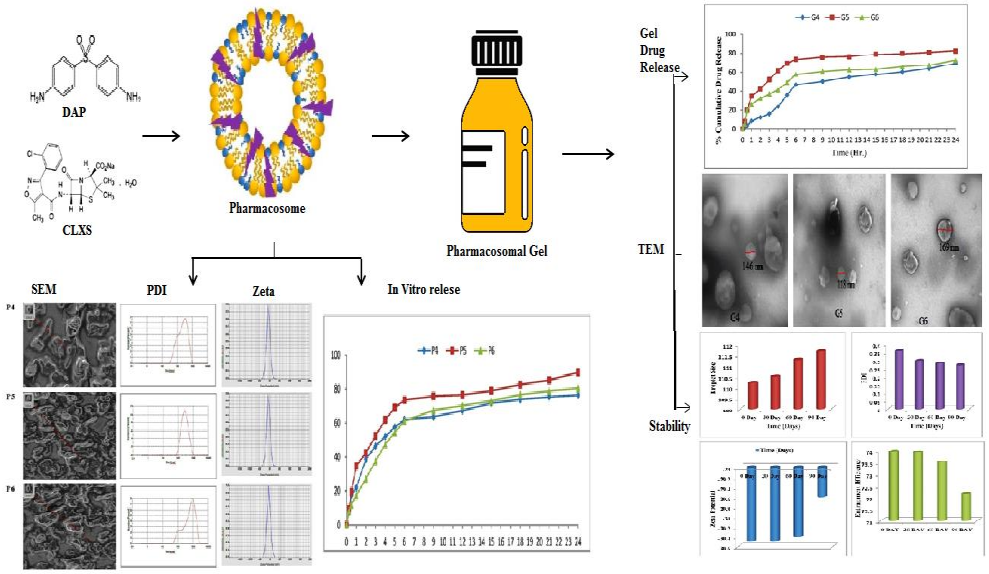
[3]Dr Ritu Gilhotra, Professor, Pharmacy Department, Suresh Gyan Vihar University, Jaipur, Rajasthan, India.

***Corresponding Author:** Priyanka Maurya, Email.- priyankamauryapharma@gmail.com

ABSTRACT

This work is based on to evaluate pharmacosome-based topical gel formulations for enhanced transdermal supply of Dapsone (DAP) and Cloxacillin (CLXS). Drug-excipient compatibility was confirmed by FTIR, indicating no any type of interaction. pharmacosomes (P1–P9) were categorized for vesicle size (110.6–168.2 nm), zeta potential (–14.7 to –30.5 mV), and high encapsulation efficiency (%EE), with optimized formulations (P4–P6) showing greater physicochemical properties. Among these, P5 exhibited optimal discharge behavior and smallest vesicle size. Pharmacosomal gels (G1–G9) were formulated using Carbopol 934 and calculated for drug content, spreadability, pH, and viscosity. Optimized gel G5 confirmed high drug content (83.54%), suitable pH (6.8), and ideal spreadability. In-vitro and ex-vivo studies show sustained drug release (up to 85.36 % over 24 h) and increased skin permeation compared to other conventional gels. TEM and SEM analyses show spherical morphology with even vesicle distribution. Stability studies over three months presented no major changes in vesicle characteristics, approving the formulation are stable. The presence of PEG 400 and low Carbopol concentration in G5 enhanced vesicle flexibility and skin permeation. Overall, the pharmacosomal gel (G5) show a stable vasicular delivery, active transdermal delivery system for enhanced topical delivery of DAP and CLXS. This vesicular gel was ready by using different optimization parameters. By comparing all the gel formulations, we observe that the vesicular gel exhibits the best drug release. In summary, the existence of DAP and CLXS in pharmacosomes is capable to enhance the anti-leprotic preparation, and it provide the cumulative effect on the patients.

Graphical Abstract:



Keywords: *Pharmacosomes, Leprosy, Ether injection Method, Ex Vivo drug release*

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1. INTRODUCTION

Hansen's disease (HD), commonly known as leprosy, is a chronic infectious condition caused by the slow-growing bacterium Mycobacterium leprae. Although the average incubation period is approximately five years, symptoms may appear as early as one year after exposure.[1] Despite significant advances in leprosy treatment—particularly following the World Health Organization's (WHO) introduction of multidrug therapy (MDT) over three decades ago—more than 200,000 new cases are still reported annually across more than 140 countries. The highest prevalence is seen in countries such as Brazil, India, and Indonesia. Leprosy continues to pose a major public health challenge, especially in many underdeveloped and developing nations.[2]

Pharmacosomes are colloidal drug delivery systems wherein drugs are covalently bonded to lipids. Depending on the chemical structure of the drug-lipid complex, they may exist in ultrafine vesicular, micellar, or aggregate forms. Pharmacosomes are amphiphilic phospholipid complexes, typically hexagonal in shape, in which drugs with active hydrogen groups bind to phospholipids. These systems offer enhanced biopharmaceutical properties, including improved drug bioavailability.[3]

In this study, Dapsone (DAP) and Cloxacilline (CLXS) were co-encapsulated within a single vesicular system to reduce adverse effects, prevent the development of microbial resistance, and enhance overall therapeutic efficacy. Delivering both drugs in a single topical formulation offers additional advantages for leprosy treatment, including improved healing of skin lesions—one of the common manifestations in affected patients.

2. MATERIALS AND METHODS:

2.1. Materials

Dapsone (DAP) and Cloxacillin (CLXS) both were bought from Yarrow Chem Products in Mumbai, India. Cholesterol and Soy Lecithin were bought from CDH, New Delhi. Polypropylene glycol (PPG), Polyethylene glycol (PEG 400), Carbopol 934, Isopropyle myristate, Triethenolamine and Ethanol were baught from SD Fine Mumbai. Distilled water was arranged by our lab.

2.2. Pharmacosomal Preparation:

DAP-CLXS incorporated Pharmacosomes were formulated by using ether injection method.[4] An organic phase was prepared by dissolving 50 mg of dapsone in calculative amount of ether and the aqueous phase was prepared by dissolving 50 mg of cloxacilline in calculative amount of water. A lipid mixture of phospholipid, as detailed in Table 1, was combined with the organic phase under continuous stirring at 60° C. Then aqueous phase is slowly introduced to the hot organic-lipid phase, with continuous mixing at 700RPM. After pouring of organic phase the suspension is stirred for 15 min.

Table 1: Formulation design of all Pharmacosomal formulations

S.No	Formulation Design	INGREDIENTS				
		Di ethyl Ether (ml)	Phospholipid (mg)	Water (for 20ml)	DAP (mg)	CLXS (mg)
1	P1	5	100	Q.S.	50	50
2	P2	7.5	100	Q.S.	50	50
3	P3	10	100	Q.S.	50	50
4	P4	5	90	Q.S.	50	50
5	P5	7.5	90	Q.S.	50	50
6	P6	10	90	Q.S.	50	50
7	P7	5	80	Q.S.	50	50
8	P8	7.5	80	Q.S.	50	50
9	P9	10	80	Q.S.	50	50

2.3. Physicochemical characterization of pharmacosomal formulation

2.3.1. Drug-Excipient compatibility Analysis:

The infrared range is imperative evidence which provide an adequate data about the structural compatibility with the compound.[5] During analysis, physical mixture was placed under probe, FTIR spectrum was recorded to analyzed for the changes in peaks. The FTIR study was done by using PerkinElmer Spectrum and the range was fixed in this limit of 400-4000 cm^{-1} at $20^{O}C$ - $25^{O}C$.

2.3.2. Droplet size, PDI, and Zeta potential:

The pharmacosomal suspension were diluted in distilled water (1:10v/v) and evaluated for droplet size, PDI and Zeta potential using (Nano-ZS, Malvern instrument, Malvern, U.K.). Previously loading the cell into the equipment, carefully wipe the estimating windows with lens paper, it was recommended to keep running in manual mode and started at a low voltage.[6]

2.3.3. Entrapment efficiency study:

The encapsulation efficiency was evaluated through the centrifugation technique. 10 ml of ethosomes dispersion was transferred into a cold centrifuge (R-4 C, Remi centrifuge, Vasai, India) at 15,000 rpm for 60 min at 4ºC. The untrapped drug is separated, and supernatant liquid is obtained. The amount of entrapped pharmacosomes was examined at 295 by U.V Spectroscopy (Pharma spec 1700, Shimadzu, Japan) and was calculated by using this equation.[7]

$$\%\ \textbf{Entrapment Efficiency} = \frac{\textbf{Total amt. of entraped drug} - \textbf{Total amt. of unentraped drug}}{\textbf{Total amt of unentraped drug}} \times \mathbf{100}$$

2.3.4. *In-vitro* drug release study:

A Diffusion cell (Dinesh scientific, New Delhi) was used in this study, with egg membrane for the release profile.[8] 1ml of pharmacosomes was applied to the membrane, and the donor compartment was filled with 15ml 6.8 pH buffer. The setup was placed on a magnetic stirrer (Bharat Electrical Industries, Varanasi), where the solution 6.8 pH buffer is filled in the receptor compartment at 50 rpm, at 37°C±5ºC temperature. 1 ml sample was withdrawn and exchanged with fresh buffer solution. The drug concentration of aliquote was withdrawn at different time durations of 0, 0.25, 0.5, 1, 2 upto 24hr and analyzed at 295nm by using simultaneous estimation of DAP+CLXS via UV (Pharma spec 1700, Shimadzu, Japan).[9, 10]

2.3.5. Vesicular morphology determination:

The optimized samples were visualized by SEM (JEOL Jsm–6490LV, Japan) to give 3D image of the globules.

2.4. Formulation of DAP+CLXS loaded pharmacosomal gel:

Optimized vesicle P5 is used for formulation of a gel by using dispersion method.[11] Carbopol 934 is add in aqueous phase (1% w/v) with continuous stirring at 25ºC followed by the addition of 1ml isopropyl myristate with continuous stirring at 500 rpm with care to escape air encapsulation. The pH was maintained by adding (Q.S.) triethanolamine. [12] After that, final volume was maintained by adding of PEG 400. All formulation design was prepared as given in Table 2.

Table 2: Formulation design of gel formulation:

F. Code	P5 Formulation (100mg-1ml)	Carbopol 934 (mg)	PFG 400 (ml)	Isopropyle myristate (ml)	Triethenolamine (0.5ml Q.S.)	Water (10ml Q.S.)
G1	100	10	1.25	1	Q.S.	Q.S.
G2	100	10	2.5	1	Q.S.	Q.S.
G3	100	10	5	1	Q.S.	Q.S.
G4	100	30	1.25	1	Q.S.	Q.S.
G5	100	30	2.5	1	Q.S.	Q.S.
G6	100	30	5	1	Q.S.	Q.S.
G7	100	50	1.25	1	Q.S.	Q.S.
G8	100	50	2.5	1	Q.S.	Q.S.
G9	100	50	5	1	Q.S.	Q.S.

2.5. Evaluation of pharmacosomal gel formulation:

2.5.1. Drug content in Pharmacosomal gel:

100mg of optimized vesicular gel is dispersed in a 10 ml of methanol by using probe sonicator (Hicon Products India Private Limited) until the complete solubility was not reached.[13] The solution was then filtered and analyzed using a UV. (Pharma spec 1700, Shimadzu, Japan) at 295 nm.

2.5.2. Spreadiblity:

The spreadibility of gel is calculated by take 1g of the optimized pharmacosomal gel is placed between two glass plates, and a weight is applied to one of the plates to simulate pressure. The spreadability is determined by measuring the area covered by the gel after applying a 1gm force.[14]

2.5.3. pH:

pH can be measured with the help of a **digital pH meter (**Hicon, Grover Enterprises, New Delhi). 1g optimized pharmacosomal gel is dissolved in buffer solution 5.5 pH, and the pH of the resulting solution is measured.[12]

2.5.4. Viscosity:

The viscosity of prepared formulations was prepared carried out by Brookfield Viscometer (Synchro Electric Viscometer).10g of sample was taken in a appropriate container, and spindle groove no. 4 was dipped and rotated at 0.3 rpm for a predetermined duration of 3 min. The spindle was moved in this gel until a constant reading was shown. Repeat this method for obtained the average values.[15, 16]

2.5.5. In-vitro study of pharmacosomal gel:

The study was carried out using a Franz diffusion cell.[17] The egg membrane was sandwiched in between the donor and receptor compartment. 10mg optimized pharmacosomal gel was placed on the egg membrane. The reservoir compartment was filled with 15 ml of 6.8 pH buffer. The study was done at 37± 1°C at 50 rpm for 24 hrs. Samples were withdrawn from reservoir compartment at periodic interval for 24 hrs, solution was replaced with fresh buffer to maintain the volume. The content was analyzed spectrophotometrically at 295 nm.

2.5.6. Stability studies:

Vesicles were stored in a glass vial under static conditions $40^0C \pm 3^0c$ at 75% RH in glass bottle over a period of 0, 1, 2 and 3 months. The samples were collected and evaluated for PDI, Particle size, Zeta potential and % EE.[18]

2.5.7. FTIR spectral analysis:

The FTIR of pure drug, physical mixture and optimised formulation was carried out to ascertain the identify of drugs. The 10 mg of the optimized sample was placed on the NaCl plate, and the FTIR spectrum was recorded to analyze the changes. The sample was scanned between wave number 400-4000 cm^{-1} at room temperature, using Perkin Elmer Spectrum and.

2.5.8. TEM Analysis:

The morphology was determined by using TEM (Tecnai 20, Philips, Eindhoven, The Netherlands). TEM provides detailed, high magnification quality and stability of vesicular drug delivery systems, helping to ensure their efficacy to examine the surface morphology, size and shape.

2.5.9. *Ex-vivo* permeation studies of pharmacosomal gel:

Ex vivo study was done with the help of diffusion cell. Conventional gel was used as reference to study the effect of pharmacosomal formulation on drug diffusion. The abdominal skin of pig was pre-equilibrated in PBS (pH 7.4) for 30min. The skin was sandwich in between the two compartments (Doner and Receptor), then optimized pharmacosomal formulation was applied. 15 ml of PBS (pH 6.8) phosphate-buffered was filled in the receptor compartment, and 1% PEG 400 to maintain sink conditions. It was agitated continuously at 700 rpm at 37 ±2ºC throughout the experiment. The sample (~50mg drug) was placed in donor compartment, at specific time interval withdrawn and replacement with fresh buffer. The drug content of samples was analyzed at 295 nm using UV spectrophotometry.[19]

3. RESULTS AND DISCUSSION

3.1: Compatibility study:

The compatibility study was done with the help of FTIR. Individual samples of drug and excipient and a combination of physical mixture were arranged and analysed for interaction. In Figure 1, the FTIR spectra shown no chemical interaction among the drug and excipients.

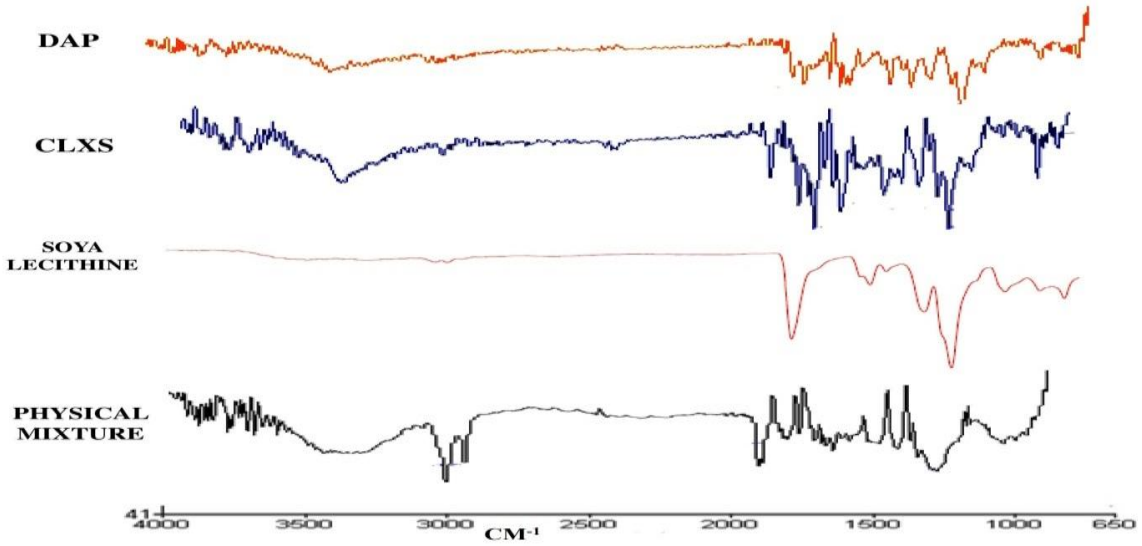

Figure 1: Drug-Excipient compatibility analysis by FTIR Spectra

3.2 Droplet size, size distribution, Zeta potential, pH and Encapsulation Efficiency

The droplet size, distribution and zeta potential's outcome of P1-P9 were studied and shown in Table 3 and Figure 2.and the vesicle is in ranging from 110.6 to 168.2 nm. The results showed that the ether concentration increases from 5 to 10 ml, the droplet size was affected due. Higher ether concentration may cause bilayer leakage, leading to the slight enlargement of vesicle and a significant reduction in % entrapment efficiency. As the phospholipid concentration increased from 80mg to 100mg, a slight rise in vesicle size was observed due to the greater number of phospholipid molecules forming the vesicle bilayers in which drug is incorporated.[13] All pharmacosomal preparations displayed PDI of 0.36 or less, representing narrow vesicle size distribution and decent homogeneity. The vesicular charge shifted from positive to negative, with zeta potential values measured in ranges from -14.7 to -30.5. The entrapment of the vesicles is given in Table 3, at higher ether concentration (10ml), the %EE shows decrease in results (64.5 to 66.54%) in comparison to 7.5 ml of ether concentration. This could be due to the ether ability of leaking of encapsulated drug in the vesicle.[14] Outstanding small vesicle size, low PDI, zeta potential lower than -36 Mv, and high % EE the pharmacosome with P4-P6 was shortlisted for further development.

So, the pharmacosomal formulation (P4-P6) demonstrated small vesicle size , low PDI, high zeta potential and high entrapment efficiency (%EE) were identified as optimised formulation.

Table 3: Entrapment, vesicle size and Zeta potential value of all formulations

	P1	P2	P3	P4	P5	P6	P7	P8	P9
Size (nm)	148.6	168.2	151.8	126.8	110.6	119.8	120.3	148.1	162.7
PDI	0.22	0.23	0.29	0.28	0.36	0.30	0.28	0.25	0.33
ZP(mv)	-18.2	-15.7	-19.8	-25.9	-30.5	-21.2	-17.5	-14.7	-16.7
pH	5.1	4.4	5.2	6.2	6.8	7.0	6.9	7.1	7.5
%EE	58.72	63.26	64.5	70.51	73.95	68.58	59.27	70.09	66.54

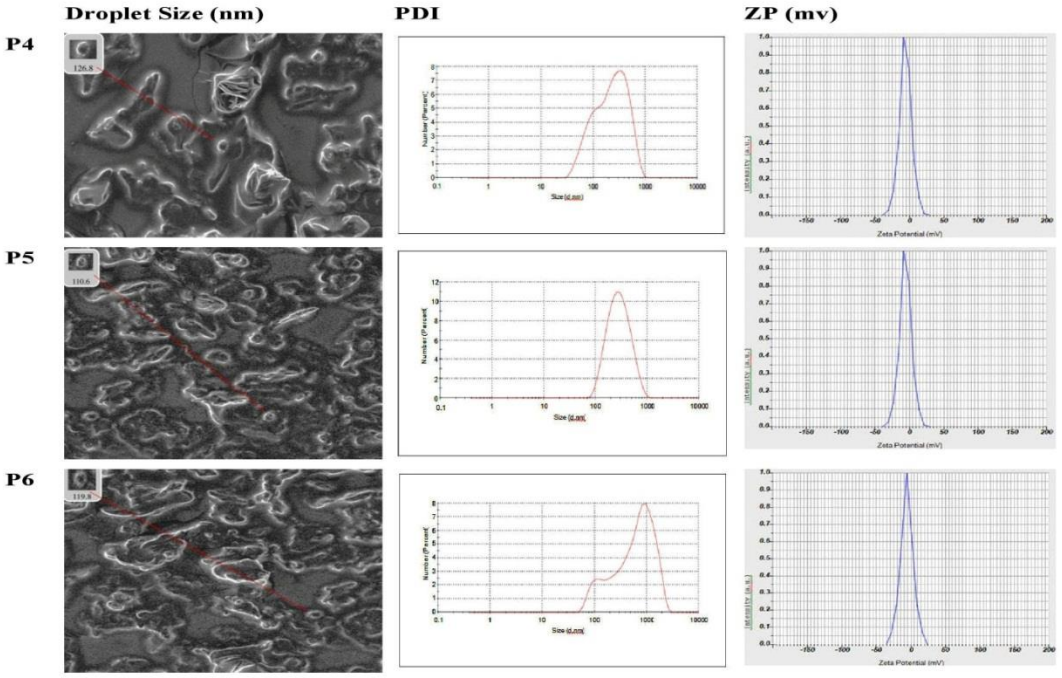

Figure 2: SEM, Particle size, PDI and ZP of optimised vesicle (P4-F6)

3.3 In-vitro drug release study

The in-vitro drug diffuse profiles of DAP+CLOX from the shortlisted batches (P4, P5, and P6) at pH 6.8 were measured by a graph in the cumulative percentage of drug released over time, and that are given in the Figure 3. The study showed the drug was released in high concentration with in 1 hour, approximately 21.9%, 34.75%, and 17.26% in P4, P5 and P6. This was followed by a sustained release, with the maximum drug release observed over 24 hours. On the basis of results, P5 is selected for the best vesicular formulation in comparison to others.

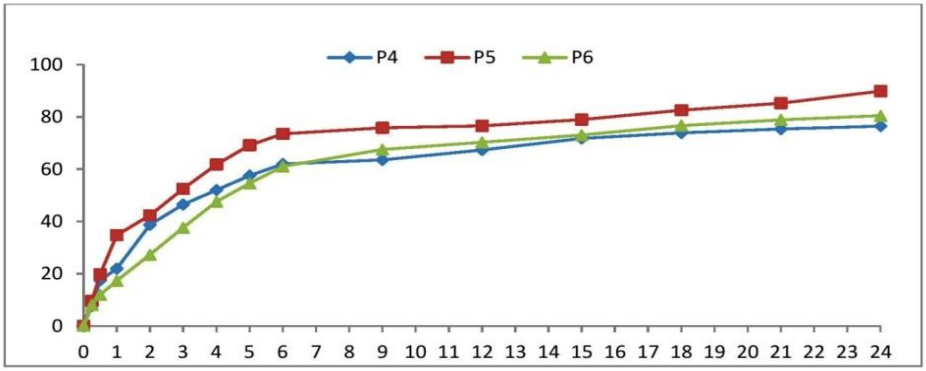

Figure 3: In-vitro drug release study of all vesicular formulations

3.4 Vesicular morphology:

SEM image of pharmacosome was given in Figure 2, and it was spherical in shape. By comparing all the vesicle sizes, we saw that P5 showed the smallest particle size, and consuming a diameter in 110.6 nm. This confirms the existence of vesicular structure at 7.5 ml ether concentration, resulted in decrease in vesicle size. However, ether concentration showed the lipid bilayer leading to thinner of membranes. It also add in a negative energy in to the pharmacosomal system and may alter stabilization,play a main role in the reduction in vesicular size.[20] This examination also approves the flat and smooth surface of pharmacosome.

3.5 Characterisation pharmacosomal gel

The pharmacosomal gel was formulated by using Carbopol 934 as a polymer, and the finalise gel showed a remarkably smooth texture, free from visible imperfections or roughness shown in Table 4. The constant texture enhances the overall appearance and indicates that the material has been carefully processed to achieve a refined, even finish. It was characterized by measuring % drug content, pH, viscosity, and spreadability, shown in Table 4. These values fall within

the normal physiological pH range of the skin (6.0–8.0), indicating that the pharmacosomal gels are non-irritating and safe for topical application. The drug content plays a vital role in determining the effectiveness and performance of drug-loaded particles. It directly impacts the therapeutic potential and stability of the formulation. The drug content of the prepared formulation was found to be greater than 60% which revealed a uniform distribution of drugs throughout the formulation, and the drug loss during the gel formulation was minimal. From the results, it was observed that spreadability decreases (7.54g/cm^2 to 11.12g/cm^2) with increase in carbopol concentration (10-50mg). This indicates that Carbopol provided spreadable gels by shearing force of low magnitude. The gel prepared by 10mg Carbopol (G4-G6) showed viscosity of 39, 40, 41 cps while those prepared by 50mg Carbopol shows 47689 cps. However, an increase in Carbopol concentration leads to larger in the distance traveled by the gel due to higher viscosity of the polymer. This outcome can be attributed to the gelling mechanism of carbopol, which strongly binds with the solvent and form cross-link.[21]

Table 4: Evaluation parameter of Pharmacosome loaded gels.

S.No.	Formulation Code	Texture	Drug Content	Spreadability (g/cm^2)	pH	Viscosity (CP)
1	G1	Smooth Texture	67.25	07.54	6.8	33551
2	G2	Smooth Texture	64.52	07.95	6.3	35758
3	G3	Smooth Texture	69.24	08.51	7.4	24158
4	G4	Smooth Texture	79.51	08.98	6.7	39453
5	G5	Smooth Texture	83.54	09.12	6.8	40154
6	G6	Smooth Texture	80.14	09.45	6.8	41264
7	G7	Smooth Texture	77.15	10.06	7.4	42523
8	G8	Smooth Texture	73.71	11.12	7.2	46115
9	G9	Smooth Texture	70.05	11.05	6.9	47689

3.6 In-vitro drug release study of gel

The drug release profiles of the improved formulations (G4-G6) were evaluated to predict their in-vitro performance. Improved drug penetration shows high vesicular permeation due to the presence of ether in the core, which solubilizes the lipid. Ether in the pharmacosomal system imparts flexibility, enhancing membrane diffusion and reducing the hydration layer around the vesicles, thus facilitating drug permeation. Figure 4 shows the release profiles of the short listed pharmacosomal gel, showing the cumulative percentage of drug release from different formulations (G4-G6), which ranges from 69.45% to 82.45%.

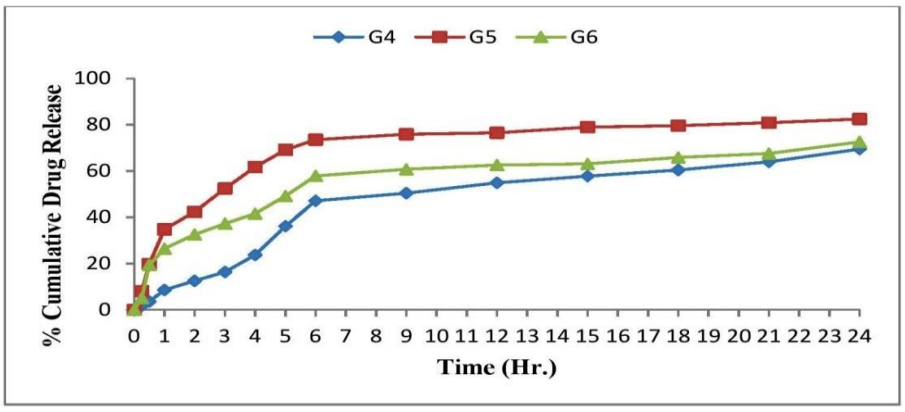

Figure 4: Drug release study of optimised gel formulation (G4-G6)

3.7 Stability study

The stability study was started in the study of the stability of topical gel preparation strategies as per ICH guidelines .[22] The stability studies for the selected formulation G5 gel were conducted for three months. The examination results shows there is no significant changes were observed on the all analyzed parameter, Figure 5.

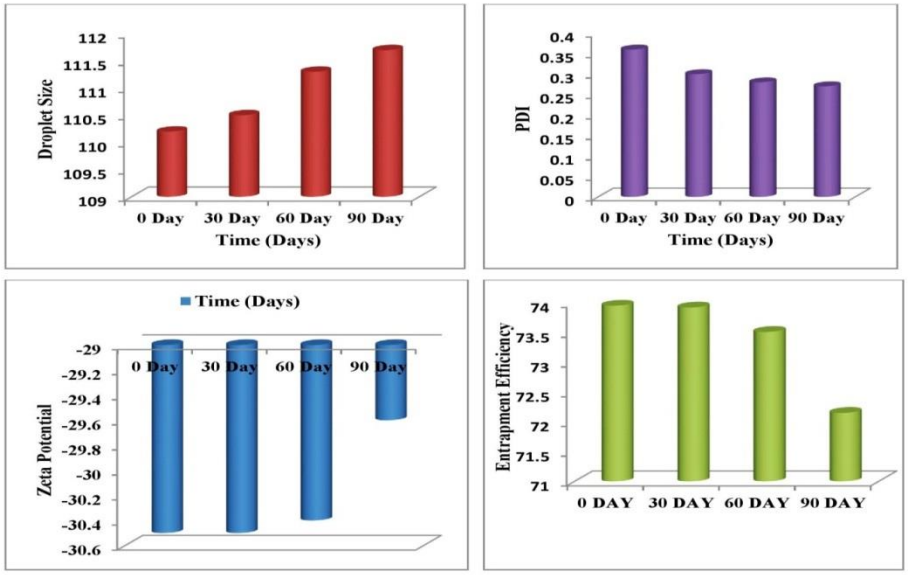

Figure 5: Droplet Size, PDI, Zeta potential and Entrapment Efficiency of G5 for three months at $40^0C \pm 3^0c$ at 75% RH

3.8 FTIR Spectral Analysis:

To presence of organic functional groups in the selected gels (G4-G6), FTIR studies were conducted. The results show the existence of characteristic absorption band of drug is present in optimized G5 formulation, shown in Figure 6. The spectrum also shows no major alteration in the position of peak of drug in the G5. This result exposed that there is no probable interaction between drug and excipient.

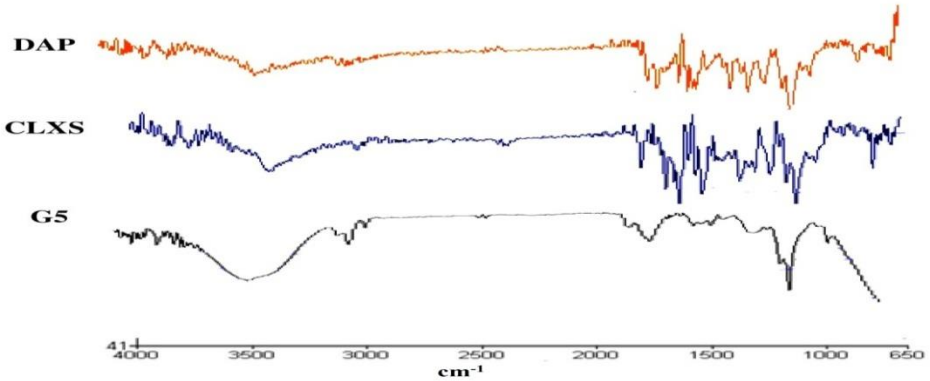

Figure 6: FTIR spectra of pure drug (DAP and CLXS) and optimised gel (G5)

3.9 TEM Analysis:

The TEM image of selected gel (G5) is shown in Figure 7. The drops display a dark spherical disc appearance, with diameters ranging from 146, 118 and 169 nm for G4, G5, and G6, respectively. In the middle of the three formulations, G5 revealed the narrowest size distribution, which can be attributed to the inclusion of 30 mg of Carbopol and 2.5 ml of PEG 400. This mixture contributed to a decrease in globule size, confirming the formation of a vesicular structure.

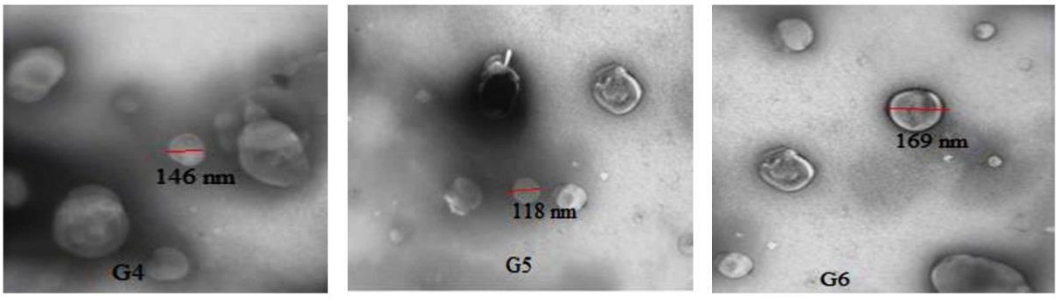

Figure 7: TEM Analysis of optimised gel (G4-G6)

3.10 Ex-vitro skin penetration study of optimised formulation:

To effectually penetrate the skin, vesicular systems are used. Pharmacosomes have been exposed to improve a drug's residence time in the epidermis, possibly improving its penetration.[23] In order to realize the ability of the pharmacosomal gel to aid drug penetration through the skin, ex-vitro studies were conducted for enhanced formulation (G4-G6) and compared with conventional drug loaded gel (CG) to present better evaluation of the permeation behaviour through the pig abdominal skin with franz diffusion cell as shown in Figure 8.

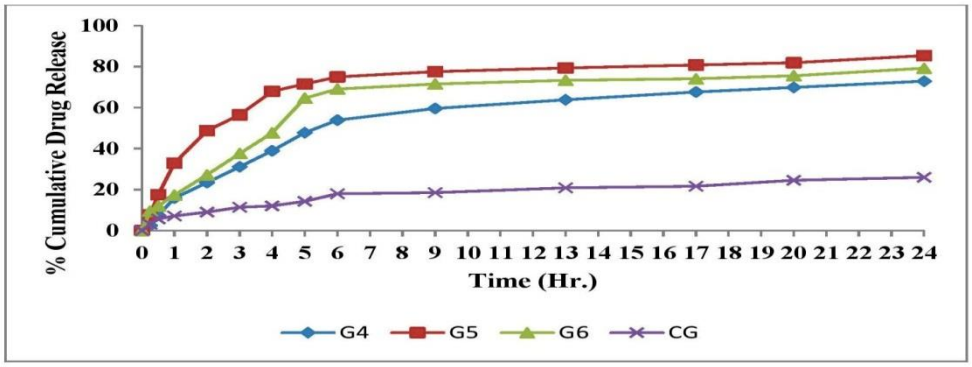

Figure 8: Cumulative percentage of drug permeated via pig abdominal skin vs time profile of pharmacosomal gel (G4-G6) and conventional gel (CG).

In contrast from the outcomes that the pharmacosomal gel (G4-G6) have a meaningfully longer release (72.89±0.45, 85.36±0.33, 79.21±0.27%) in comparison to conventional gel, GG (25.96±1.17%) in 24hr. This demonstrated that formulated pharmacosomes had a controlled release characteristic. The results shows that increasing the concentration of the penetration enhancer (PEG 400) in preparation G5 may improve skin permeability, vesicular flexibility, and their ability to deform, allowing them to penetrate the skin more effectively. This leads to greater vesicle penetration. The inclusion of 30 mg of Carbopol results in an extended residence time for the drug at the absorption site by interacting with the skin. Additionally, the viscosity of the gel formulation (G5) significantly influences drug release, affecting the rate of drug diffusion from the carrier.[24, 25]

4. CONCLUSION

In this study evaluated an pharmacosomal gel system for the topical delivery of Dapsone (DAP) and Cloxacillin (CLXS), directing to improve drug permeation and sustain release with in the skin. The study involved the formulation of pharmacosomal vesicles using variable concentrations of ethanol and phospholipids, followed by their presence into gels using Carbopol 934. This analysis exposed that formulation P5 exhibited optimal vesicle characteristics, with small particle size (110.6 nm), low PDI (0.36), high zeta potential (–30.5 mV), and maximum encapsulation efficiency (73.95%). FTIR analysis show the absence of any chemical interaction among drugs and excipients, supportive the compatibility of components. The vesicular preparations show desired morphological features, as confirmed through SEM and TEM analysis, with P5 forming spherical, uniformly distributed vesicles. In vitro drug release from P5 exposed a biphasic release pattern with an initial burst followed by release over 24 hours, indicating well-organized drug entrapment and sustained release behavior. P5 was further prepared into gels (G4–G6), with G5 selected as the optimized gel based on highest physic-chemical properties such as appropriate pH (6.8), high drug content (83.54%), viscosity (40154 cps), and high spreadability (09.12 g/cm²). PEG 400 enhanced drug solubilization and potential, whereas the low conc. of Carbopol confirmed high spreadability and drug release. The in vitro release study of pharmacosomal gel G5 show a cumulative drug release of 82.45% over 24 hours, and higher than conventional preparation. The ex-vitro skin penetration study was conducted by using pig abdominal skin and show the superior penetration ability of G5 (85.36 ± 0.21%) compared to conventional gel (25.96 ± 1.17%). Stability studies shown over three months confirmed that G5 show its physic-chemical properties without microbial growth. In conclusion, the pharmacosomal gel system, particularly G5, presented potential for topical delivery of DAP and CLXS, offering increase penetration, sustained release, stability, and patient compliance.

Consent for Publication:

Authors are willing to publish the article in your reputed journal.

Conflict of Interest:

There is no conflict of interest.

Acknowledgements:
Declared none.

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