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FORMULATION AND EVALUATION OF ALLOPURINOL AND DICLOFENAC SODIUM EMULGEL FOR THE MANAGEMENT OF GOUT

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Abstract

BACKGROUND: Emulgels offer a promising approach to delivering poorly water-soluble drugs through a gelled system. When gels and emulsions are combined, they form an emulgel a hybrid that merges the properties and benefits of both emulsions (either oil-in-water or water-in-oil) and gels, created by incorporating a gelling agent. This dual advantage makes emulates an attractive medium for transdermal drug delivery. **OBJECTIVE:** The objective of this study was to develop an emulgel formulation containing Allopurinol, an anti-gout medication, and Diclofenac Sodium, a nonsteroidal anti-inflammatory drug (NSAID). The goal was to enhance the penetration and systemic availability of these drugs while reducing the severe gastric distress commonly associated with their oral administration. The emulgel was formulated using carbopol 940 as the gelling agent and propylene glycol as the penetration enhancer. The emulsion was prepared and then incorporated into the gel base. **RESULT:** In our study of eight emulgel formulations (EG1 to EG8), EG7 emerged as the best. It showed the highest drug content (91.05%) and drug release (89.75%), good spreadability (27.33 gm.cm/s), and extrudability (16 g/cm²). Despite a slightly lower pH (6.3), it remained suitable for topical use. With a viscosity of 5998.7 mPas, EG7 ensures both ease of application and retention on the skin, making it the optimal formulation. **CONCLUSION:** This study developed an emulgel containing Allopurinol and Diclofenac Sodium to enhance drug penetration and minimize gastric distress from oral use. Among eight formulations, EG7 was the best, with high drug content (91.05%) and release (89.75%), good spreadability (27.33 gm.cm/s), and extrudability (16 g/cm²). Despite a slightly lower pH (6.3), it is suitable for topical use, and its viscosity (5998.7 mPas) ensures easy application and good skin retention. EG7 shows promise for effective transdermal delivery of these drugs, offering an alternative to oral administration.

Keywords: Emulgel, Gout, Allopurinol, Hydrophobic Drugs, Diclofenac Sodium.

INTRODUCTION

One or more joints that are swollen and painful are referred to as arthritis. Joint stiffness and pain are the main symptoms of arthritis, and they get worse with age. There are two primary forms of arthritis: rheumatoid arthritis and osteoarthritis [1]. High blood uric acid levels can cause inflammatory arthritis, also known as "gout," in certain persons. Abrupt and intense bouts of pain, swelling, and soreness are caused by needle-like crystals that grow in the joints as a result of elevated blood levels of uric acid. Warmth and redness also appear.[2] Gout is the best type of inflammatory arthritis. Emulgels are emulsions that are mixed with a gelling agent to create a gel, either of the water-in-oil or oil-in-water kind. Drugs that are hydrophobic or weakly soluble in water are shown to work better in emulsified gels, which are stable formulations.[3]

They have a high patient acceptance rate because they combine the benefits of topical medication administration with the qualities of both gel and emulsions.[4] The main goal of the study was to create an emulgel that included the goudal allopurinol, an inhibitor of the xanthine oxidase enzyme, and the NSAID diclofenac sodium to improve medication absorption and penetration as well as therapeutic efficacy. The created formulations attempt to minimize the severe adverse effects induced by oral traditional preparations of the offered medications, while also addressing decreases in uric acid levels and gout-related pain and edema.[5]

MATERIALS AND METHODS

Materials:

Alembic Pharmaceutical Pvt. Ltd. of Vadodara, Gujarat, India, gave away Febuxostat. A free sample of diclofenac sodium was received by Sun Pharmaceuticals Pvt. Ltd. in Dewas, M.P., India. The suppliers of Span 20, Tween 20, and Carbopol 934 were Loba Chemicals Pvt. Ltd. in Mumbai, India. Analytical-grade chemicals and solvents were utilized for the production of the formulation.[6]

Software

Design Expert 13.0: Micro Math Inc., USA was used to formulate topical emulgel.

Experimental design

Initially, the primary variables and their concentrations were determined by preliminary testing. Three variables were chosen as the independent factors out of all the excipients: mentha oil, carbopol 940, and liquid paraffin. The drug release and viscosity were the chosen dependent parameters. The concentrations of the independent variables (listed in Table 2) were chosen following a preliminary screening process.[7, 8]

Preformulation studies

Preformulation studies are essential steps in the development of pharmaceutical formulations. They involve the characterization of the physical, chemical, and mechanical properties of drug substances to aid in the design of optimal drug delivery systems. Here, we present the preformulation studies of two active pharmaceutical ingredients (APIs): allopurinol and diclofenac sodium.[9, 10]

Pseudo-ternary phase diagrams

Based on solubility studies, a light liquid paraffin was chosen as the oil phase. Tween-80 and Span 80 were selected as the surfactant and cosurfactant, respectively, with distilled water as the aqueous phase.[11] The surfactant and cosurfactant (Smix) were mixed at various mass ratios to study the phase diagrams. Oil and Smix were combined in ratios from 1:9 to 9:1, creating sixteen different mixtures.[12] Pseudo-ternary phase diagrams were developed using aqueous titration, with the physical state of the nanoemulsion noted on the diagram. As shown in Fig 1, This detailed approach ensured a comprehensive study of the phase boundaries and the formation of stable, transparent, and easily flowable o/w nanoemulsions. [13]

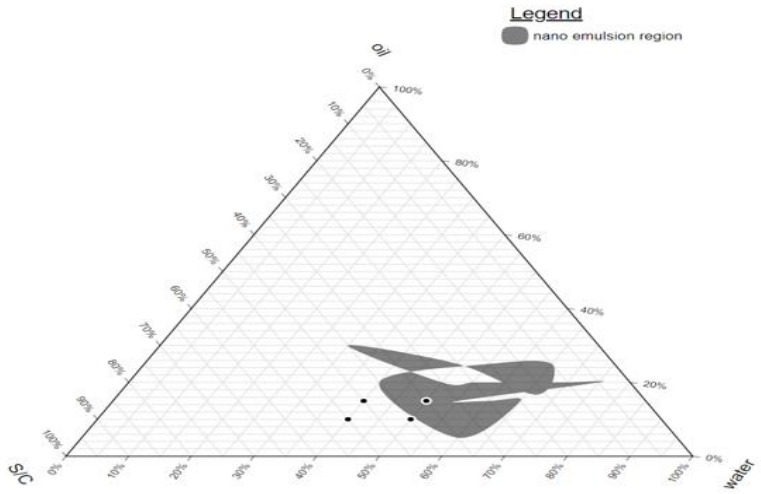


Fig 1: Pseudo ternary phase diagram

Preparation of allopurinol and diclofenac sodium-loaded nanoemulsion

Different formulas were selected from the nanoemulsion region from each phase diagram constructed. The oily phase of the emulsion was prepared by mixing 1 milliliter of span 80 with 7.5 milliliters of light liquid paraffin.[14] The aqueous part of the emulsion was prepared by taking tween 80 and thoroughly mixing it with water. Keepers After adding methyl and propylparaben to propylene glycol and stirring to create a solution, medications (dicofenac sodium and allopurinol) were combined and dissolved in ethanol. The resulting solutions were combined with the aqueous phase and heated separately to 70–80°C. [15] The oily phase was added to the aqueous phase and thoroughly mixed after both solutions had been heated. As seen in Fig.2,

Emulgel's preparation

A gelling agent in varying amounts was used to make the formulations in each batch. The emulgel's gel phase was created by dissolving carbopol 940 in water and stirring it continuously. Triethanolamine (TEA) was used to alter the pH of the mixture. The obtained emulsion was then gradually stirred into the gel to create an emulgel.[16, 17] As seen in Fig.2, Physical assessment tests were performed on all topical emulgels, as indicated in Table.

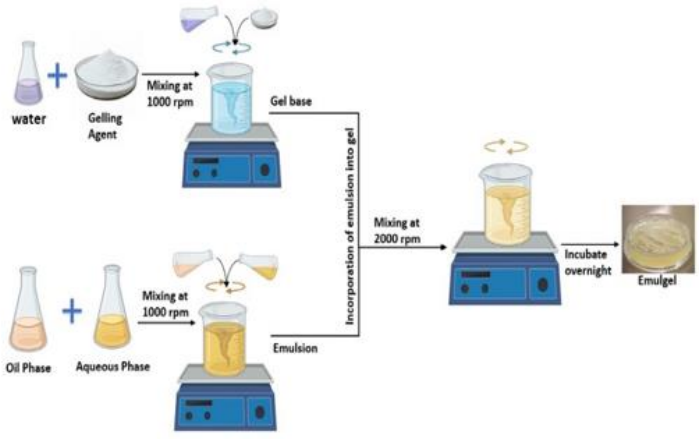


Fig 2: Method of preparation of emulgel.

Optimization of formulation

To ascertain how each independent variable impacted the dependent ones, researchers employed one of 23 distinct factorial designs, contingent upon the results of the pilot testing. [18, 19] Tables No. 1 and 2 list the independent variables and dependent factors that were employed in the design. Using this design, eight trial batches were produced. Table 3

Table 1: List of dependent and independent variables in 2^3 factorial designs

A. Independent factors	A	Concentration of Liquidparaffin
	B	Concentration ofCarbopol 940
	C	Concentration of Mentha oil
B. Dependent Factors	Y_1	Viscosity
	Y_2	Drug release

Table 2: Independent variables and their concentrations used for formulations

Sr. No.	Independent variables	Coded levels	
		-1	+1
1	The concentration of Liquid paraffin (ml)	5	7.5
2	Concentration of Carbopol 940 (gm)	0.5	1.5
3	Concentration of Mentha oil (ml)	2	4

Table 3: DOE formulation Batches

Contents	EG1	EG2	EG3	EG4	EG5	EG6	EG7	EG8
Allopurinol (mg)	300	300	300	300	300	300	300	300
Diclofenac sodium (mg)	200	200	200	200	200	200	200	200
Liquid Paraffin (ml)	5	5	7.5	5	7.5	5	7.5	7.5
Carbopol 940 (gm)	1.5	0.5	0.5	1.5	1.5	0.5	0.5	1.5
Tween 80 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propylene glycol (ml)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Methyl paraben (gm)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Propyl paraben (gm)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Span 80 (ml)	1	1	1	1	1	1	1	1
Mentha oil (ml)	4	2	4	2	4	2	4	2
Ethanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s	q.s.
Distilled water (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Physical evaluation of topical emulgel

Visual inspections were performed to ensure a high-quality standard in terms of color, finish, and uniformity. [20]

Appearance/color

Physical analysis of the prepared topical emulgel was observed.

pH

The pH of the formulation's one percent aqueous solution was determined by employing a temperature- and pH-calibrated digital meter. [21]

Viscosity

A Brookfield viscometer with spindle 50 and 50 rpm was used to measure the resultant emulgel's viscosity three times at room temperature.

Spreadability

For the experiment, two glass slides of conventional size were employed. Between the two slides, an emulgel was put to create a sandwich that measured 60 mm. After cleaning the slide surfaces of excess emulgel, the slides were securely affixed to a stand. The top slide was given a 20 g weight, and the reaction time to the weight's contact on it—60 mm of movement—was timed. The experiment was run three times to determine the meantime, and spreadability was determined using a predetermined formula. [22, 23]

Spreadability = (Weight × Length) / Time

Extrudability

The standard collapsible aluminum tubes were filled with the formulas (10 gm), and the ends were sealed shut. The weight of each tube was accurately noted. The tubes were then clamped between two glass slides to seal them. A 500 g weight was placed over the slides, and the cap was removed. The amount that was extruded was gathered, and weighed, and a percentage was calculated to determine the formulation's extrudability. Extrudability values of more than 90% were regarded as exceptional, more than 80% as good, and more than 70% as fair. [24, 25]

In-vitro diffusion study

Franz diffusion cells with a 25 ml cell capacity were employed in the drug release investigations. A single section of the cellophane membrane received a homogenous application of 1 gram of the formulation. A pH 7.4 Phosphate Buffer solution was placed inside the receptor chamber and swirled with a magnetic stirrer. At appropriate intervals, fresh buffer solutions were added to 1.0 ml aliquots that were collected. A UV-visible spectrophotometer operating at 227 and 237 nm was used to ascertain the drug concentration in the acquired samples following the proper dilution process. This made it possible to evaluate the drug's efflux across the membrane about time. [26, 27]

Release Kinetics

There are several theories and mathematical models that explain how medications are extracted from pharmaceutical formulations. By creating kinetic models from in vitro drug release data, one may look at the underlying process of drug release. [28, 29]

Stability study

A four-week physical stability test was conducted on the emulgel at two different temperatures and relative humidity levels (250°C±20°C, 60% RH ± 5% and 400°C±20°C, 75 % RH ± 5%). As seen in Tables 10 and 11. [30, 31]

RESULT

Physical evaluation

The prepared emulgels had a glossy look, a smooth, uniform texture, and a white, thick, creamy consistency. as indicated in Table number 4.

Table 4: Physical evaluation of formulated emulgel

Batch code	Color	Grittiness	Phase separation
EG1	Off-White	-	None
EG2	White	-	None
EG3	Off-White	-	None
EG4	White	-	None
EG5	Off-White	-	None
EG6	White	-	None
EG7	White	-	None
EG8	White	-	None

Drug content uniformity

The drug content of the formulated Emulgel was estimated spectrophotometrically at 227 and 237 nm. shown in Fig. 3

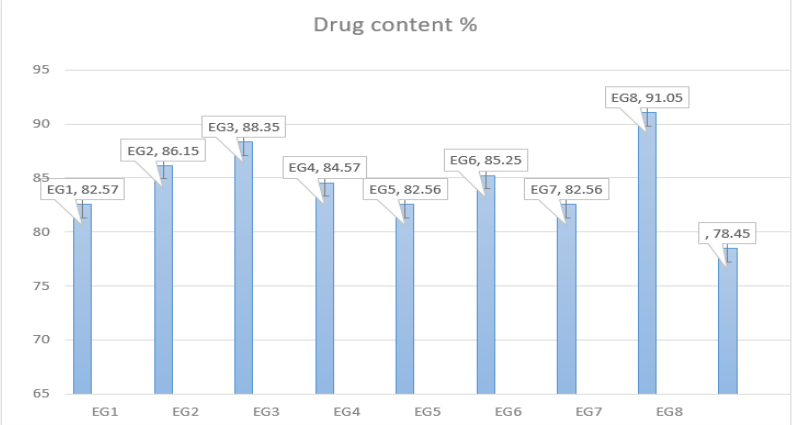


Fig 3: Drug content %

Spreadability

Every formulation was put through a spreadability test. According to the spreadability, a little shear can readily spread the Emulgel. As the concentration of the polymer increases, the emulgel's spreadability diminishes. Spreadability is crucial because it demonstrates how emulgel behaves when it is taken out of the tube. All formulations were confirmed to have spreadability within the limitations. as seen in Figure 4.

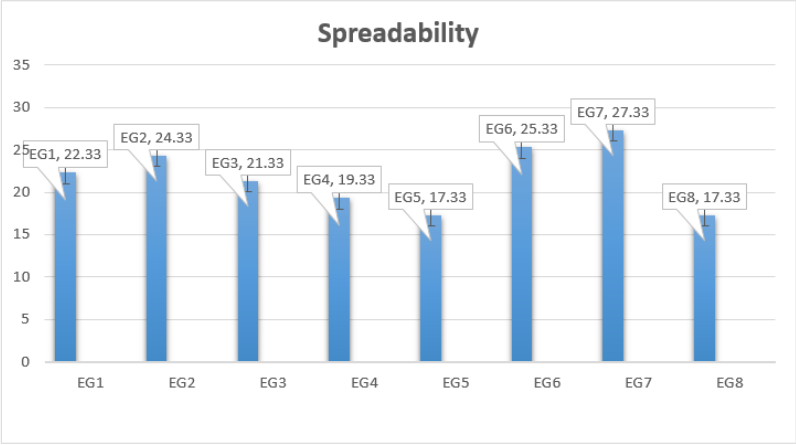


Fig 4: Spreadability of emulgel

pH

A digital pH meter was used to examine the pH of the prepared formulations. pH of each prepared batch was examined in triplicates and average values were calculated. As seen in fig.5

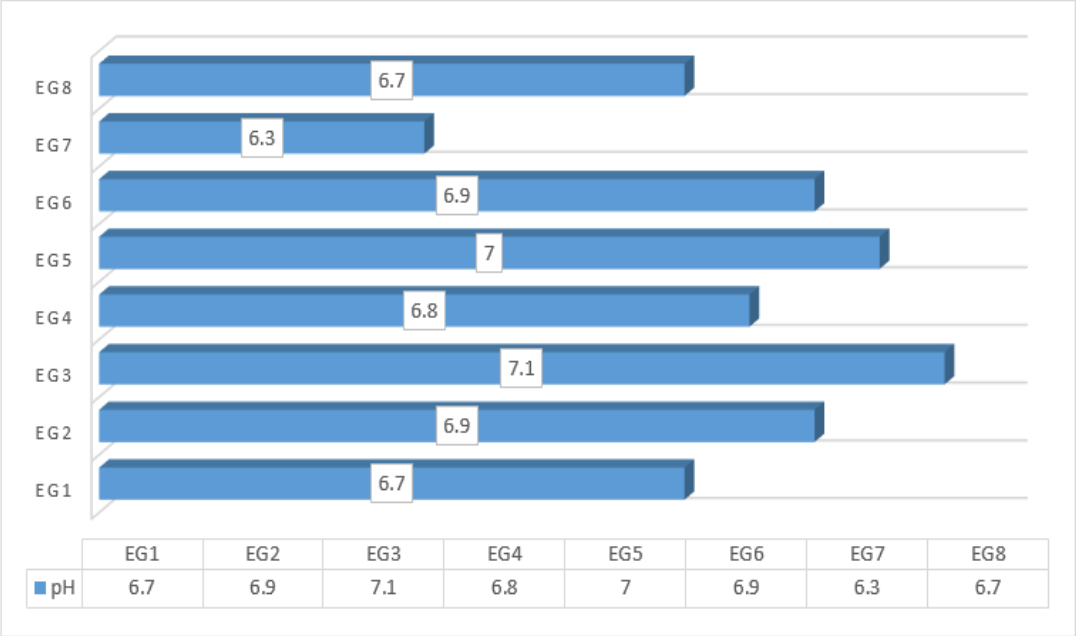


Fig. 5: pH of formulated emulgel

Transmission electron microscopy. – The nanoemulsion appeared dark and with bright surroundings and a positive image (Fig. 6). The droplet size ranged between 19 and 78 nm and was in agreement with the droplet size distribution measured using photon correlation spectroscopy

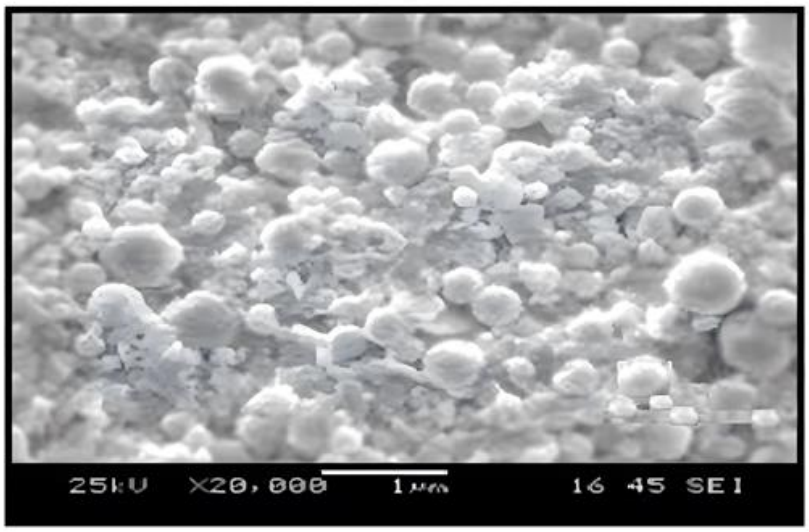


Fig 6: Transmission electron microscopic positive image of nanoemulsion.

Table 5: Factorial design variables with their responses

Formulation	Factor1 (A)	Factor2 (B)	Factor 3 (C)	pH	Viscosity (m.Pas)	Spradability (gm.cm/sa)	Extrudability (g/cm²)	Drug content(%)	Drug Release(%)
EG1	-1	+1	-1	6.7± 0.02	16204.5± 1.2	22.33 ± 1.2	16.1± 1.2	82.57 ± 1.2	62.35 ± 1.25
EG2	-1	-1	-1	6.9± 0.03	8570.5± 1.2	24.33 ± 2.1	17± 2.1	86.15 ± 1.1	77.54 ± 2.75
EG3	+1	-1	+1	7.1± 0.03	8347.7± 1.2	21.33 ± 3.2	16± 3.2	88.35 ± 2.2	87.52 ± 3.10
EG4	-1	+1	-1	6.8± 0.02	11300.2± 1.2	19.33 ± 3.7	13± 3.7	84.57 ± 1.7	67.56 ± 6.65
EG5	+1	+1	-1	7.0± 0.03	15506.3± 1.2	17.33 ± 2.5	12.5± 2.5	85.25 ± 2.5	71.27 ± 2.45
EG6	-1	-1	+1	6.9± 0.02	6201.4± 1.2	25.33 ± 2.1	15± 2.1	82.56 ± 2.7	68.75 ± 3.45
EG7	+1	-1	-1	6.3± 0.02	5998.7± 1.2	27.33 ± 3.7	16± 3.7	91.05 ± 1.5	89.75 ± 3.50
EG8	+1	+1	-1	6.7± 0.02	15750.5± 1.2	17.33 ± 1.5	13± 1.5	78.45 ± 2.1	62.42 ± 3.47

± Mean value with a standard deviation of three replicates

Table 6: Viscosity ANOVA analysis

Source	Sum of Squares	df	Mean Square	F-value	p-value	Source
Model	1.145	3	3.817	9.24	0.0285	significant
A-Liquid paraffin	1.383	1	1.383	0.3350	0.5937	
B-Carbopol 934	1.098	1	1.098	26.60	0.0067	
C-Mentha oil	3.288	1	3.288	0.7963	0.4226	
Residual	1.652	4	4.129			
Cor Total	1.310	7				

These can indicate a problem with your data or model, or they might be a symptom of a large block effect. For every empirical model, confirmation runs should be carried out. Adeq Precision is used to calculate the signal-to-noise ratio. Ideally, the ratio should be greater than 4. You have a sufficiently strong signal with a ratio of 6.629. This model may be used to explore the design space.

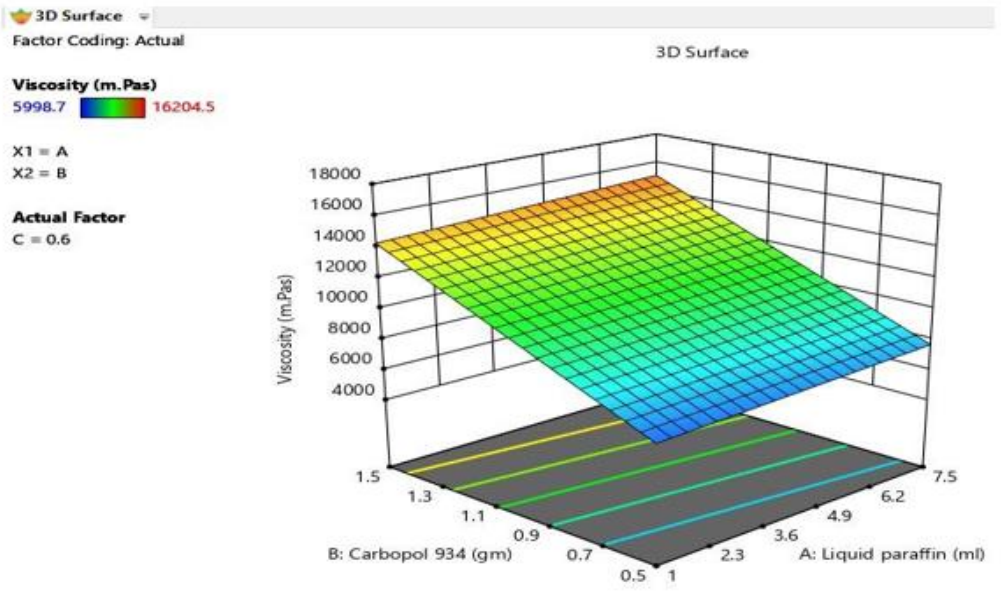
Table 7: R^2 value for viscosity Fit Statistics

Std. Dev.	2031.94	**R^2**	0.8740
Mean	10984.98	**Adjusted R^2**	0.7794
C.V. %	18.50	**Predicted R^2**	0.4958
		Adeq Precision	6.6290

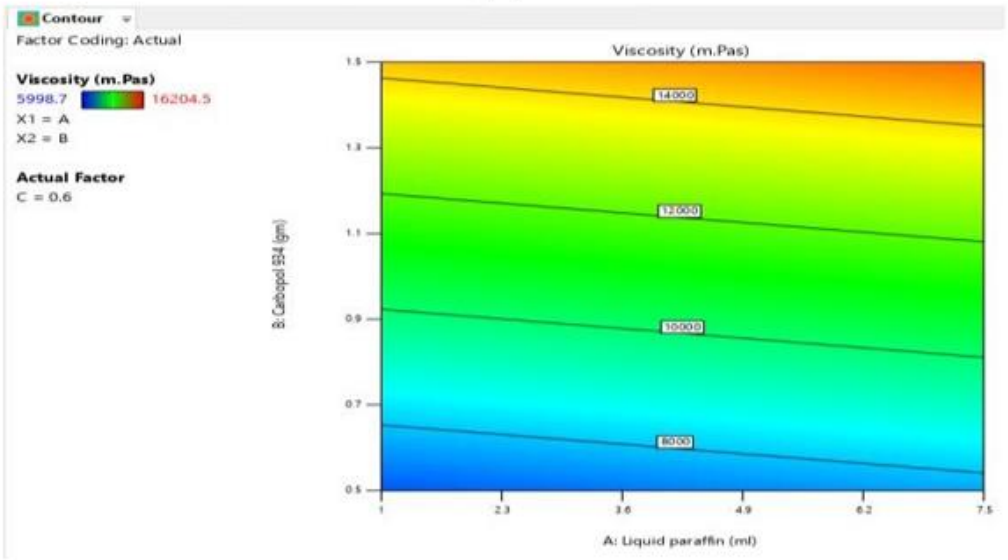
The final formula for viscosity based on coded factors: +10984.98 +415.82 A +3705.40 B + 641.05C The final equation is based on real variables. -815.89615 + 127.94 + 7410.80 + 6410.50 is the viscosity. Concerning the real factors, the appropriate equation may be used to forecast the result for a certain amount of each element. The model has an F-value of 9.31, which indicates statistical significance. 2.82 percent of the time, an F-value this high could only result from random chance. A p-value of less than 0.05 indicates the importance of the model terms. The model term B is crucial in this situation. A model term is not significant if its evaluation is higher than 0.1. In case your model has a lot of words that aren't essential to support hierarchy, you can consider doing a model reduction.

The Adjusted R2 of 0.7807 differs from the Expected R2 of 0.4987 by more than 0.2, which is not as close as one might assume. It might be a sign of a massive block effect, or it could be a problem with your model and/or data. Considerations include finding outliers, converting answers, and minimizing models. Every empirical model should be tested using confirmation runs. Adeq Precision allows for the determination of the signal-to-noise ratio. Ideally, the ratio should be greater than 4. Your ratio of 8.606 indicates a strong enough signal. This model may be used to explore the design space. Formula Using Coded Elements +4.29+0.0553A -0.1005B - 0.0448 C is the drug release. Equation in Terms of Actual Factors

Drug Release = +4.684 + 0.0170A – 0.2010 B –0.4479 C



(a)



(b)

Fig. 7: (a) & (b) 3Dimentional response surface plots and contour plot for the viscosity of topical emulgel

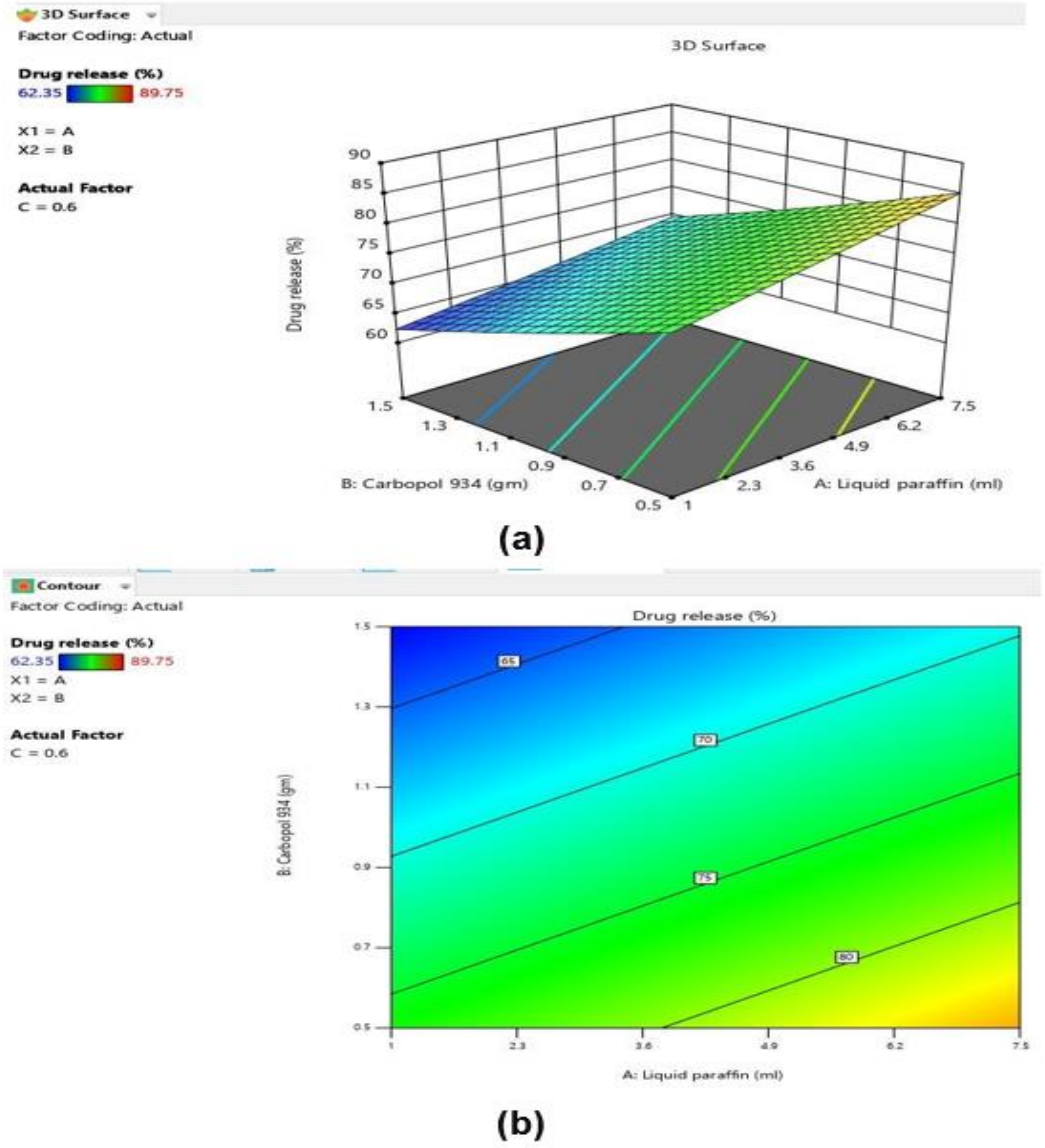


Fig 8: (a) & (b) Three Dimensional response surface plots and Contour plots for drug release of topical emulgel

Table 8: Response 2 Drug release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.1213	3	0.0404	9.31	0.0282	significant
A-Liquid paraffin	0.0244	1	0.0244	5.63	0.0767	
B-Carbopol 934	0.0808	1	0.0808	18.60	0.0125	
C-Mentha oil	0.0160	1	0.0160	3.69	0.1270	
Residual	0.0174	4	0.0043			
Cor Total	0.1387	7				

Table 9: Fit Statistics

Std. Dev.	0.0659	**R^2**	0.8747
Mean	4.29	**Adjusted R^2**	0.7807
C.V. %	1.54	**Predicted R^2**	0.4987
		Adeq Precision	8.6061

Table 10: The Stability study of emulgel formulations at 25°C ± 2°C/60%

Emulgel	pH	Viscosity(mPas)	Spreadability (cm/s)	Extrudability	Drug release
EG1	6.7±0.02	16204.5±50	18±0.03	64±4.6	62.35±0.91
EG2	6.9±0.03	8570.5±45	16±0.02	81.2±5.6	77.54±1.35
EG3	7.1±0.03	8347.7±35	14.2±0.45	80±4.3	87.52±1.25
EG4	6.8±0.02	11300.2±43	15.5±0.14	74.2±5.3	67.56±1.10
EG5	7.0±0.03	15506.3±78	13.0±1.42	72±3.1	71.27±0.65
EG6	6.9±0.02	6201.4±48	16.5±0.09	78±4.6	68.75±2.05
EG7	6.3±0.02	5998.7±69	14.5±0.03	92±5.6	89.75±0.02
EG8	6.7±0.02	15750.5±61	14.5±0.11	71±4.6	62.42±0.37
± Mean value with a standard deviation of three replicates					

Table 11: The Stability study of emulgel formulations at 40°C ± 2°C/75% RH ± 5%

Emulgel	pH	Viscosity(mPas)	Spreadability(cm/s)	Extrudability(Pa)	Drug release
EG1	6.5±0.01	16201.7±50	18±0.01	64±4.5	62.32±0.80
EG2	6.7±0.02	8570.3±42	15±0.02	80.2±5.5	75.55±1.32
EG3	7.0±0.01	8345.5±37	14.1±0.47	81±4.2	86.37±1.15
EG4	6.7±0.02	11302.1±42	15.5±0.14	75.2±5.2	65.70±1.07
EG5	6.8±0.03	15505.2±75	13.0±1.41	71±3.0	71.25±0.55
EG6	6.9±0.01	6202.5±45	15.5±0.07	75±4.5	67.85±2.15
EG7	6.3±0.02	5997.5±65	14.7±0.02	93±5.7	89.70±0.11
EG8	6.2±0.03	15747.7±62	14.5±0.10	72±4.5	62.50±0.25
± Mean value with a standard deviation of three replicates					

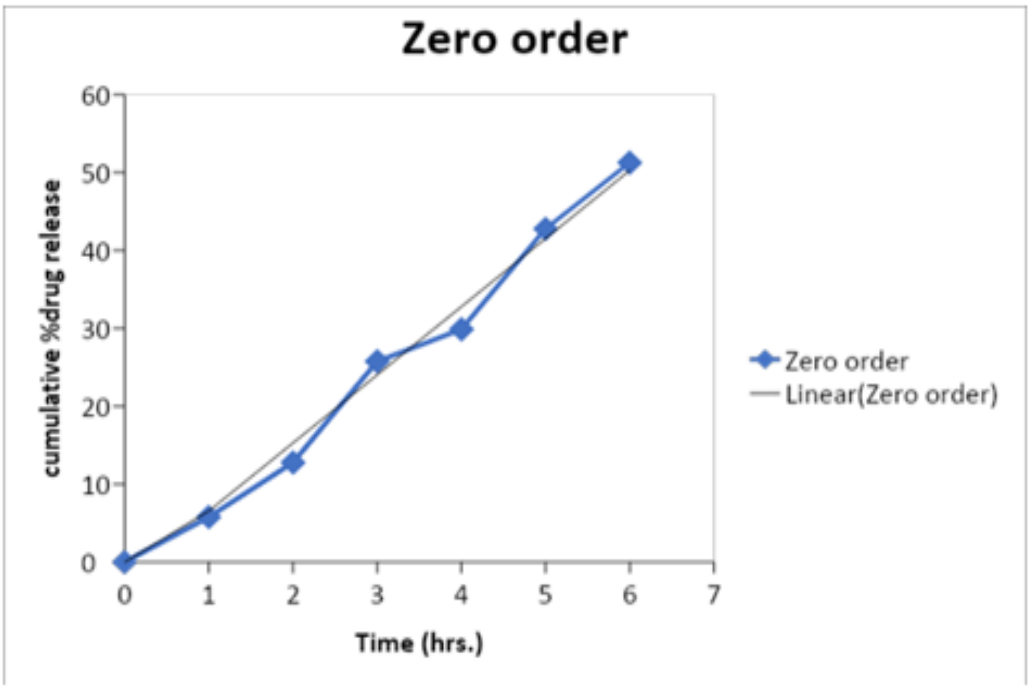


Fig 9: Zero-order drug release kinetics for optimized formulation

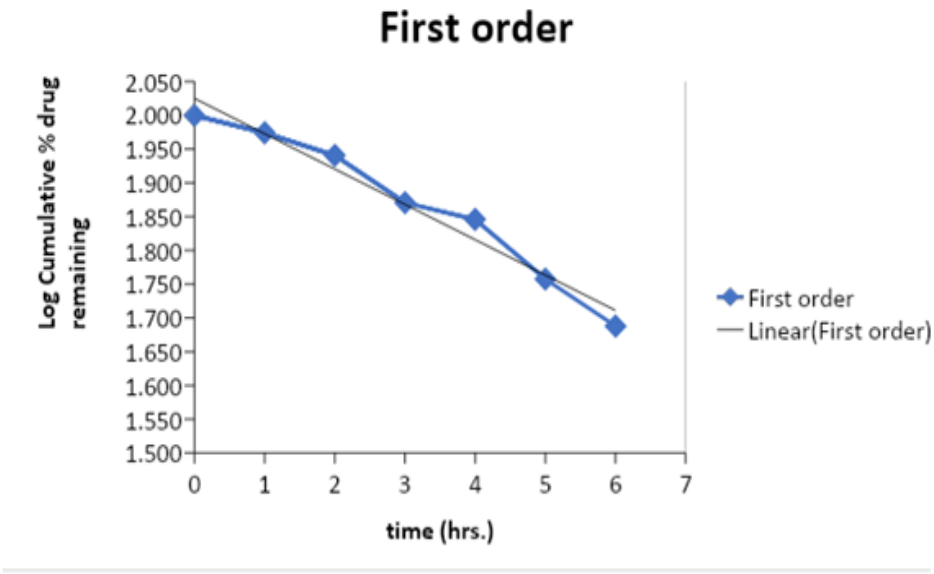


Fig 10: First-order drug release kinetics for optimized formulation

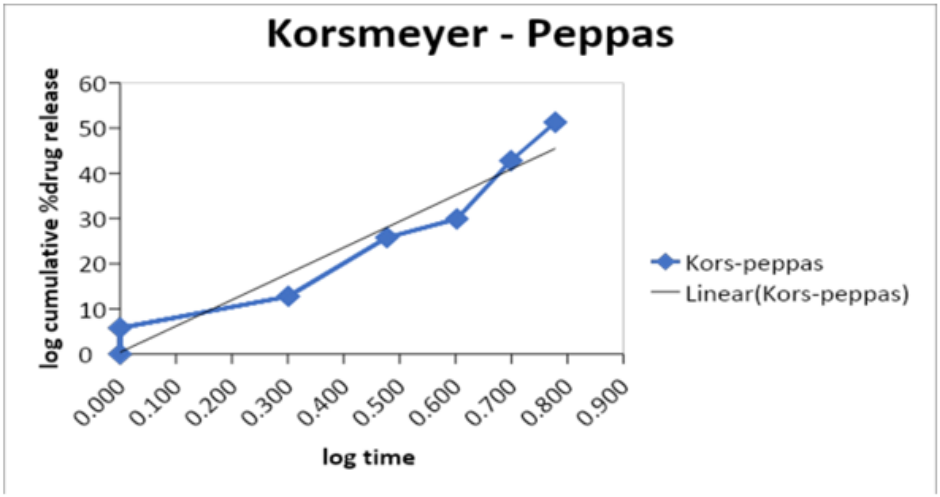


Fig 11: Korsmeyer- Peppas drug release kinetics for optimized formulation

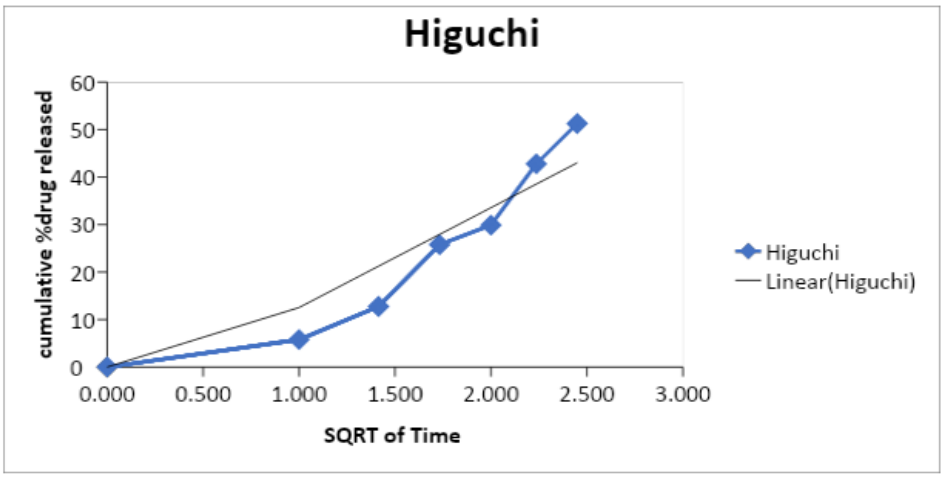


Fig 12: Higuchi model drug release kinetics for optimized formulation

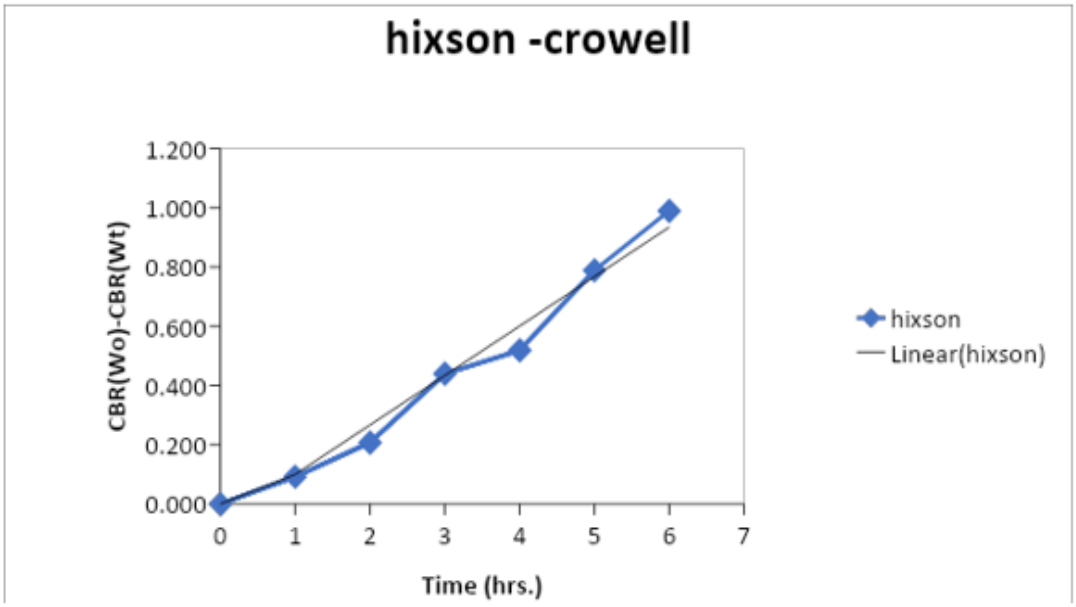


Fig 13: Hixson-Crowell model drug release kinetics for optimized formulation

Table 12: The regression coefficients obtained from model fitting

MODEL	Linear Regression Coefficient(R^2)	K Value
Zero-order	0.988	8.74
First-order	0.968	0.05
Korsmeyer and Peppas	0.941	57.93
Higuchi	0.864	21.02
Hixon-Crowell	0.977	0.16

Using the matching equation in terms of real factors, one may anticipate the result for a certain amount of each element.

Kinetics of drug release

Researchers were able to get more insight into the kinetics or mechanism of drug release by fitting in vitro release data from various formulations using a variety of kinetic models.

RESULT

EG7 exhibited the highest drug content (91.05%) and drug release (89.75%) among all formulations, indicating excellent bioavailability and efficacy. The formulation also showed good spreadability (27.33 gm.cm/s) and extrudability (16 g/cm²), ensuring ease of application and dispensing.

While the pH of 6.3 is slightly lower than the ideal skin pH range, it is still within an acceptable range for topical formulations. The viscosity of 5998.7 mPas ensures a good balance between ease of application and retention on the skin.

DISCUSSION

This study on allopurinol Diclofenac sodium-loaded emulgel for gout demonstrates a significant improvement over previous formulations, with an 89.75% cumulative drug release as compared to the 58.58% release in prior studies [32].

The emulgel's unique combination of emulsion and gel properties enhances allopurinol's solubility and permeability, ensuring a more efficient and rapid drug delivery. This makes the emulgel formulation superior for managing acute gout attacks, providing both rapid and sustained drug release for better patient outcomes. Further research and clinical trials are needed to fully establish its therapeutic benefits and potential for widespread use in gout management.

CONCLUSION

In the current research, an emulgel containing Allopurinol and Diclofenac Sodium was successfully formulated and evaluated. The formulations were prepared using varying concentrations of carbopol 940 as the gelling agent. The method proved to be straightforward and efficient, yielding positive results. The emulgel formulations underwent physicochemical evaluations, including rheological studies, spreadability tests, and in vitro drug release studies. The results indicated that all formulation batches (EG7) possessed acceptable physical properties. It was also observed that drug release varied with the concentration of the polymer used. Notably, batches EG7 exhibited superior in vitro drug release, with 89.70% release, respectively. Consequently, batches were identified as the optimized batches, demonstrating the best performance among all tested formulations. In conclusion, the emulgel formulation of Allopurinol and Diclofenac Sodium shows promise as a drug delivery system, potentially mitigating the issues associated with conventional administration routes.

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