Original Article

INTERNATIONAL JOURNAL OF EXPERIMENTAL AND BIOMEDICAL RESEARCH

Published by Pharma Springs Publication Journal Home Page: https://pharmasprings.com/ijebr

Formulation and evaluation of dipotassium clorazepate topical gels

B. Leela Gayathri*[1], T. Pavani[2], P. Ram Prathap[2], V. Ashok kumar[2], B. Divya sree[2], M. Teja Divya[2], T. Siva Prasad[2]

[1]Department of Pharmaceutics, Saastra College of Pharmaceutical Education & Research, Near Varigonda Jwalamukhi Temple, Muthukur Raod, Kakupalli, Nellore-524 311 Andhra Pradesh, India.

[2]Saastra College of Pharmaceutical Education & Research, Near Varigonda Jwalamukhi Temple, Muthukur Raod, Kakupalli, Nellore-524 311 Andhra Pradesh, India.

Article History:

Received on: 24 Oct 2024
Revised on: 04 Jan 2025
Accepted on: 19 Feb 2025

Keywords:

Dipotassium clorazepate,
Gel,
HPMC,
Sodium alginate,
DMSO,
Invitro study.

Abstract

This investigation aimed to formulate and evaluate a topical gel containing dipotassium clorazepate. To achieve the desired drug release, a topical gel containing dipotassium clorazepate was synthesized using the dispersion method. Three different gelling agents, carbopol 934p, HPMC K100, and sodium alginate, were used in four different ratios. Twelve gel formulations of dipotassium clorazepate that had been prepared were assessed for stability, drug release kinetics, drug diffusion, pH measurement, viscosity, and drug content. Drug-polymer compatibility studies were done using the Fourier Transform Infra Red (FTIR) spectrophotometer. The absence of extraneous interactions among excipients was established using FTIR. F4 released 98.53% of the drug after the eighth hour and was regarded as the best formulation. Thus, formulations containing Carbopol outperformed other formulations. Even after 6 months, the stability investigation revealed no significant change in the optimum formulation's drug content analysis or in-vitro dissolution study. The stability data were analyzed using the "Stab" software, and the anticipated shelf life term for the best formulation was 12.14 months.

∗Corresponding Author

Name: B. Leela Gayathri
Phone: +91 7675803603
Email: leelagayathri93@gmail.com

eISSN: 2583-5254
DOI: https://doi.org/10.26452/ijebr.v4i1.719

Production and hosted by
Pharmasprings.com

INTRODUCTION

When applied to undamaged skin, transdermal drug delivery systems' discrete, self-contained dose forms allow the drug to enter the systemic circulation at a controlled rate. Currently, drug distribution is the most used method. Although this has the noteworthy benefit of being simple to administer, it also has some serious disadvantages, such as poor bioavailability because of hepatic metabolism (first pass) and a propensity to cause abrupt spikes in blood levels that require high and/or frequent dosage, which can be expensive and inconvenient. The name "gels" refers to a large

category of semisolid materials with various properties, including reasonably complex gelatin slabs, suspensions of colloidal clays, and specific greases [1]. Two interpenetrating phases—the gelling agent and a fluid component can be thought of as making up a gel. Semisolid gels are either big organic molecules interspersed with liquid or suspensions of small inorganic particles. The first scenario involves the inorganic particles, such as bentonite, forming a three-dimensional structure inside the gel that resembles a "house of cards." The inorganic particles in this system are insoluble and are only distributed throughout the continuous phase, making it a real two-phase system. Generally speaking, if the melting point increases by 100ºC, the maximum drug flux through the skin should fall by 10, and if the MW increases by 100Da, it should decrease by a factor of 5. The highly ordered crystalline lipid lamellae are widely acknowledged to be crucial for the stratum corneum's barrier functions. To improve drug transport across intact skin or to boost the driving power for drug penetration through this skin barrier, numerous methods have been developed to disturb and weaken highly ordered intercellular lipids [2].

MATERIALS AND METHODS

MATERIALS

The gift sample Clorazipate Dipotassium is from Sigma-Aldrich Pvt Ltd, Bangalore, and other polymer mixtures such as Hydroxy Propyl Methyl Cellulose, Carbopol 934p, Sodium Alginate, Triethanol amine, PEG 400, Propylene Alcohol, Ethanol, DMSO [3].

METHODS

Pre-Formulation Study

Formulation scientists must first characterize novel pharmacological compounds' physical, chemical, and mechanical characteristics to create stable, secure, and effective dosage forms. This process is known as preformulation [4].

FT-IR Studies

The preformulation research was completed before the dosage forms were developed. IR spectrum investigations are primarily used to identify chemicals qualitatively, whether in their pure form or combined with polymers and excipients. They also serve as a tool for determining the nature of chemical interactions. IR is associated with covalent bonding. Hence, the spectra can provide intricate details about the composition of molecules [5]. Comparisons between the compounds' spectra and the pure compound were done to prove this conclusion. Based on the foregoing comments, it appears that infrared data can be used to verify the drug's identity and identify drug-carrier interactions. A Thermo Nicolet was used to record FTIR spectra in Japan. Utilizing 16 scans and a resolution of 4 cm−1 in the 400–4000 cm−1 range. Samples were diluted with KBr mixing powder and then pressed to create self-supporting discs. Liquid sample compositions were examined to form a thin layer between two KBr discs [6].

Table 1 Formulation data of Clorazepate Dipotassium gels

Formulation code	Drug (mg)	Carbopol 934 (mg)	HPMC K4 (mg)	Sodium Alginate (mg)	Permeation enhancer (Ethanol: PG)	PEG
F1	400	110	-	-	10%	4%
F2	400	130	-	-	10%	4%
F3	400	150	-	-	10%	4%
F4	400	170	-	-	10%	4%
F5	400	-	110	-	10%	4%
F6	400	-	130	-	10%	4%
F7	400	-	150	-	10%	4%
F8	400	-	170	-	10%	4%
F9	400	-	-	110	10%	4%
F10	400	-	-	130	10%	4%
F11	400	-	-	150	10%	4%
F12	400	-	-	170	10%	4%

Formulation of Topical gel

Principle

Clorazipate Dipotassium topical gel was prepared using the dispersion method. This process involved continuously stirring the polymers in distilled water to distribute them. To create a gel, warm the colloidal viscous dispersion. A penetration booster was added after dissolving the medication in an appropriate solvent and churning it into the gel. To maintain the drug release, gelling agents such as carbopol 934p, HPMC K100, and sodium alginate were employed. As permeation enhancers, ethanol and propylene glycol were used. PEG 400 was used as a soothing agent. Water and DMSO were used as solvents. Triethanolamine was used as a pH adjustifying agent [7].

Method of Formulation

A topical gel containing dipotassium chlorazipate was made using the dispersion process. This approach involved dissolving weighed amounts of polymers, such as HPMC K100, sodium alginate, and carbopol 934, in a known volume of distilled water (Solution-A). The polymer solution was allowed to fully dissolve before being set aside for 24 hours to allow for swelling. A predetermined amount of DMSO was used to dissolve an accurately weighed amount of chlorazipate dipotassium. A predetermined amount of polyethylene glycol was added to this solution and dissolved (Solution-B) [8]. With a high-speed magnetic stirrer operating at 500 rpm, solutions A and B were mixed entirely while carefully preventing air from becoming trapped. Ultimately, adding ethanol and propylene glycol produced a uniform gel dispersion.
After the gel was created, the pH was increased to 6.8 by adding enough triethanolamine. With water, the gel's final weight was generated to a maximum of 1 gram [9].

Evaluation of Topical Gel

The drug content, in vitro release tests, and physicochemical characteristics of the formulated gel were assessed.

Clarity

Each formulation's clarity was evaluated visually against a black-and-white backdrop. The findings were graded as turbid: +, clear: ++, and very clear (glassy): +++.

Measurement of pH

With a digital pH meter, the pH of the crisoprodol gel formulation was ascertained. 100ml of distilled water was used to dissolve 1 gram of gel. Each formulation's pH was measured three times, and the average results were calculated.

Homogeneity

After the gels were stored in the container, their appearance and the presence of any aggregate were visually inspected to ensure homogeneity in all generated gels [10].

Spreadability

Glass plate apparatus, which was appropriately adjusted in the laboratory and employed for the investigation, was used to measure spreadability. Spreadability was evaluated based on the gel's "slip" and drag properties. By measuring the spreading diameter of one gram of gel between two glass plates after one minute, the spreadability of the formulations was ascertained 48 hours after preparation. The upper plate's bulk was standardized at 125 grams. A 1 kg weight was positioned on each slide for five minutes to release trapped air and create a consistent gel layer between them. The excess gel around the edges was scraped off. After that, an 80-gram pull was applied to the top plate. Shivhare UD (2009) The formula below was used to calculate the spread ability **[**11].

$$S = \frac{ML}{T}$$

Viscosity

Using a brook field viscometer (DV II Plus), the viscosity of the produced gels was determined. Initially, the spindle was submerged in the gel until the spindle's notch made contact with the gel's surface. In the investigation, 100 g of gel I and gel II were utilized each. At a regulated temperature of 25±20 rpm, spindle no. 4 was chosen for both recipes based on the gel's viscosity. The spindle was turned at fifty revolutions per minute, and the dial was read until two identical readings were obtained. The gel's viscosity was observed [12].

Drug content

The drug concentration of the gel was ascertained by dissolving a precisely weighed one-gram gel in a 6.8 pH phosphate buffer. Absorbance was measured using a UV visible spectrometer at 240 nm following an appropriate dilution. The standard curve's slope was used to calculate the drug content. Drug content = (concentration× volume taken) × conversion factor.

***In vitro* diffusion studies**

An egg membrane was used to conduct the in vitro diffusion analysis of the produced gel in a Franz diffusion cell. After adding 14 milliliters of phosphate buffer to the receptor compartment, 1 gram of chlorazipate dipotassium gel was evenly distributed across the membrane. The donor compartment was connected to the receptor compartment, and 37±0.50C was the constant temperature. At preset intervals, externally driven Teflon-coated magnetic bars agitated the solution on the receptor side. Five milliliters of the solution were pipetted out of the receptor compartment at specific times for one, two, three, four, five, and six hours. They were promptly replaced with a fresh five-millilitre phosphate buffer. The cumulative percentage of medication release was computed vs time [13].

Kinetic study

Pharmacokinetics of Drug Release Mechanism

Zero-order kinetics

This formula can represent the dissolution of drugs from pharmaceutical dosage forms that do not break down and release the drug gradually, as long as the area stays the same and no equilibrium circumstances are created [14].

$$Q_t = Q_o + K_o \, \mathrm{t}$$

First order kinetics

The first-order release kinetics were examined by fitting the release rate data to the following equation.

$$\mathrm{Log}\, Q_t = \log Q_o + \frac{\mathrm{K\,t}}{2.303}$$

Higuchi model

Higuchi created several theoretical models to investigate the release of medications incorporated into semisolids or solid matrices yet are water-soluble or low-soluble. For drug particles distributed in a homogeneous matrix acting as the diffusion media, mathematical formulas were obtained; the equation is

$$Q_t = K_H . t_{\frac{1}{2}}$$

Korsemeyer and Peppas Release model

The release rate data are fitted to the following equation to study this model.

$$\mathrm{F} = \frac{M_t}{M} = K . t_n$$

A linear plot of drug release against time will have an intercept equal to log K and a slope of n.

STABILITY STUDIES

According to the ICH guidelines for the Evaluation of stability data, extrapolation should be considered when suggesting a shelf life for a drug product or an additional testing period for a drug substance that exceeds the time frame covered by the available data from the stability under the long-term storage condition. The ANCOVA statistical modeling, probability tests, and linear regression were used to analyze the data from numerous batches.

The data could be analyzed for quantitative qualities, with 90% of the label claim serving as the lower acceptance criteria and 110% as the upper acceptance criteria. It is assumed that time and residuals have a linear relationship. The upper and lower acceptance criteria of the label claimed to intersect with the two-sided 95% confidence intervals of the regression line for residuals (%) relative to the original amount) of a drug product. The shelf life was the next shortest. The difference in the slopes and intercepts of the regression lines was tested using analysis of covariance (ANCOVA) [15].

RESULTS AND DISCUSSION

Preformulation Studies

FTIR spectral analysis was used to characterize the drug and polymers to look for any physical or chemical changes to the drug's properties. The prominent peaks of the chlorazipate dipotassium were unchanged in the spectra of the drug polymer mixture, indicating no interference in the functional groups, according to the data.

Table 2 Physical Evaluation Method of Drug

Description	Method Evaluated	0th day	1st week	2nd week
Clorazipate Dipotassium	Physical Evaluation	Crystalline white powder	Crystalline white powder	Crystalline white powder

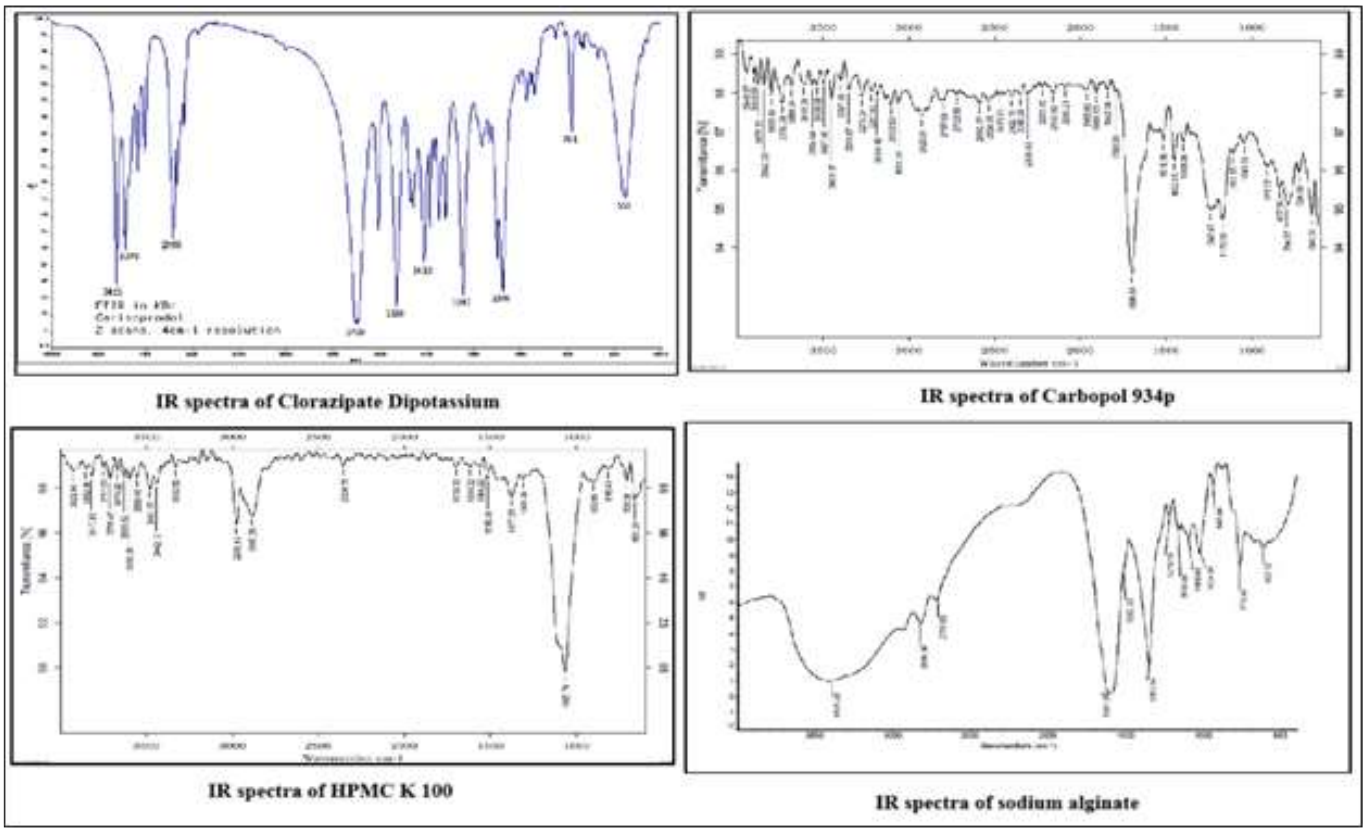

Figure 1 FT – IR Spectrums of Drug and Polymers

Table 3 IR Interpretations for Pure Drug and Polymers

Functional groups	Clorazipate Dipotassium		Carbopol 934p		HPMC K 100		sodium alginate	
	Character-istic peak	Observed peak	Character-istic peak	Observed peak	Character-istic peak	Observed peak	Character-istic peak	Observed peak
O-H (stretch, free)	3500	3451	3700	3793.38	3700-3500	3711.45	3500	3404.04
C-H alkyl stretch	~2850	2968	~2950	2923.91	~2850	2887.29	~2850	2830.98
C=O stretch	1810-1775	1700	1775	1700.79	1775	1601.98	1775	1601.98
N-H bend	1640-1500	1528	~1250	1242.47	~2250	2354.11	1640-1500	1513.53
CH_3 bend	~1375	1247	~1375	1398.34	~1375	1377.28	~1375	1219.19
C-H bend (meta)	~880	816.43	~880	837.36	~880	816.43	~880	775.460

Evaluation of Gels

Clarity

Gels containing carbopol were seen to be transparent and sparkling, while gels containing sodium alginate and HPMC were discovered to be translucent and white viscous. There were no particles present in any of the gels.

pH

All the gel formulations produced (F1 through F12) had pH values between 6.3 and 6.9.

Homogeneity

Every developed sample (F1–F12) exhibited good homogeneity and no lumps. The developed plans were far more open and lucid.

Spreadability

The spreadability rating reflects how easily the gel spreads with a small amount of shear. The gel spreadability ranged from 23.82 to 19.09 g.cm/sec.

Viscosity measurement

The viscosity of variously prepared Clorazipate Dipotassium gels was tested with a Brookfield viscometer. The rheological behavior of all prepared gel systems was investigated. The solid-to-liquid fraction ratio determines consistency in a gel system. The viscosity of several prepared gels ranged from 9354 to 9425 centipoises.

Drug content

The percentage drug concentration of all manufactured gel formulations ranged from 99.92

Table 4 Values of evaluation parameters of developed gel

Formulation code	Clarity	pH	Homogeneity	Spread ability (g.cm/sec)	Viscosity (cps)	% Drug Content
F1	++	6.3	Good	23.82	9354	99.92
F2	++	6.2	Good	24.51	9657	99.54
F3	+++	6.3	Good	27.32	9436	102.31
F4	++	6.4	Good	29.87	8562	98.57
F5	+++	6.1	Good	19.78	8491	97.83
F6	++	6.5	Good	21.57	8722	98.04
F7	++	6.3	Good	23.42	8482	97.96
F8	+	6.6	Good	19.09	9425	102.65
F9	+	6.9	Good	26.47	8678	99.81
F10	++	6.2	Good	19.09	9425	97.16
F11	+	6.4	Good	23.79	8926	98.28
F12	+	6.9	Good	17.23	8863	99.67

Kinetic Models Data Analysis

Table 5 Release Order kinetics data for Formulation F4

Zero-order		First order	Higuchi's data		Korsmeyer-Peppas data	
Time (h)	% CDR	Log % CD Remaining	SQR Time	% CDR	Log Time	Log % CDR
1	21.06	1.8972971	1	21.06	0	1.3234584
2	35.76	1.8078055	1.414	35.76	0.301	1.5533975
3	44.56	1.7438232	1.732	44.56	0.477	1.6489452
4	56.24	1.6410773	2	56.24	0.602	1.7500453
5	66.22	1.5286596	2.236	66.22	0.698	1.8209892
6	78.9	1.3242825	2.449	78.9	0.778	1.897077
7	89.34	1.0277572	2.645	89.34	0.845	1.9510459
8	98.53	0.1673173	2.828	98.53	0.903	1.9935685

to 102.65%. The % drug content of formulations was found to be adequate. As a result, the methods used for gel compositions were determined to be appropriate.

In vitro drug diffusion studies

In vitro, drug release studies were conducted using the Franz diffusion cell dissolution test apparatus. These release studies showed that the following was the order of release:

Carbopol 934p Series (F1-F4): F4 gives Maximum Release.

HPMC K 100 Series (F5- F8): F8 gives Maximum Release. Sodium Alginate Series (F9-F12): F12 gives Maximum Release.

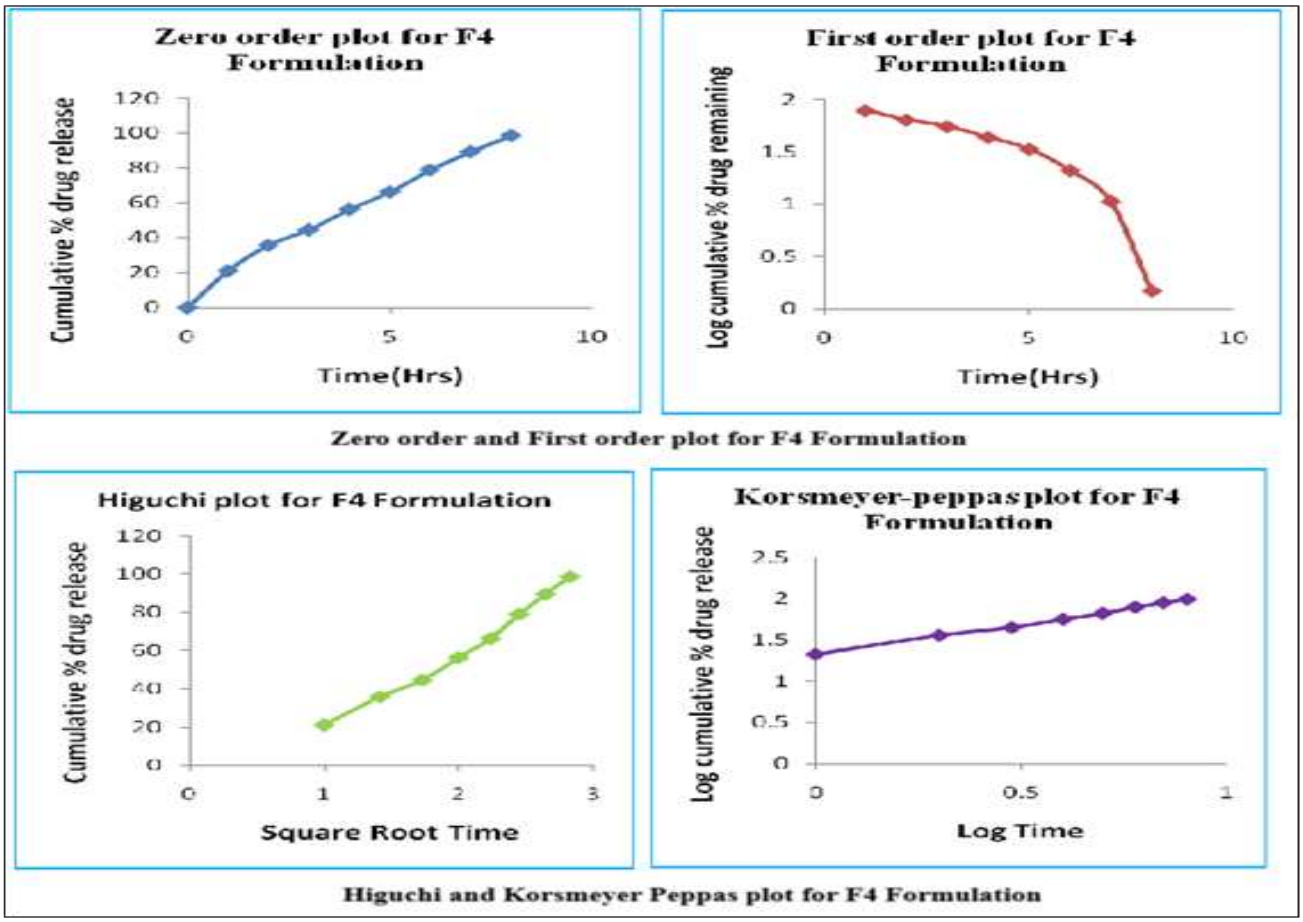

Figure 2 Release Order Kinetics for Formulation F4

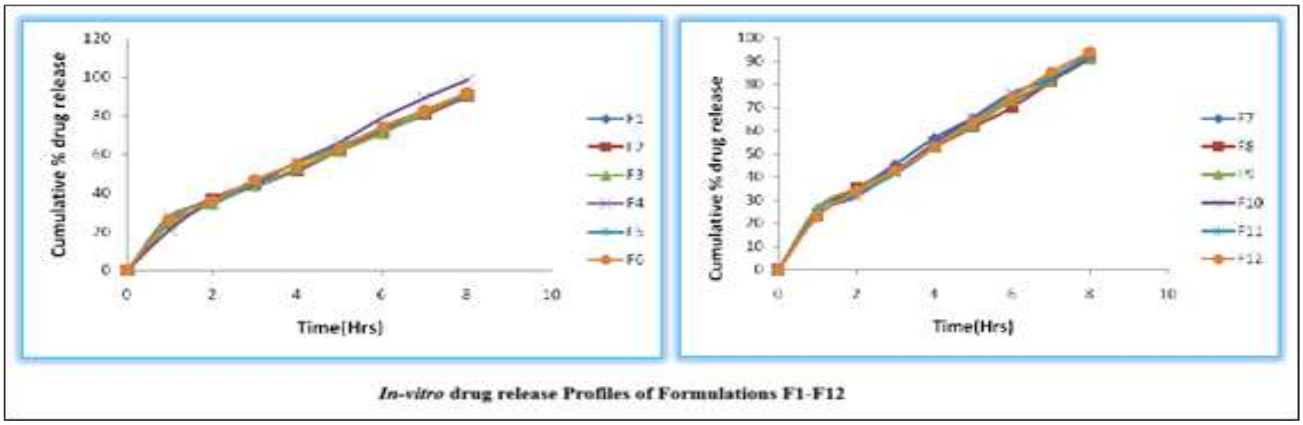

Figure 3 In-vitro drug release of Formulations F1-F12

Table 6 Kinetics of drug release in vitro Data for formulations F1–F12

Formulation code	Correlation Coefficient values (R^2)				Diffusion Exponent value (n)
	Zero-order	First order	Higuchi	Korsmeyer-Peppas	
F1	0.9708	0.9240	0.9747	0.9781	0.5902
F2	0.9700	0.9135	0.9781	0.9881	0.6021
F3	0.9795	0.9076	0.9805	0.9910	0.6439
F4	0.9883	0.7922	0.9858	0.9968	0.7380
F5	0.9689	0.9326	0.9802	0.9763	0.5911
F6	0.9711	0.9154	0.9833	0.9885	0.6052
F7	0.9720	0.9093	0.9861	0.9892	0.6206
F8	0.9799	0.8730	0.9769	0.9916	0.6546
F9	0.9743	0.9139	0.9737	0.9768	0.6036
F10	0.9807	0.9349	0.9827	0.9830	0.6759
F11	0.9850	0.9115	0.9772	0.9828	0.6806
F12	0.9865	0.8933	0.9790	0.9901	0.6884

Table 7 Comparing the calculated Assay of the optimal formulation F4

Time in months	Observed Assay (%) Mean ± SD	Calculated Assay (%) Mean ± SD
0 Month	100.35±0.7	99.91±0.45
1 Month	98.31±0.3	99.36±0.72
2 Month	97.58±0.4	98.74±0.67
3 Month	96.78±0.5	98.12±0.76
4 Month	96.42±0.3	97.52±0.72
5 Month	95.92±0.3	96.91±0.72
6 Month	95.57±0.3	96.27±0.72

Table 8 Comparing the calculated Assay of the optimal formulation F4

Cumulative % drug release of the best formulation			
Standard	After 2 months	After 4 months	After 6 months
22.07	21.57	21.12	18.37
34.77	34.27	35.81	33.09
43.55	43.09	44.62	43.87
55.23	54.77	56.27	53.55
65.21	64.73	64.25	63.55
77.91	77.43	76.95	76.23
88.35	87.85	87.37	86.65
97.54	97.04	96.55	95.84

The Korsemeyer-Peppas formulas for F1, F2, F3, F5, F6, F7, F8, F9, F10, F11, and F12 were used, and the correlation coefficient R2 was 0.9781, 0.9881, 0.9910, 0.9763, 0.9885, 0.9892, 0.9916, 0.9768, 0.9830, 0.9828, and 0.9901, in that order. F4 formulation shows a diffusion release mechanism followed by non-fiction transport, and it adheres to both the Zero order and Korsemeyer-Peppas models.

Stability Studies

"R-Stab" software was used to analyze the stability data. **Table 7** provides the calculated and observed values.

In **Figure 4**, the anticipated shelf life is shown. **Table 8** presents the time versus cumulative % drug profile data. The pattern of release is displayed in **Figure 5**.

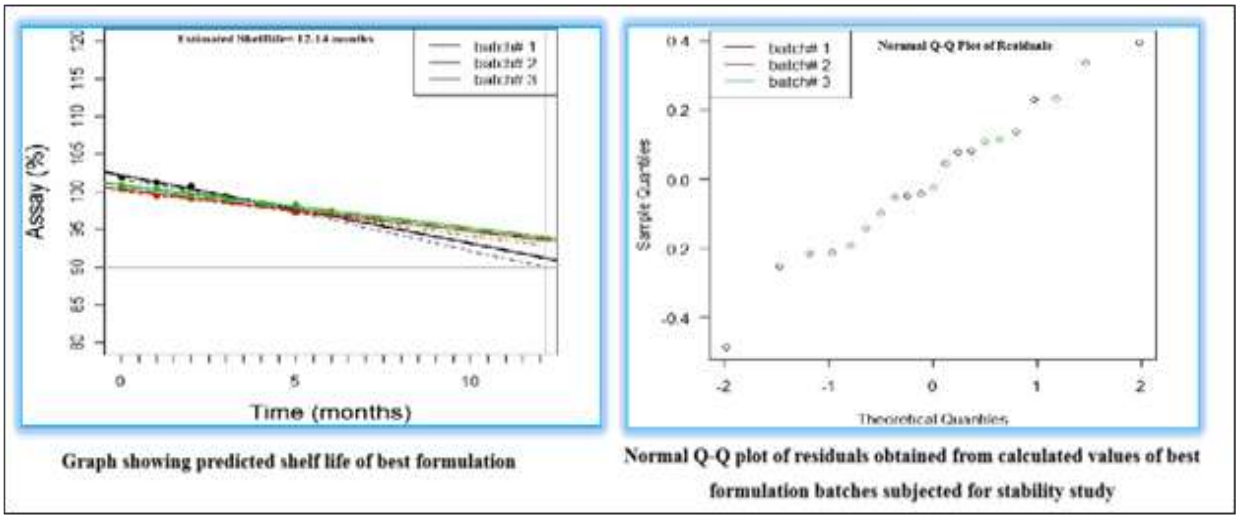

Figure 4 Comparing the calculated Assay of the optimal formulation F4

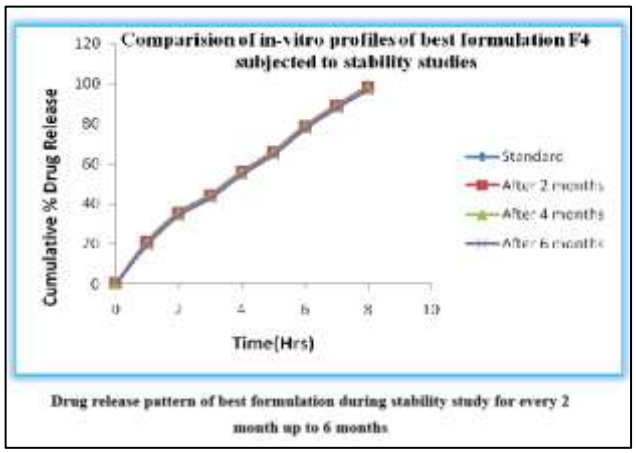

Figure 5 Stability study's dissolving results for optimal formulation F4

The overall results from various assessment investigations were made, including assessments of prepared formulations, drug-polymer interactions, and in vitro drug release tests. The optimal formulation was the focus of additional stability research based on the results obtained. Over six months, the stability research was carried out by ICH requirements under three accelerated temperature and humidity conditions: 25°C/60%RH, 40°C/70%RH, and 60°C/80%RH.

ANCOVA statistical modeling, probability tests, and linear regression were used to analyze the data from numerous batches. These data were suitable for quantitative attribute analysis, with upper and lower acceptance standards of 90% and 110% of the label claim, respectively. While there was no significant variation in the slope (-0.549) across the batches, there was a substantial difference in the intercepts (Y= 100.17, 100.26, and 100.84). It was discovered that the anticipated shelf life was 12.14 months. After six months, it was noted that the dissolution profile had not changed significantly. According to the stability analysis, the optimal formulation might remain stable for 12.14 months.

CONCLUSION

From the current study, it can be concluded that designing and developing a transdermal drug delivery system requires careful drug and polymer selection. The FT-IR investigations indicate that the medication was compatible with the polymer chosen, namely carbopol 934p, HPMC K 100, and sodium alginate. It was found that the three polymers' different concentrations affected the drug's viscosity, spreadability, and release. Gel formulations with sodium alginate, HPMC K 100, and carbopol 934p have demonstrated good stability and homogeneity. However, the Carbopol 934p (F4) based gel was the formula of choice since it has shown the highest percentage of drug release and good rheological properties. *An in vitro release study has demonstrated that increased polymer concentration improves* drug release. The best formulation has shown stability conditions within the limit.

ACKNOWLEDGEMENT:

We want to express our profound appreciation to our management principal of Saastra College of Pharmaceutical Education & Research, Near Varigonda Jwalamukhi Temple, Muthukur Raod,

Kakupalli, Nellore, for their support, without which it would not have been possible to complete our dissertation.

Author Contribution

All authors made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for the work. They were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Funding Support

The authors declare that they have no funding for this study.

REFERENCES

[1] Hussain A, Majid Khan G, Jan S U, Shah S, Shah K, Akhlaq M, Rahim N, Nawaz A, Wahab A, et al. Effect of olive oil on transdermal penetration of flurbiprofen from topical gel as an enhancer, Pakistan Journal of Pharmaceutical Sciences. 2012:25(2):365-369.

[2] Samy Ahmed A M, Ghorab M M, Gad S, Mazyed E, et al. Formulation And Evaluation Of Different Transdermal Drug Delivery Systems Of Ketoprofen. International Journal of Pharmacy and Pharmaceutical Sciences. 2013;5(2):600-607.

[3] Mekkawy A, Fathy M, El-Shanawany S, et al. Formulation and In vitro Evaluation of Fluconazole Topical Gels. British Journal of Pharmaceutical Research. 2013:3(3): 293-313.

[4] Negi A, Sharma N, Singh M F, et al. Formulation and Evaluation of a Herbal Anti-Inflammatory Gel Containing Eupatorium Leaves Extract. Journal of Pharmacognosy and Phytochemistry. 2012:1(2):112-117.

[5] Abrar B, Anis S, Tanu B, Singh S, et al. Formulation and in–vitro Evaluation of NSAID'S gel, International Journal of Current Pharmaceutical Research. 2012:4(3):56-58.

[6] Misal G, Dixit G, Gulkari V, et al. Formulation and Evaluation of herbal gel. Indian Journal of Natural Products and Resources. 2012:3(4):501-505.

[7] Shingade G, et al. Development of nabumetone topical gels: effect of Formulation variables on the release of nabumetone, World Journal of Pharmaceutical research. 2012:1(3):776-785.

[8] Grassi M, Grassi G, et al. Mathematical modeling and controlled drug delivery: Matrix systems. Current Drug Delivery, 2005:2(1):97-116.

[9] Idson B, Jack L, et al. Semisolids. In:Lachman L, Liberman HA and Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Varghese Publishing House.1990;534-563.

[10] Pathan I B, Mallikarjuna Setty C, et al. Chemical Penetration Enhancers for Transdermal Drug Delivery Systems. Tropical Journal of Pharmaceutical Research. 2009;8(2):173-179.

[11] Patel J, Patel B, Banwait H, Parmar K, Patel M, et al. Formulation And Evaluation of Topical Aceclofenac Gel Using Different Gelling Agents, International Journal of Drug Development & Research. 2010:3(1):15-164.

[12] Baboota S, Shakeel F, Kohli K, et al. Formulation and Evaluation of once-a-day transdermal gels of diclofenac diethylamine. Methods and findings in experimental and clinical pharmacology. 2006;28:109Y114.

[13] Modi J D, Patel J K, et al. Nanoemulsion-Based Gel Formulation of Aceclofenac for Topical Delivery, International Journal of Pharmacy and Pharmaceutical Science Research. 2011:1(1):6-12.

[14] Madan J, Singh R, et al. Formulation and Evaluation of Aloe vera topical gels. International Journal of Pharmaceutical Sciences. 2012:2-2(2):551-555.

[15] Sreenivasa Reddy M, Mutalik S, Veerabhadra Rao G, et al. Preparation and Evaluation of minoxidil gels for topical application in alopecia. Indian Journal of Pharmaceutical Sciences. 2006;68(4):432-436.