

Formulation and Characterization of Prednisolone Loaded Ethosomal Gel for Alleviating Joint Pain

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Abstract—Aim: Prednisolone is a potent synthetic glucocorticoid valued for its anti-inflammatory and immunosuppressive activity, but its poor aqueous solubility and the side effects linked to long-term oral or intra-articular use limit its suitability for chronic joint pain management. This study explores a Prednisolone-loaded Ethosomal gel as a non-invasive, localized alternative for topical anti-inflammatory therapy.

Methods: Prednisolone Ethosomes were prepared by the cold method using a 2³ factorial design, varying soya lecithin, ethanol and cholesterol concentration across eight formulations (F1-F8). Formulations were evaluated for vesicle size, entrapment efficiency, drug content, surface morphology, zeta potential, in-vitro drug release and release kinetics. The optimized Ethosomal dispersion was incorporated into a Carbopol 934 gel base and evaluated for physical appearance, pH, viscosity, spreadability, drug content, in-vitro release and stability. **Results:** Preformulation studies confirmed the purity, excipient-compatibility and analytical suitability of Prednisolone. Entrapment efficiency across the eight batches ranged from 61.96% to 86.94%, and drug content from 81.89% to 94.71%. Formulation F2 was identified as the optimized batch, with 79.84% entrapment efficiency, 89.62% drug content and 76.83% cumulative drug release over 12 hours, following a diffusion-controlled, anomalous-transport release mechanism (best fit: Korsmeyer-Peppas model). The corresponding Ethosomal gel showed a skin-compatible pH (6.2), suitable viscosity and spreadability, 87.62% drug content, 72.65% cumulative release over 12 hours, and satisfactory stability on refrigerated storage over 90 days.

Conclusion: The developed Prednisolone Ethosomal gel showed favourable physicochemical properties, sustained drug release and good stability, indicating its potential as a patient-friendly topical alternative for localized anti-inflammatory therapy in joint pain conditions. Further ex-vivo permeation and in-vivo anti-arthritic evaluation are warranted before clinical translation.

Index Terms—Ethosomes; Transdermal delivery; Joint pain; Carbopol gel; Sustained release; Factorial design

I. INTRODUCTION

Joint pain arising from osteoarthritis and related inflammatory joint disorders is among the most common causes of chronic disability worldwide, affecting close to 600 million people, or nearly 8% of the global population, and this number is projected to keep rising as populations age [1]. Since no cure currently exists, treatment largely revolves around controlling pain and inflammation, and corticosteroids remain among the most effective agents for this purpose. Oral corticosteroids are effective but carry the well-known burden of systemic side effects with prolonged use, while intra-articular injections, though targeted, are invasive, require clinical supervision, and provide only short-lived relief. Topical corticosteroid application would seem an obvious middle path, yet clinical trials of conventional topical corticosteroid ointments applied to painful joints have shown disappointing results, most likely because the drug simply fails to reach the joint tissue in adequate quantity through ordinary formulations [2]. This gap between the theoretical promise of topical corticosteroid therapy and its practical performance is precisely what novel skin-penetration-enhancing carriers aim to close.

Delivering a drug through the skin offers several advantages over oral dosing: it avoids first-pass hepatic metabolism, reduces dosing frequency, keeps plasma drug levels steadier, and is generally more comfortable and easier for patients to self-administer [3,4]. The persistent challenge, however, is the skin itself its outermost stratum corneum is a densely packed lipid barrier that most drug molecules cannot cross in therapeutically useful amounts without

assistance [5]. This is where penetration-enhancing vesicular nanocarriers such as Ethosomes become relevant.

Ethosomes are soft, ethanol-rich phospholipid vesicles that are structurally similar to liposomes but contain a much higher proportion of ethanol, typically 20-45% v/v. This extra ethanol does two things simultaneously: it loosens the tightly packed lipid bilayers of the stratum corneum, and it also makes the vesicle membrane itself more fluid and deformable, allowing the vesicles to squeeze through the disrupted skin layers rather than merely accumulating on the surface, as classical liposomes tend to do [6,7]. Because of this combined “Ethanol effect” and “Ethosome effect,” these carriers markedly improve the penetration of both hydrophilic and lipophilic drugs, and they are being increasingly explored as topical delivery platforms for arthritis-related therapeutics [8,9]. Recent studies, for example, have reported Ethosomal gels loaded with etodolac, a curcumin-cyclosporine combination, and betamethasone valerate, each demonstrating enhanced skin permeation and encouraging anti-inflammatory performance compared with conventional gels [10,11]. Corticosteroid-loaded Ethosomal systems in particular, such as those developed for clobetasol propionate, have shown that potent steroidal anti-inflammatory agents can be efficiently entrapped and delivered through this vesicular route.

Prednisolone is a well-established synthetic glucocorticoid with strong anti-inflammatory and immunosuppressive activity, commonly prescribed systemically for arthritis and other joint disorders. However, its poor aqueous solubility complicates conventional topical formulation, and its systemic use is limited by the same long-term corticosteroid side effects seen with other agents in this class. Loading Prednisolone into an Ethosomal carrier offers a way to address both limitations together the lipid vesicle can efficiently accommodate the lipophilic drug, while its ethanol-driven permeation-enhancing properties could help deliver the drug locally to an inflamed joint rather than distributing it throughout the body. [12,13]

With this rationale, the present study formulated Prednisolone-loaded Ethosomes using a 2^3 factorial design, identified the best-performing batch based on entrapment efficiency, particle size and release behaviour, and incorporated this optimized dispersion into a Carbopol gel base suitable for topical

application. The resulting Ethosomal gel was characterized for its physicochemical properties, in-vitro drug release, release kinetics and stability, with the broader aim of evaluating its potential as a non-invasive topical option for managing joint pain.

II. MATERIALS AND METHODS

2.1. Materials

Prednisolone was procured as a pharma-grade gift sample. Soya lecithin, ethanol, cholesterol, propylene glycol, triethanolamine and Carbopol 934 (all laboratory-reagent grade) were obtained from commercial suppliers. All other chemicals and reagents used were of analytical grade.

2.2. Preparation of Prednisolone Ethosomes

Ethosomes were prepared by the cold method. Prednisolone, soya lecithin and cholesterol were dissolved in ethanol at room temperature to form the organic phase, and distilled water was added slowly in a fine stream under continuous magnetic stirring (700-2000 rpm) to yield the Ethosomal dispersion. Sonicate prepared Ethosomal suspension for 15 mins to achieve a uniform size distribution and then stored at 4°C in refrigerator. [14]

Table 1: Formulation design by using 2^3 Factorial design

Formulation code	Run	Factor 1	Factor 2	Factor 3
		A	B	C
F1	1	-1	-1	-1
F2	2	+1	-1	-1
F3	3	-1	+1	-1
F4	4	+1	+1	-1
F5	5	-1	-1	+1
F6	6	+1	-1	+1
F7	7	-1	+1	+1
F8	8	+1	+1	+1

Factors

1. Soya lecithin: (-1) 1g, (+1) 3g
2. Ethanol: (-1) 20 ml, (+1) 40 ml
3. Cholesterol: (-1) 0.5g, (+1) 1.5g

Table 2: Formulation table for the preparation of Ethosomes (F1-F8)

F. Code	Drug (%w/v)	Soyal lecithin (%w/v)	Ethanol (%v/v)	Cholesterol (%w/v)	Propylene glycol (%v/v)	Water (ml)
F 1	0.5	1	20	0.5	20	q.s
F 2	0.5	3	20	0.5	20	q.s
F 3	0.5	1	40	0.5	20	q.s
F 4	0.5	3	40	0.5	20	q.s
F 5	0.5	1	20	1.5	20	q.s
F 6	0.5	3	20	1.5	20	q.s
F 7	0.5	1	40	1.5	20	q.s
F 8	0.5	3	40	1.5	20	q.s

2.5. Preparation of Ethosomal gel

A 1% Carbopol 934 gel base was prepared by dispersing the polymer in hot distilled water containing glycerin and methyl paraben, followed by neutralization with triethanolamine to obtain a transparent gel. The optimized Ethosomal dispersion was incorporated into this gel base under gentle mechanical stirring [15].

Table 3: Formulation table for the preparation of Prednisolone Ethosomal gel

SI. No.	Ingredients (mg)	EG
1	Optimized Ethosomal suspension	20 ml
2	Carbopol 934	1%W/W
3	Glycerin	5% W/W
4	Methyl Paraben	0.1% W/W
5	Triethanolamine	q.s
6	Distilled water	q.s to 10gm

III. Evaluation of Ethosomes

3.1 Reformulation Studies

Table 4: Melting point report of Prednisolone.

Reported	Method	Results observed			
230-240°C	Thiele's tube method	Trail 1	Trail 2	Trail 3	Average
		232 °C	234 °C	232 °C	232.66 °C
	DSC	239.45°C			

Table 5: Data for standard calibration curve of Prednisolone

Absorbance at λ_{max} 243 nm				
Conc.	T-1	T-2	T-3	AVG $\pm$ SD n = 3
0	0	0	0	0
3	0.172	0.175	0.182	0.176 $\pm$ 0.005
6	0.339	0.326	0.332	0.332 $\pm$ 0.006
9	0.498	0.494	0.497	0.496 $\pm$ 0.002
12	0.648	0.653	0.658	0.653 $\pm$ 0.005
15	0.802	0.798	0.805	0.801 $\pm$ 0.003
18	0.936	0.938	0.941	0.938 $\pm$ 0.002

Medium: Phosphate buffer pH 6.8 and Methanol (80:20)

Standard stock: 1000 μ g/ml

Working stock: 100 μ g/ml

λ_{max} : 243nm

Regression coefficient (r^2): 0.998

Slope(n): 0.053

Table 6: FTIR Comparison: Prednisolone pure drug vs Physical mixture

Vibration	Standard Range (cm ⁻¹)	Prednisolone (cm ⁻¹)	Physical Mixture (cm ⁻¹)	Short Interpretation
O-H stretching	3300–3400	3345	3313	O-H peak Retained with slight shift
C-H stretching	2850–2950	2951	2974	C-H peak retained with slight shift
C=O stretching	1700–1715	1709	—	Carbonyl peak not clearly resolved
Conjugated C=O	1650–1665	1662	1652	Peak retained with minor shift
C=C stretching	1600–1620	1612	—	Peak not clearly observed
CH ₂ bending	1380–1450	1446	1379	Band shifted and retained

C–O stretching	1050–1250	1097, 1035	1040	C–O band retained
=C–H bending	800–900	824, 893	836, 925	Fingerprint bands retained with shifts

3.2 Evaluation of Ethosomes

Table 7: Vesicle size analysis for formulation F1-F8

Range	F1	F2	F3	F4	F5	F6	F7	F8
10 - 20	8	12	9	6	3	2	8	7
20 - 40	48	32	35	40	32	28	27	45
40 - 60	43	25	40	23	27	42	41	39
60 - 80	27	40	28	45	46	34	46	37
80 - 100	24	41	38	36	42	44	28	22

Table 8: %Entrapment Efficiency of Ethosomes

F. code	%EE ± SD
F1	74.41 ± 1.28
F2	79.84 ± 1.16
F3	69.2 ± 1.34
F4	61.96 ± 1.09
F5	82.79 ± 1.21
F6	86.94 ± 0.97
F7	64.30 ± 0.81
F8	77.66 ± 0.88

Table 9: %Drug content of Ethosomes

F. code	%DC
F1	86.41
F2	89.62
F3	81.89
F4	84.52
F5	91.88
F6	94.71
F7	85.47
F8	87.92

Table 10: In-vitro drug release study of formulation F1-F8

Time (hrs)	Cumulative drug release (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.5	16.30	17.96	23.62	21.20	10.26	8.23	22.79	13.05
1	25.58	26.18	34.86	30.79	17.21	13.06	35.69	24.60

2	39.77	36.45	46.49	43.54	27.92	22.26	51.84	37.35
4	57.66	53.66	60.23	62.79	44.07	36.75	69.73	58.41
6	69.66	59.92	73.88	74.56	58.26	46.64	74.86	65.05
8	76.07	67.54	84.22	79.85	64.53	59.77	79.24	71.47
12	83.62	76.83	91.62	87.54	75.62	72.90	89.51	80.90

Table 11: Data for different kinetic model

F. CODE	ZERO ORDER	FIRST ORDER	HIGUCHI	PEPPAS MODEL	
				R ²	'n' Value
F1	0.852	0.970	0.981	0.982	0.527
F2	0.855	0.963	0.986	0.991	0.563
F3	0.846	0.990	0.984	0.993	0.528
F4	0.829	0.972	0.976	0.987	0.561
F5	0.917	0.987	0.989	0.991	0.642
F6	0.964	0.997	0.983	0.998	0.700
F7	0.777	0.958	0.954	0.963	0.522
F8	0.848	0.963	0.976	0.990	0.584

Table 12: Results of stability studies

Parameters	Duration in days at 4°C		
	0	45	90
%DC	89.62	89.05	88.43
%CDR	76.83	75.46	74.38

IV. EVALUATION OF ETHOSOMAL GEL

Table 13: Physical appearance of Ethosomal gel

F. Code	Physical Appearance		
	Colour	Odour	Texture
EG1	Creamy	Characteristic alcoholic odour	Smooth, non-greasy

Table 14: pH, Viscosity & Spreadability of Ethosomal gel

F.Code	pH	Viscosity(cps)	Spreadability gm*cm /sec	%Drug content
EG1	6.2	4563±2.38	11.56±0.63	87.62±0.06

Table 15: In-vitro drug release study of Ethosomal gel

Time (hrs)	%Cumulative drug release
0	0
0.5	12.09
1	28.63
2	39.97
4	46.25
6	57.96
8	63.34
12	72.65

Table 15: Results of stability studies of Ethosomal gel

Parameters	Duration in days at 4°C		
	0	45	90
%DC	87.62	87.07	86.15
%CDR	72.65	73.06	73.89

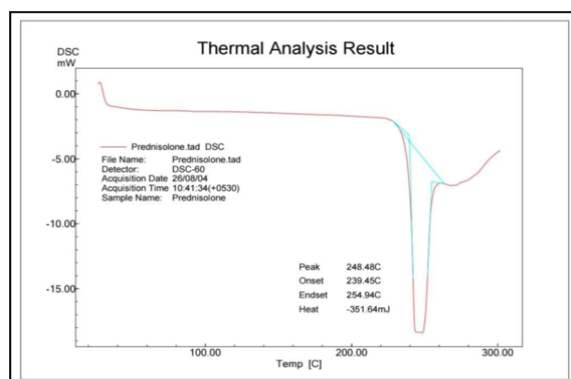


Fig.1: DSC graph of pure Prednisolone.

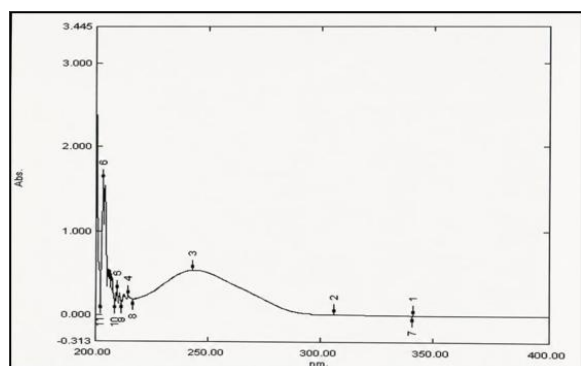


Fig.2: UV-spectra of Prednisolone at 10µg/ml concentration

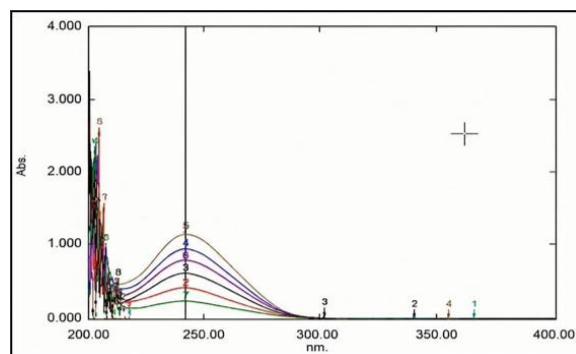


Fig.3: UV spectrum of Prednisolone at different concentration of 0-18 µg/ml

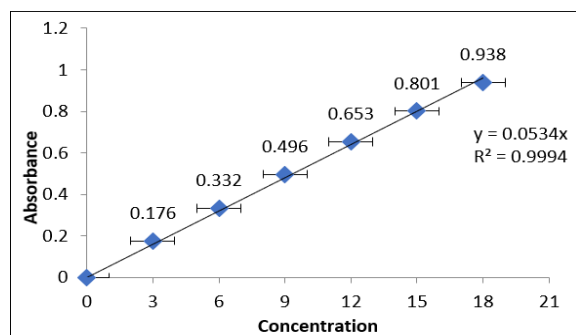


Fig.4: Plot of standard calibration curve of Prednisolone

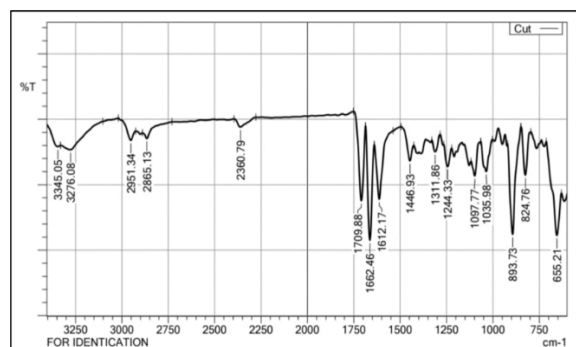


Fig.5: FTIR Spectra of Prednisolone

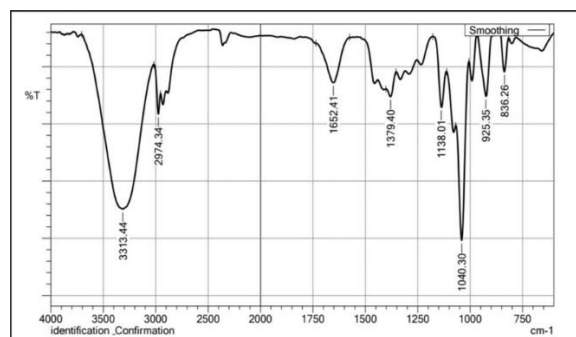


Fig.6: FTIR Spectra of Prednisolone and physical mixture

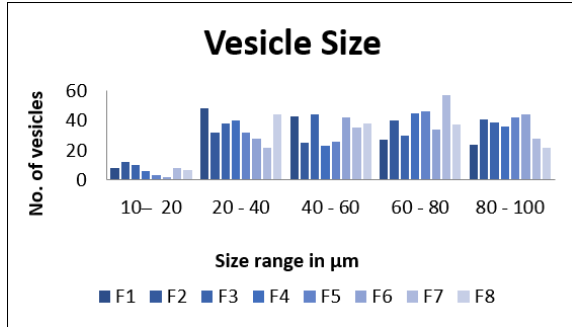


Fig. 7: Vesicle size analysis for formulation F1-F8

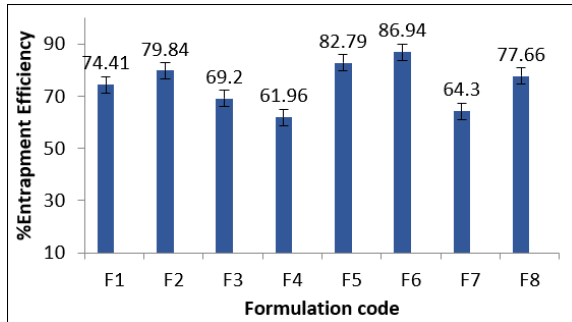


Fig.8: %Entrapment Efficiency of formulation F1-F8

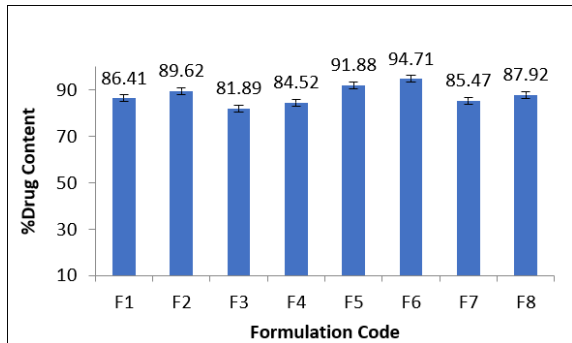


Fig.9: Drug content of Ethosomal formulation F1-F8

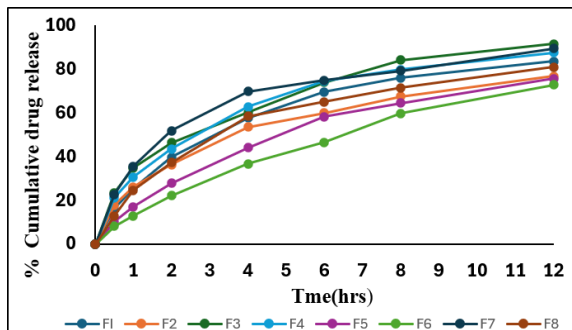


Fig.10: %Cumulative drug release of F1-F8

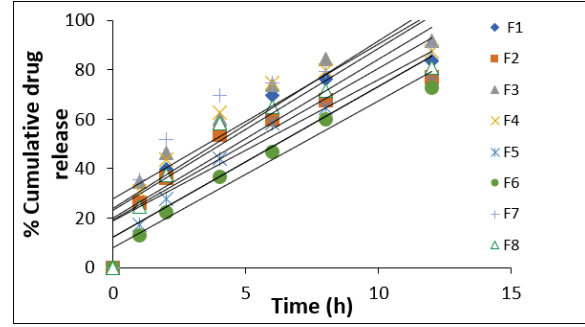


Fig.11: Zero order kinetics profile of Formulation F1-F8

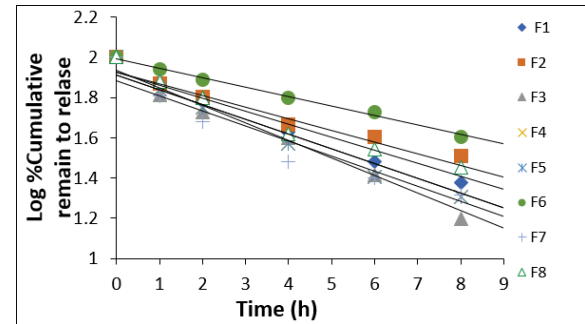


Fig.12: First order kinetics profile of Formulation F1-F8

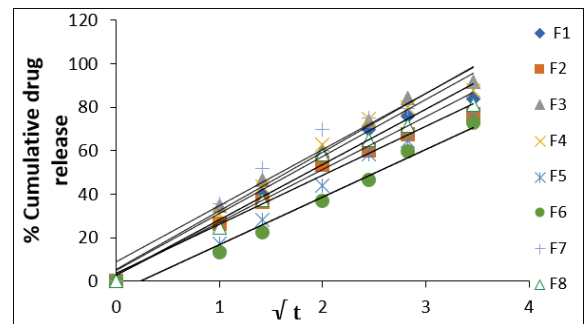


Fig.13: Higuchi release profile of Formulation F1-F8

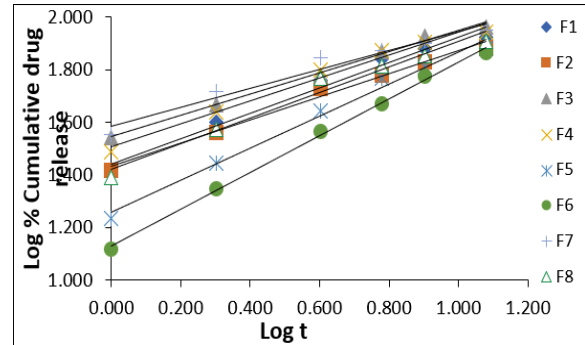


Fig.14: Peppas release profile of Formulation F1-F

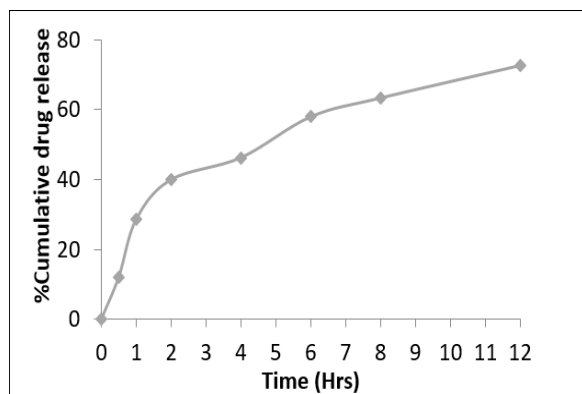


Fig.15: In-Vitro drug release of Ethosomal gel

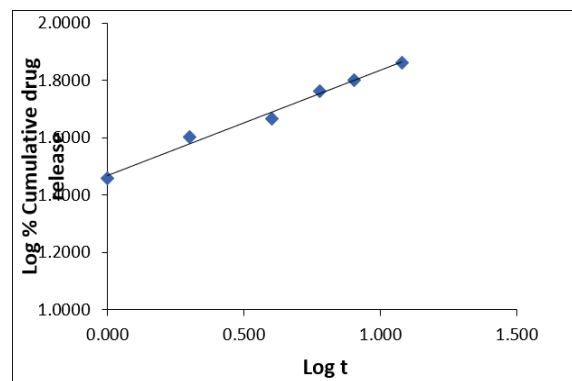


Fig.19: Peppas release profile of Formulation EG

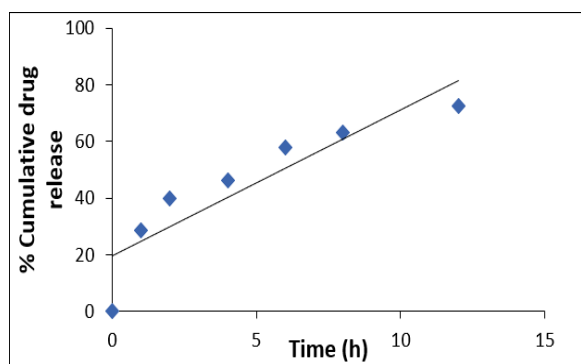


Fig. 16: Zero order kinetics profile of Formulation EG

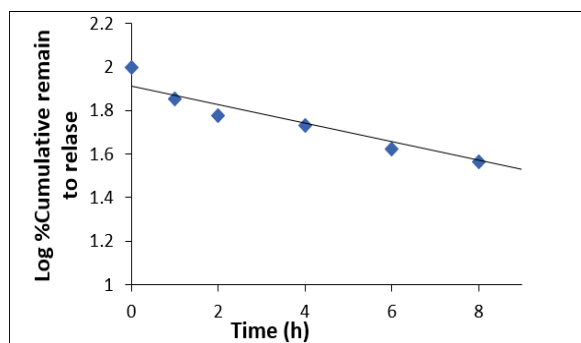


Fig.17: First order kinetics profile of Formulation EG

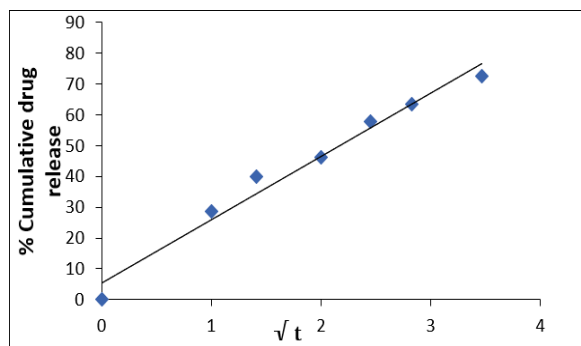


Fig.18: Higuchi release profile of Formulation EG

V. DISCUSSION

The reformulation studies supported the suitability of Prednisolone and the selected excipients for formulation development. The prepared Ethosomal formulations exhibited differences in entrapment efficiency, drug content and drug release, indicating that formulation composition influenced their performance. The optimized F2 formulation showed satisfactory entrapment efficiency (79.84%) and prolonged drug release (76.83% at 12 hrs). Incorporation into Carbopol 934 gel further moderated drug release, with 72.65% release at 12 hrs, while maintaining acceptable pH, viscosity, spreadability and stability. The release profile followed an anomalous (non-Fickian) mechanism, suggesting contributions from both diffusion and matrix-related processes. These findings indicate that the developed formulation has potential as a topical Prednisolone delivery system; however, further ex-vivo permeation and in-vivo studies are necessary to establish its skin penetration, therapeutic effectiveness and safety.

VI. CONCLUSION

The study successfully developed a Prednisolone-loaded Ethosomal gel using Carbopol 934 for topical delivery. The optimized F2 formulation demonstrated satisfactory entrapment efficiency, drug content, physicochemical properties, prolonged drug release, and stability. The gel exhibited controlled release with an anomalous (non-Fickian) mechanism, indicating its potential for prolonged local delivery of Prednisolone in inflammatory joint conditions. Further in-vivo studies are warranted to confirm its therapeutic efficacy and safety.

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