IJBPAS, March, Special Issue, 2025, 14(3): 417-428

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION AND EVALUATION OF AZITHROMYCIN EMULGEL FOR TOPICAL DELIVERY

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Received 15th Dec. 2024; Revised 27th Dec. 2024; Accepted 7th Feb. 2025; Available online 15th March 2025

https://doi.org/10.31032/IJBPAS/2025/14.3.1048

ABSTRACT

Azithromycin is a widely used antibiotic for treating skin conditions such as acne vulgaris, psoriasis, ocular infections, and rosacea fulminans. However, oral administration of azithromycin is often associated with various side effects. To avoid these, a topical emulgel formulation is an ideal alternative. As azithromycin is hydrophobic and does not dissolve easily in aqueous solutions, an emulsion-based approach is employed to enable its topical application. In this approach, azithromycin can be solubilized in light liquid paraffin, which facilitates the effective delivery of this hydrophobic drug. Additionally, research shows that Carbopol 971P forms a loosely compacted polymer matrix, enhancing the release of the drug, while Carbopol 974P contributes to improving the formulation's viscosity.

Keywords: Azithromycin, Carbopol 974P, Emulgel, Topical Drug Delivery, antibiotic

INTRODUCTION:

Emulgel is a recent advancement in novel drug delivery systems (NDDS), designed for dual control release, combining the properties of both emulsions and gels for topical application **[1]**. When gels and emulsions are used together, the resulting

formulation is known as an emulgel **[2]**. The inclusion of a gelling agent in the water phase can convert a standard emulsion into an emulgel **[3]**.

Azithromycin, a water-insoluble drug, is commonly available in tablet form for treating conditions like acne vulgaris, psoriasis, ocular infections, and rosacea fulminans. However, due to its hydrophobic nature, azithromycin does not easily dissolve in aqueous solutions. Despite the benefits of gels, delivering hydrophobic drugs through them remains a challenge **[4-5]**.

MATERIAL AND METHODS:

Equipment: Digital weighing balance, Franz Diffusion cell assembly, Hot air oven UV-Visible Spectrophotometer, FT-IR Spectrometer, Zetasizer, Viscometer and pH meter.

Chemicals and Reagents: Azithromycin, Oleic acid, Light liquid paraffin, Acetonitrile, Span 20, Tween 20, Propylene glycol, Methyl paraben, Propyl paraben, Carbopol 971P, and Carbopol 974P.

Preparation of Emulgel:

Emulgel preparation was carried out in three steps:

1. Preparation of emulsion (oil in water emulsion)
2. Preparation of gel base (Using polymer and water)
3. Preparation of emulgel using 1:1 ratio of gel base and emulsion

- **Preparation of emulsion [6-10]**

The preparation and stabilization of the emulsion posed a key challenge for the formulator. The Azithromycin emulsion was made by dissolving Span 20 in light liquid paraffin for the oil phase. For the aqueous phase, Tween 20 was dissolved in distilled water, and methyl and propyl parabens were dissolved in propylene glycol, then mixed with the aqueous phase. Azithromycin, being hydrophobic, was added to the oil phase along with a permeation enhancer. Both phases were heated separately to 60-65°C to ensure proper mixing. The oil phase was then added to the aqueous phase with continuous stirring. After several trials, the F8 formulation was found to be a stable emulsion. The composition of different emulsions is shown in the following **Table 1**.

Table 1: Composition of emulsion formulations (F1 - F8)

Excipients	F1	F2	F3	F4	F5	F6	F7	F8
Azithromycin	1	1	1	1	1	1	1	1
Oleic acid	-	-	-	-	-	-	1	2
Light Liquid Paraffin	4	4	4	4	4	4	4	4
Span 20	1	-	0.9	0.7	0.3	0.9	0.5	0.5
Tween 20	-	1	0.1	0.3	0.7	0.1	0.5	0.5
Propylene glycol	5	5	5	5	5	5	5	5
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl Paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

➢ **Preparation of carbopol gel base**

Carbopol 971P and Carbopol 974P were dispersed in distilled water to prepare the gel bases. The mixture was stirred continuously with a mechanical stirrer at moderate speed until uniform. The pH was adjusted between 6 and 6.5 using triethanolamine to obtain a transparent, viscous, and glossy gel base.

➢ **Preparation of emulgel**

The prepared emulsion was slowly added to the gel base with continuous stirring until uniformly mixed. The ratio of Carbopol gel base to emulsion was 1:1. The composition of the various formulations is provided in **Table 2**.

Table 2: Composition of Azithromycin Emulgel Formulations (F1-F10)

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Azithromycin	1	1	1	1	1	1	1	1	1	1
Oleic acid	2	2	2	2	2	2	2	2	2	2
Light liquid Paraffin	4	4	4	4	4	4	4	4	4	4
Spans 20	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propylene Glycol	5	5	5	5	5	5	5	5	5	5
Tweens 20	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Carbopol 971P	1	1.2	-	-	0.8	0.6	0.4	0.2	0.7	0.5
Carbopol 974P	-	-	1	1.2	0.2	0.4	0.6	0.8	0.3	0.5
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Analytical Methods: [7-8]

Preparation of pH 5.5 Phosphate Buffer: Dissolve 68 g of potassium dihydrogen orthophosphate (KH_2PO_4) in 1000 ml of distilled water and adjust the pH with NaOH.

Ultraviolet absorption maxima (λmax): Dissolve 5 mg of azithromycin in 5 ml of acetonitrile, then dilute to 50 ml with pH 5.5 phosphate buffer. The solution was scanned between 200-400 nm using a Shimadzu 1601 spectrophotometer, with the respective blank solution as reference.

Preparation of Calibration curve of azithromycin in 5.5 pH phosphate buffers: Accurately weigh 50 mg of azithromycin and dissolve it in 5 ml acetonitrile in a 50 ml volumetric flask. Make the volume up to the mark with pH 5.5 phosphate buffer. From this stock solution, prepare dilutions in the concentration range of 100-500 µg/ml. Measure the absorbance of each solution at 205 nm.

Preparation of Calibration curve of azithromycin in 6.8 pH phosphate buffers: Accurately weigh 50 mg of azithromycin and dissolve it in 5 ml acetonitrile in a 50 ml volumetric flask. Make the volume up to the mark with pH 6.8 phosphate buffer. Prepare dilutions in the concentration range of 100-500 µg/ml from this stock solution and measure the absorbance at 205 nm.

RESULTS AND DISCUSSSION: [11-15]

Ultraviolet absorption maxima (λmax): The drug showed maximum absorption at 205 nm. So it shows that azithromycin drug can be detected in UV visible range.

Calibration curve of azithromycin in 5.5 pH phosphate buffer: The absorbance of Azithromycin solutions at concentrations of 100, 200, 300, 400, and 500 µg/ml was measured at 205 nm. A graph of concentration vs. absorbance is shown in **Table 3**.

Evaluation of emulsion: The final formulation (F8) of Emulsion was evaluated for particle size, viscosity, pH, stability, drug content and microbial change. All parameters was optimized.

Evaluation of emulgel: [16-20]

- **Physical examination:** The prepared emulgel formulations were inspected visually for their colour, homogeneity, consistency and phase separation. The prepared azithromycin emulgel formulations were white viscous creamy preparations with a smooth and homogeneous appearance. They were easily spreadable with acceptable bioadhesion and fair mechanical properties **(Table 3)**.
- **Measurement of pH:** The pH values of all the prepared formulations ranged from 5.5 to 6.5, which are considered acceptable to avoid the risk of irritation upon application to the skin. pH of azithromycin formulations (F1 - F10) is shown in **Figure 2**.
- **Rheological study: Figure 3** shows the entire rheograms of azithromycin emulgel formulations. The figure shows that as we speed increases shear rates also increases and there is decrease in viscosity with high shear rate. This shows the pseudoplastic behavior of emulgel. The viscosity of the formulated batches was determined using a Brookfield viscometer, HADV-II. The average of three readings were taken in 10 minute was noted as the viscosity of emulgels.
- **Spreading coefficient:** Spreading coefficient was determined and graphically represented in **Figure 4**. The figure shows that as concentration of carbopol 974P NF polymer increases there is increase in viscosity which leads to decrease in spreadability of emulgel. Same way as concentration of carbopol 971P NF polymer increases there is decrease in spreadibility. Here, formulation F6 gives the good

spreadibility revelent to topical preparations.

- **Extrudability test (Tube test):** Extrudability of different formulation F1 to F10 is found as per given **Figure 5**. Viscosity is negatively related to extrudability. As figure shows that F4 formulation contains the highest extrudability because of increased viscosity level while F1 contains the lowest extrudability because of decreased viscosity level. So in our study, the finding suggests that increase in polymer concentration leads to the decrease in extrudability.
- **Drug Content:** The drug content determined using standard plot. The drug content of azithromycin emulgel containing different concentration of carbopol polymer is given in table 19 and **Figure 6**. The data shows the satisfactory results of drug content in all formulations.
- **In vitro drug release study**: The drug release samples were analyzed spectrophotometrically at 205 nm, and cumulative % drug release was calculated. As shown in **Figure 7**, all emulgel formulations demonstrated good release. F1, F2, and F6 showed better release, likely due to lower viscosity from reduced Carbopol 974P NF concentration. Carbopol 971P NF, creating a loosely compacted structure, enhanced drug release. Higher polymer concentrations improved release, while increased viscosity from higher concentrations reduced release.
- **Microbiological assay:** The obtained minimum inhibitory concentration of all formulations is given **Figure 8**. The %inhibition was taken as a measure of drug antibacterial activity. The study was performed for F2 and F6 formulation which gives highest in vitro drug release profile. From both the formulation we found that F6 formulation gives the better %inhibition. Thus, high the drug release was found with highest antimicrobial activity.
- **Comparison with marketed formulation:**
  - **In vitro drug release (Table 8)**
- **Comparison of antimicrobial activity with marketed formulation:** The antimicrobial activity of the marketed Azithromycin emulgel was compared with formulation F6 by assessing percent inhibition against

Staphylococcus aureus, a major cause of acne vulgaris. Formulation F6 demonstrated better drug release and superior antimicrobial activity compared to the marketed formulation, as shown in **Figure 9**.

- **Release kinetics study:** Dissolution profiles were fitted to various model and release data were analysed on the basis of koresmeyer peppas equation, zero order, first order and higuchi kinetics. The R^2 value of all formulation is listed in following **Table 10**.

The best fit model was selected on the basis of R2 values. Thus, it may be concluded that From above data Higuchi model and Korsmeyer Peppas model were followed by formulation.

- **Stability study:** The stability studies were carried out on the most satisfactory formulations (Batch F6) as per ICH guidelines at 40 ± 1 °C / 75 ± 5 % RH conditions for 1 month. Initial % Drug content 94.93 ± 0.94 & After 1 month storage at 40 ± 1 °C/ 75 ± 5 % RH it was 92.67 ± 0.23

Table 3: Spectrophotometric analysis of azithromycin in phosphate buffer 5.5 pH

Sr no.	Concentration(ug/ml)	Absorbance
1	0	0
2	100	0.121
3	200	0.299
4	300	0.490
5	400	0.678
6	500	0.883

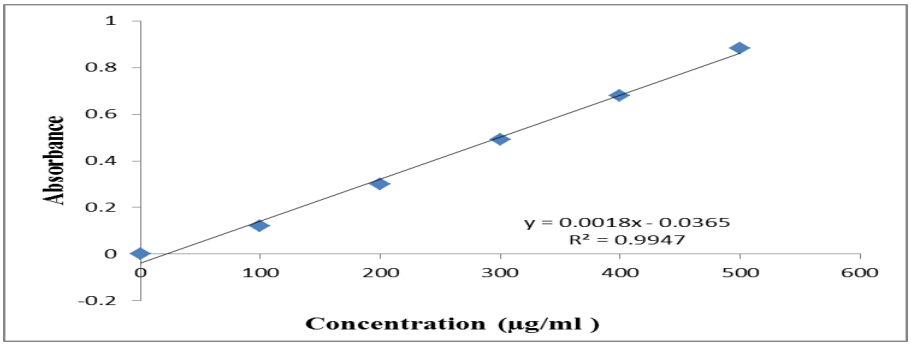

Figure 1: Standard plot of azithromycin in phosphate buffer 5.5 Ph

Table 4: Physicochemical characteristics of azithromycin emulgel

Sr. no.	Formulation	Colour	Phase separation	Homogenity	Consistency
1	F1	White	None	Excellent	+
2	F2	White	None	Good	+
3	F3	White	None	Good	+++
4	F4	White	None	Fair	+++

Sr. no.	Formulation	Colour	Phase separation	Homogenity	Consistency
5	F5	White	None	Excellent	++
6	F6	White	None	Excellent	+++
7	F7	White	None	Excellent	+++
8	F8	White	None	Excellent	+++
9	F9	White	None	Excellent	+++
10	F10	White	None	Excellent	+++

Excellent +++, Good ++, Satisfactory +

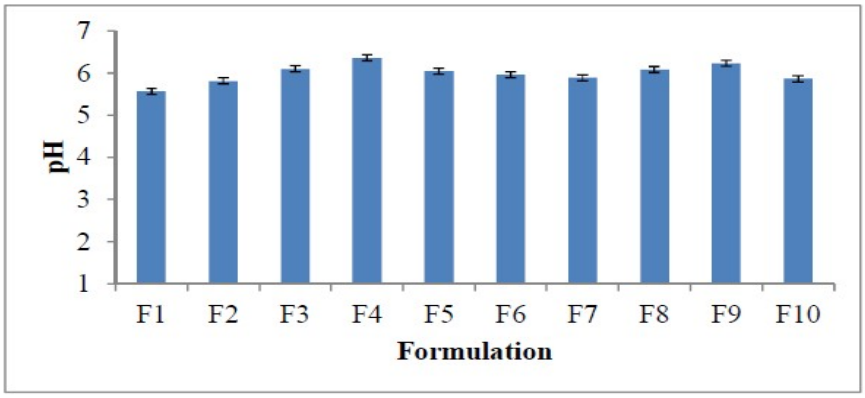

Figure 2: pH of azithromycin formulations (F1 - F10)

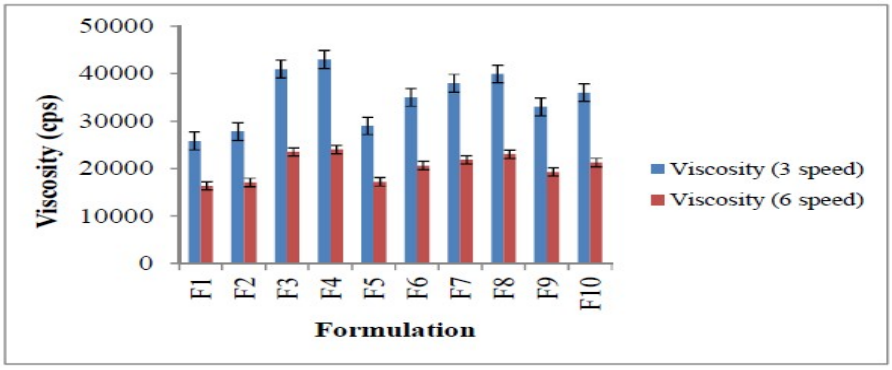

Figure 3: Viscosity of azithromycin formulations (F1 - F10)

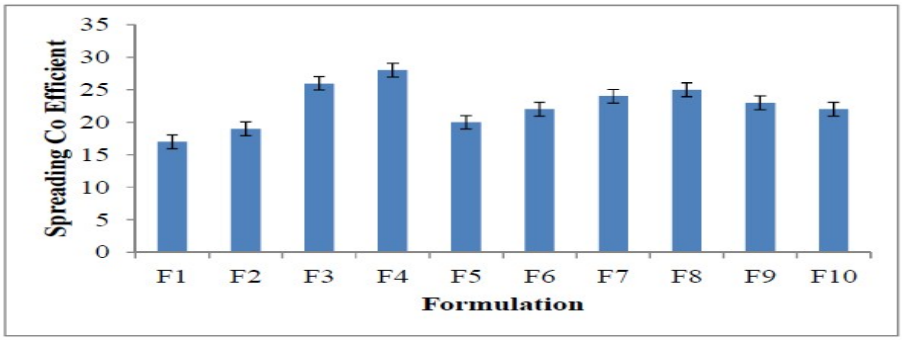

Figure 4: Spreading co efficient of azithromycin formulations (F1- F10)

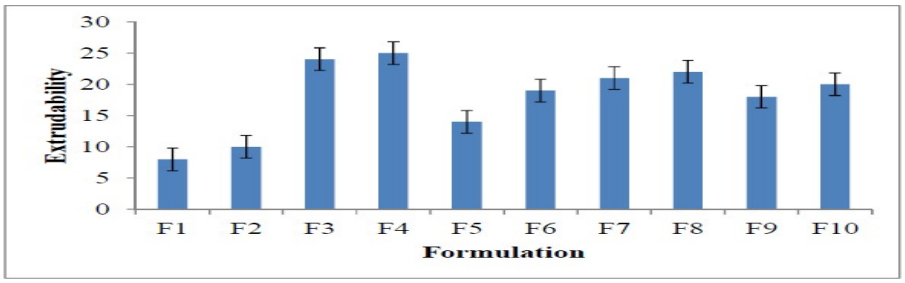

Figure 5: Extrudability of azithromycin formulations (F1 - F10)

Table 5: Drug content of azithromycin formulations (F1 - F10)

Sr no.	Formulation	Drug content
1	F1	92.23 ± 0.83
2	F2	93.42 ± 0.68
3	F3	94.62 ± 0.39
4	F4	92.15 ± 0.45
5	F5	92.74 ± 0.17
6	F6	96.93 ± 0.94
7	F7	93.36 ± 0.73
8	F8	95.61 ± 0.42
9	F9	94.52 ± 0.17
10	F10	92.69 ± 0.28

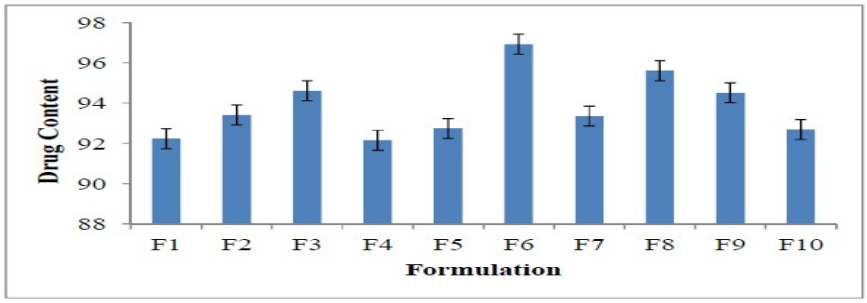

Figure 6: Drug content of azithromycin formulations (F1 - F10)

Table 6: In-vitro drug release study of azithromycin emulgel formulations (F1-F5)

Time (hr)	F1	F2	F3	F4	F5
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
1	22.04 ± 0.32	21.23 ± 2.25	20.67 ± 0.15	17.99 ± 0.39	21.30 ±0.72
2	30.32 ± 0.17	30.64 ± 1.83	30.42 ± 0.24	27.45 ±2.13	31.69 ±1.13
3	37.11 ± 1.25	39.58 ± 2.23	38.86 ± 0.93	35.48 ±0.48	40.31 ± 0.52
4	43.67 ± 1.12	46.94 ±0.57	45.69 ± 1.45	41.57 ± 1.53	48.80 ± 1.68
5	48.41 ± 0.69	52.37 ± 0.31	50.03 ± 0.65	45.16 ± 0.76	54.26 ± 0.49
6	55.28 ± 0.94	59.56 ± 0.86	55.81 ±0.82	49.04 ± 0.15	58.18 ± 0.52
7	61.73 ± 0.57	64.95 ± 0.64	59.25 ±1.33	53.92 ± 0.95	62.61 ± 1.52
8	67.13 ± 1.35	68.27 ± 0.47	62.21 ± 0.11	55.87 ± 1.32	65.24 ± 0.63

Table 7: In-vitro drug release study of azithromycin emulgel formulations (F6-F10)

Time (hr)	F6	F7	F8	F9	F10
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
1	23.07 ± 0.37	21.26 ± 0.87	20.86 ± 0.52	22.07 ± 1.48	20.98 ± 0.75
2	34.46 ± 0.58	32.35 ± 0.75	29.58 ± 0.74	33.77 ± 0.13	29.93 ± 0.63
3	43.77 ± 2.21	40.24 ± 0.56	37.27 ± 0.25	41.37 ± 2.26	38.37 ± 0.92
4	51.38 ± 0.49	49.58 ± 1.43	43.48 ±2.32	50.71 ± 0.32	46.17 ± 1.43

Time (hr)	F6	F7	F8	F9	F10
5	58.73 ± 0.83	53.74 ± 0.36	48.72 ± 0.45	54.78 ± 0.47	52.38 ± 0.48
6	64.59 ± 0.36	57.82 ± 0.24	52.63 ± 0.94	59.53 ± 0.36	57.41 ± 2.08
7	69.23 ± 0.66	60.54 ± 0.77	55.94 ±0.45	64.70 ± 2.08	61.75 ±0.13
8	72.47 ± 0.83	62.55 ± 0.84	57.63 ±1.52	66.32 ±0.93	64.89 ± 1.74

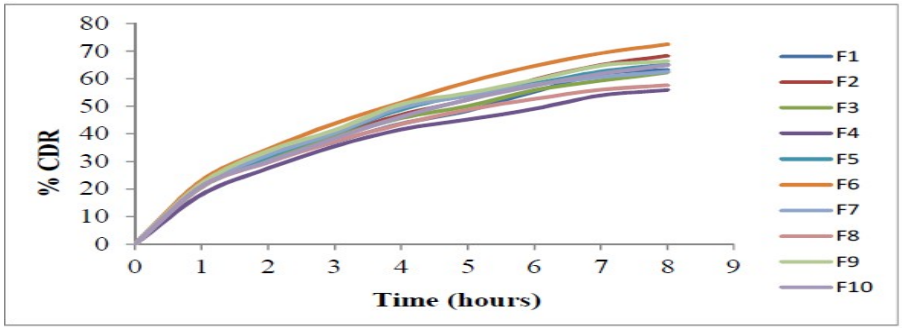

Figure 7: In vitro cumulative % drug release profile of formulation (F1-F10)

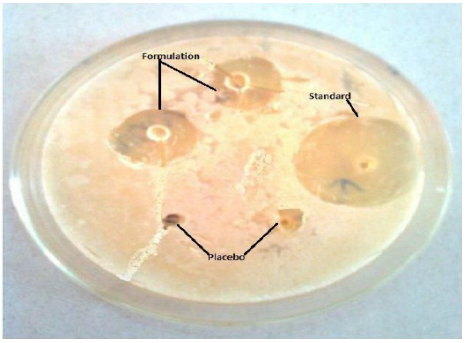

Figure 8: % Inhibition obtained in culture media with formulation (F6)

Table 8: Comparison of in vitro drug release profile with marketed formulation

Sr no.	Time (hr)	In vitro drug release	
		F6 formulation	Avindo gel (Marketed formulation)
1	0	0.00 ± 0.00	0.00 ± 0.00
2	1	23.07 ± 0.37	21.78 ± 0.73
3	2	34.46 ± 0.58	33.12 ± 0.96
4	3	43.77 ± 2.21	41.62 ± 0.23
5	4	51.38 ± 0.49	49.93 ± 1.26
6	5	58.73 ± 0.83	55.48 ± 1.08
7	6	64.59 ± 0.36	61.27 ± 1.79
8	7	69.23 ± 0.66	65.13 ± 2.14
9	8	72.47 ± 0.83	68.47 ± 0.36

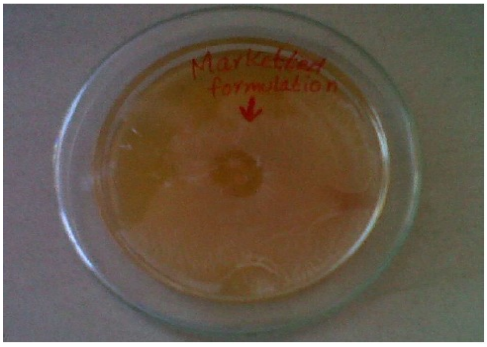

Figure 9: Showing % inhibition of marketed formulation

Table 9: Microbiological assay (comparison with marketed formulation)

Sr No.	Formulation	% Inhibition
1	F6	69.53 ± 1.23
2	Marketed Formulation	57.42 ± 1.52

Table 10: Release kinetics of azithromycin emulgel formulations (F1 –F10)

Batch code	Zero order	First order	Higuchi	Korsmeyer peppas model
	R^2	R^2	R^2	R^2
F	0.9511	0.9395	0.9799	0.9902
F	0.9421	0.9306	0.9724	0.9850
F	0.9376	0.9651	0.9670	0.9798
F	0.9270	0.9545	0.9567	0.9671
F	0.9210	0.9279	0.9341	0.9201
F	0.9862	0.9536	0.9989	0.9991
F	0.9334	0.9606	0.9700	0.9864
F	0.9217	0.9518	0.9541	0.9704
F	0.9463	0.9733	0.9779	0.9909
F1	0.9312	0.9618	0.9702	0.9887

CONCLUSION:

Azithromycin, a macrolide antibiotic, has 38% bioavailability and is used for both topical and systemic infections. This study aimed to improve its skin delivery by formulating a topical emulgel. Azithromycin solubilized easily in light liquid paraffin, making it suitable for topical application. UV spectrophotometry revealed maximum absorption at 205 nm in Acetonitrile and phosphate buffer (pH 5.5), with a high correlation coefficient (r^2 = 0.9947), confirming Beer's law applicability. FT-IR studies showed no drug-excipient interactions. Ten formulations (F1-F10) using different Carbopol polymers were evaluated for drug content, viscosity, spreadability, extrudability, pH, and diffusion. Formulation F6, with the optimal drug release (8 hrs), rheological properties, and release characteristics, was selected as the best. Carbopol 971P allowed better drug release, while Carbopol 974P enhanced viscosity. The 0.6:0.4 ratio in F6 provided the best overall performance.

In a separate study, Diltiazem HCl extended-release tablets were developed using HPMC K100M DC and Xanthan gum as rate-controlling polymers. Formulation F11 showed the best drug release (99% in pH 5.8 and 100% in hydro-alcoholic media), with stability studies confirming its release profile under accelerated conditions. F11 was chosen for sustained release up to 12 hours.

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