

Variables Affecting *In-Vitro* Evaluation of Loxoprofen Sodium Topical Emulgel

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Received 26/3/2023, Accepted 8/6/2023, Published 27/6/2024



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Abstract

Although topical preparations like creams, ointments, and gels were used for many years to achieve local or sometimes systemic effects, they have many limitations, mostly the inability to control the release of medications. In this research, a new emulgel preparation of loxoprofen sodium was formulated as a suitable alternative possessing the properties of both emulsion and gel preparation making it suitable to prolong the release of the hydrophilic drug. Five different emulgel formulas of loxoprofen sodium 1% w/w were prepared using different percentages of liquid paraffin (5% and 10% w/w), tween 80 & span 80 emulsifier mixture (2.5% and 5% w/w), and xanthan gum (1% and 2% w/w). These formulations were evaluated for their physicochemical, rheological, and spreading properties, in addition to content uniformity and *in-vitro* release properties. Furthermore, the optimum selected emulgel formula was subjected to a skin irritation test, stability, and compatibility study besides an *in-vitro* release comparison with the marketed Loxonin® gel. Results of all formulated emulgels showed excellent homogeneity and consistency with no phase separation, accepted pH (6.12±0.76 to 6.51±0.92) and content uniformity (99.02±0.45 to 99.48±1.49). Moreover, all the formulas showed a thixotropic shear-thinning behaviour. The optimum formula F3 exhibiting the highest spreadability value of (8.3±0.1 cm), and the highest extent of drug (94.81±1.30 %) liberated after 6 h. additionally, the selected loxoprofen emulgel F3 showed no irritation to human skin, and no significant (P<0.05) change upon storage at 4±2°C and 25±2°C with acceptable compatibility. Eventually, the selected formula displayed a slower rate of loxoprofen release than the marketed gel. These results proved the effectiveness of the newly formulated loxoprofen emulgel for a prolonged release giving better patient compliance.

Keywords: Loxoprofen, Topical, Slow release, Emulgel.

المتغيرات المؤثرة على التقييم المختبري لمستحضر لوكسوبروفين ايمجل الموضعي زينب حسن مهدي^{1*}، اسيل سهيل نجم²، نضال خزعل مرعي³ وهدى صالح كاظم⁴

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الخلاصة

المستحضرات الموضعية مثل الكريم، الدهون، الجل (الهلام) على الرغم من استخدامها لعدة سنوات للعلاج الموضعي او ممكن يصل الى الدورة الدموية، لكن لديها العديد من المعوقات منها عدم قابلية المستحضر على تحرير الدواء بشكل منتظم. من خلال هذا البحث مستحضر الايمجل لدواء اللوكسوبروفين صوديوم تم تحضيره كبديل مناسب يمتلك صفات مستحضر المستحلب بالإضافة لصفات الهلام مما يمكنه من اطالة تحرير الدواء الذائب بالماء. تم تحضير 5 صيغ مختلفة من الايمجل الحاوي على اللوكسوبروفين صوديوم 1% وزن/وزن باستخدام نسب مختلفة من البرافين السائل (5% و 10% وزن/وزن)، مادة التويين 80 والسبان 80 المكونة للمستحلب كمزيج بنسبة (2.5% و 5% وزن/وزن) وصمغ الزنتان بنسبة (1% و 2% وزن/وزن). هذه الصيغ المختلفة تم تقييم صفاتها الكيماوية، الفيزيائية، الانسيابية ودرجة الانتشار بالإضافة الى محتوى المادة الفعالة وتحرر الدواء من الصيغة. اما بالنسبة للصيغة الامثل تم مقارنتها مع الصيغة التجارية اللوكسونين من ناحية عدة فحوص مثل تحسس الجلد، الاستقرار، وتحرر الدواء.

نتائج الفحوص المختبرية لكل الصيغ اظهرت صفات ممتازة من حيث التجانس للمادة و معدل الحموضة المناسب الذي يتراوح من (٠,٧٦±٦,١٢ الى ٠,٩٢±٦,٥) ومحتوى المادة الفعالة يتراوح من (٠,٤٥±٩٩,٠٢ الى ٠,٤٩±٩٩,٤٨). الصيغة الامثل صيغة رقم ٣ اظهرت اعلى القيم بالنسبة لانتشار المادة الفعالة (٠,١±٨,٣ سم) واعلى كمية من تحرر الدواء بعد ٦ ساعات بنسبة (١,٣±٩٤,٨١)، وايضا الصيغة الافضل لم تظهر اي تحسس للجلد وعدم ظهور اي تغيير بعد الخزن بدرجات حرارة ٤±٢٥ وكذلك بدرجات حرارة ٢٥±٢٥ لهذا الاملجمل مقارنة بالصيغة التجارية وبالتالي فان الصيغ المحضرة مناسبة أكثر من ناحية التزام المريض بالعلاج لكون تحرر المادة الفعالة يكون ابطأ. الكلمات الافتتاحية: لوكسوبروفين، موضعي، تحرر دواء بطيء، ايمجل .

Introduction

Topical dosage forms can be defined as preparations applied directly to the skin to produce a local or systemic effect by drug penetration into the underlying layer of skin or mucous membranes (1-3). The main advantages of topical preparations are represented by the ease of application, patient compliance, bypassing the first-pass effect, and gastric problems providing the drug directly at the target tissue (4,5).

Different types of topical preparations are available with various consistencies ranging from solutions to solids where semisolid dosage forms (creams, ointments, foams, pastes, and gels) are the most popular ones (6). Nevertheless, gels are the most preferred semisolid dosage forms due to their higher stability and spreading coefficient, ease of application, and less stickiness compared to other topical preparations (7). Regardless of the numerous advantages of topical gels, they are only suitable to enclose hydrophilic agents with poor control of their release pattern, because gels are prepared by the entrapment of a large quantity of aqueous or hydro-alcoholic solutions within the colloidal solid network which permits a faster dissolution and migration of the drug through the vehicle compared to ointments and creams (8,9).

For this reason, the emulgels were prepared, in which O/W or W/O emulsion is stabilized by the addition of gelling agent. Therefore, both hydrophilic and hydrophobic ingredients can be incorporated into the aqueous or oily phase of the emulsion. Furthermore, since emulgels contain both emulsion and gels it acts as a dual control release system, as drug particles move from the internal phase (reservoir) to the external phase of the emulsion in a controlled manner followed by its capture by the cross-linked network of the gel phase which prolongs the contact time of the medication with the skin owing to the gel adhesive property, providing the drug to be penetrate through the skin slowly and in a controlled manner (10).

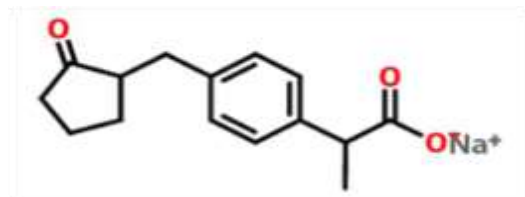


Figure 1. Chemical structure of loxoprofen sodium (11)

Loxoprofen is 2- [4-(2-oxo-cyclopentyl methyl) phenyl]-propionate (Figure1), is a non-selective

non-steroidal anti-inflammatory (NSAID) pro-drug that is converted by carbonyl reductase enzymes in the liver and skin to the active trans-alcohol (trans-OH) and inactive (cis-OH) metabolite. It is very soluble in water and methanol, freely soluble in ethanol, and practically insoluble in diethyl ether (12). This drug is widely used in Japan, Eastern Asia, the Middle East, Latin America, and Africa for the management of pain and inflammation in chronic and transient conditions (e.g., toothache, headache, menstrual cramps, common cold, etc.) (13). It acts by inhibiting the cyclooxygenase enzymes (COX I and COX-II), which are involved in the biosynthesis of prostaglandins (PGs) (14,15). Loxoprofen is available as an oral loxoprofen sodium tablet and solution, it is also available as topical preparations such as Loxonin gel (1%), Loxonin spray (1%) which could be applied 3-4 times a day (11,16). However, both loxoprofen and the trans-OH form cannot retain for a long time after oral administration because of their rapid elimination with a $t_{1/2}$ equal 1.36 ± 0.07 h and 2.04 ± 0.31 h for both loxoprofen and the trans-OH respectively (17). Therefore, an alternative route; other than oral; needed to be investigated to achieve long-term retention of the drug in the body. This study was performed to develop a new topical loxoprofen emulgel and study the effect of different variables (concentration of oil phase, emulsifying agent, and gelling agent) in controlling the release of the drug to reduce the application frequency and hence improve patient compliance.

Experimental Work

Materials and methods

Materials

Liquid paraffin (Solvochem, UK), loxoprofen sodium (Provizer pharma, India), methylparaben, and propylparaben (Samarra, Iraq), propylene glycol PG (Himedia, India), span 80 and tween 80 (Himedia, India), xanthan gum (Himedia, India), Loxonin® gel (Daiichi Sankyo, Japan). All other chemical reagents and solutions used were from analytical grades.

Preparation of loxoprofen sodium topical emulgel

Different formulas of loxoprofen sodium 1% w/w emulgel were prepared using various concentrations of the oil phase, surfactant mixture, and gelling agent concentrations as shown in table 1.

To formulate the emulgel, the emulsion was prepared initially and then mixed with the gel in equal proportions. The required amounts of the surfactants in the emulsion were calculated

according to the RHLB method as illustrated below⁽¹⁸⁾:

$$A = \frac{100(X - HLB B)}{HLB A - HLB B}$$

Where, A is the percentage of tween 80 (Hydrophilic surfactant) B is the percentage span of 80 (Hydrophobic surfactant) X is the required HLB for the formula consequently, the oil phase was prepared by dissolving span 80 in the given amount of the liquid paraffin. While the aqueous phase was obtained by dissolving methylparaben and propylparaben (As preservatives) in propylene glycol (PG as a penetration enhancer), which was added to the aqueous phase containing tween 80 and

loxoprofen. Subsequently, the aqueous and the oil phase were heated separately to 70-80 °C, followed by adding the oil phase to the aqueous phase with continuous mixing until cool to room temperature.

On the other hand, the gel phase was prepared by dissolving xanthan gum in distilled water using a magnetic stirrer for about one hour, which was kept overnight to allow complete swelling.

Finally, the prepared emulsion was mixed with the prepared gel phase in a 1:1 ratio for 1 hour using a magnetic stirrer to formulate the emulgel⁽¹⁹⁾. The composition of loxoprofen sodium emulgels was illustrated in Table 1.

Table 1. Composition of the prepared loxoprofen sodium emulgels

Ingredients (as %w/w)	F1	F2	F3	F4	F5
Loxoprofen sodium	1	1	1	1	1
Liquid paraffin	5	10	5	10	5
Span 80	0.7	0.7	1.4	1.4	1.4
Tween 80	1.8	1.8	3.6	3.6	3.6
propylene glycol	5	5	5	5	5
Methyl paraben	0.03	0.03	0.03	0.03	0.03
Propyl paraben	0.01	0.01	0.01	0.01	0.01
Xanthan gum	1	1	1	1	2
D.W	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of loxoprofen topical emulgel

Physical properties

All prepared formulas were visually inspected for their color, homogeneity, phase separation, and consistency⁽²⁰⁾.

The pH determination

The pH of the 1% aqueous mixture of the loxoprofen emulgels was determined at room temperature using a calibrated pH meter (OHAUS, USA), the measurements were accomplished in triplicate and the average value \pm SD was determined⁽²¹⁾.

Rheological study

The viscosity in centipoise of all settled formulas was determined at room temperature by Brookfield viscometer DVE- the USA using spindle 63 at 2,5,10 and 12 rpm, and the average values of 3 measurements were determined after a 30-second interval between readings⁽²²⁾.

Spreadability test

It is a direct measure of the extent to which the drug spreads over the affected area, influencing the therapeutic efficacy of the product. To determine the spreadability of the prepared loxoprofen emulgels, 0.5 g from each formula was placed between two glass slides along with a 500 g weight and allowed to rest for about 5 min (until no further change in the diameter was observed). The increase

in the diameter was determined in cm which represented the spreadability⁽⁴⁾.

Determination of drug content

For the determination of loxoprofen sodium content, 0.5 g of each formula which equivalent to (5mg) of the drug was dissolved in 10 ml methanol: water mixture (40:60). Afterward, a sample was withdrawn and suitably diluted using the methanol-water mixture and filtered to be analyzed at 223 nm using a T 80 UV-visible spectrophotometer (PG Instruments, UK)⁽²³⁾.

In-vitro dissolution study

The *in-vitro* release test was performed by a modified Franz diffusion cell consisting of a cylindrical glass tube open from the two endings (22 mm diameter, 76 mm height). One end was covered with a cellophane membrane immersed inside a 100 ml pH7.4 phosphate buffer at $37 \pm 0.5^\circ\text{C}$. One gram of each prepared emulgel was applied on the surface of the 0.22 μm cellophane membrane that was previously soaked overnight in water. Afterward, 1ml sample was withdrawn in specific time intervals up to 6 h, and suitably diluted to be analyzed using T 80 UV-visible spectrophotometer (PG Instruments, UK) at 223 nm⁽²⁰⁾.

Skin irritation test for human

Additionally, the *in-vivo* skin irritation test was performed on the optimum emulgel formula on 15 human volunteers by placing a 1g of loxoprofen

emulgel on the back of the volunteer's hand in an area of about 5 cm². The preparation was left for 12 h and repeated daily for a week to observe any skin irritation or lesion ⁽²⁴⁾.

Stability study

The stability of the optimum formula was assured by packing the emulgel in 15ml glass vials for 3 months at two different temperatures 4±2°C and 25±2°C. A sample was withdrawn bimonthly and analyzed for product consistency, pH, and drug content ⁽²¹⁾.

Drug-Excipient compatibility study

The compatibility between loxoprofen sodium and xanthan gum in the optimum formula was inspected by studying the Fourier transform infrared spectra (FTIR) for each component individually and their physical mixture using a potassium bromide disc ⁽²⁵⁾.

Kinetic modeling of drug release from the prepared loxoprofen emulgel

To determine the *in-vitro* release kinetics of the optimum formula, the data were fitted for zero-order, first-order, and Higuchi's model, where the release kinetics and mechanism could be established by comparing the values of the coefficient of determination (R²) and selecting the higher value. In addition, to depict more detailed information about the release mechanism especially when the release kinetics are not so clear, the Korsmeyer Peppas model was used to predict the exact process of release from the loxoprofen emulgel by fitting the initial 60% of the released data, and by determining the value of the release exponent (n) the exact mechanism can be established. Where the $n < 0.5$ indicates a Fickian diffusion (Case I), while $0.5 < n < 1$ suggests non-

Fickian (anomalous) transport including both diffusion and relaxation, on the other hand, if $n = 1$

it means zero-order (Case II) release mechanism involving polymer swelling and relaxation. Finally, the value of $n > 1$ signifies a Super case II transport where both polymer relaxation and erosion take place ^(26, 27).

Comparative in-vitro dissolution study between optimum loxoprofen emulgel formula and marketed Loxonin gel

To demonstrate the difference between the *in-vitro* release of the formulated loxoprofen emulgel and the marketed Loxonin® gel, the study was performed using a modified Franz diffusion cell in 7.4 phosphate buffer and the samples were analyzed for UV- absorbance at 223 nm.

Statistical analysis

The results were analyzed statistically by (ANOVA) single factor to compare and evaluate the significance of the results, where (P<0.05) was considered to be a significant difference.

Results And Discussion

Physicochemical properties

The results of the physicochemical properties as illustrated in table 2 indicated that all formulas were suitably prepared with accepted content uniformity (99.02±0.45 to 99.48±1.49), white color in addition to their excellent homogeneity and consistency without any phase separation. Furthermore, the pH of the prepared loxoprofen emulgels was arranged between 6.12±0.76 and 6.51±0.92 which was suitable to avoid any skin irritation.

Table 2. Physicochemical properties of loxoprofen sodium emulgels

Formula	Color	Homogeneity	Consistency	Phase separation	% Content uniformity	pH
F1	White	Excellent	Excellent	Nil	99.36±1.02	6.51±0.92
F2	White	Excellent	Excellent	Nil	99.02±0.45	6.24±1.03
F3	White	Excellent	Excellent	Nil	99.37±1.22	6.33±0.85
F4	White	Excellent	Excellent	Nil	99.48±1.49	6.45±0.61
F5	White	Excellent	Excellent	Nil	99.04±0.98	6.12±0.76

* Results expressed as mean ± SD, n=3

Rheological properties of loxoprofen sodium emulgels

The viscosity of the prepared emulgels was a measure of the resistance to flow or shear ⁽²⁸⁾. It is a very important parameter that affects the efficiency and performance of the final product, as the most successful emulgel formula should possess a certain degree of viscosity that is high enough to increase its contact time on the skin, but shouldn't be so high to achieve a suitable spreadability and at the same time permitting a maximum amount of drug release ⁽²⁹⁾.

The viscosity results in centipoise for all prepared emulgels were in the range of (14700-

24268 Cps) as illustrated below in Figure 2. A significant reduction in the viscosity (p<0.05%) was observed for all formulas upon increasing the shear rate from 2-12 rpm which took a certain time to return to its original viscosity. These results demonstrated the thixotropic shear thinning behavior of the prepared formulas. This effect can be explained by the alignment of the disarranged molecules of the gelling agent in the direction of the flow as the shear rate increases, which reduces the internal resistance and hence the viscosity ⁽³⁰⁾.

However, a significant reduction in the viscosity was observed in all shear rates upon increasing the concentration of the surfactant

mixture as noticed in F1 and F2 (2.5%) compared to F3 and F4 (5%), respectively. This can be explained by the fact the surfactant absorbed in the oil droplet reducing the interfacial tension between the oil phase and aqueous phase and preventing that oil droplet from re-polymerizing and facilitating its dispersion. In addition, the surfactant forms a protective monomolecular film which reduced the friction between molecules itself and also between molecules and its surrounding wall, an effect that obviously reduced the flow resistance and hence causing viscosity reduction ⁽³¹⁾.

Furthermore, lower viscosity was observed in F1 and F3 compared to corresponding F2 and F4

in all rates of shear, an effect which can be elucidated by the higher dispersed phase volume fraction in F2 and F4 (10%) caused by increasing the oil phase concentration which increased the colloidal interaction between the dispersed particles leading to a higher degree of disturbance in the system flow and generating a higher viscosity ⁽³²⁾.

Moreover, a significantly higher ($p < 0.05$) viscosity in all shear rates was observed upon increasing xanthan gum concentration as in F5 (2%) as compared to F3 (1%) owing to the generation of higher cohesive internal forces causing greater resistance and viscosity ⁽³³⁾.

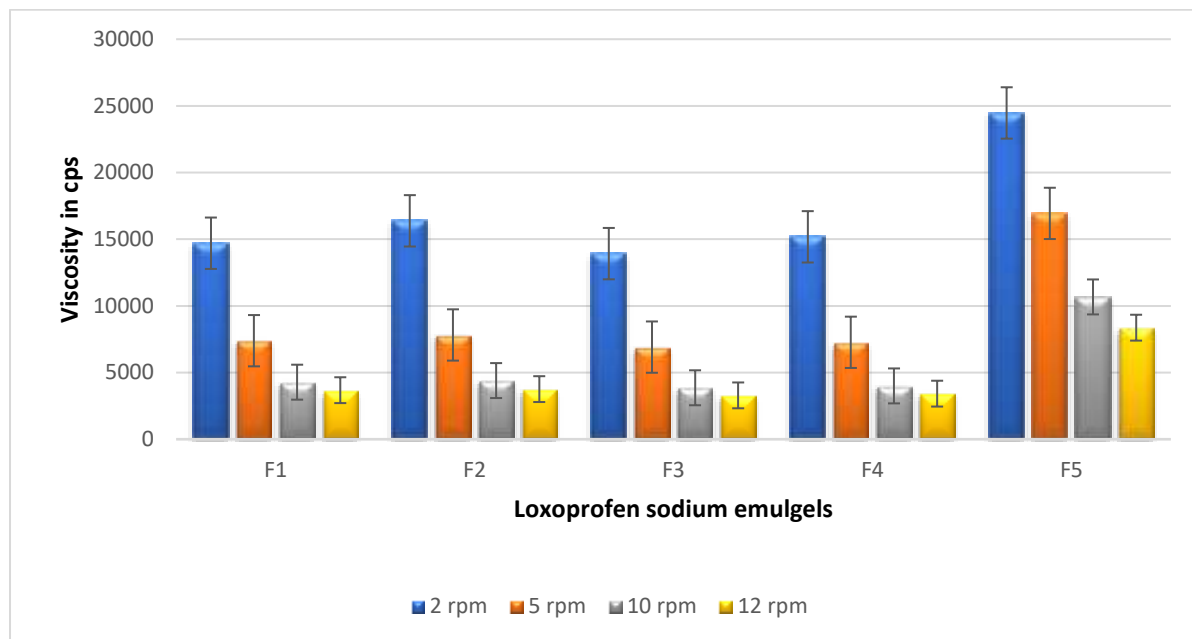


Figure 2 . Rheological data of loxoprofen sodium emulgels expressed in centipoise (cps) measured at 25°C ± 0.5°C (Results are expressed as mean± SD, n=3)

Spreadability results

Spreadability is considered an important parameter for correct dose administration, ease of extrusion from the container, application to the target site and giving consequently a higher patient preference. The results of spreadability (Figure 3) agreed with that of viscosity, as a strong negative correlation exists between the spreadability and viscosity with F3 emulgel showing a significantly ($p < 0.05$) higher spreadability value of 8.3 ± 0.1 . The result can be further explained by the lower cohesiveness or viscosity of the F3 emulgel preparation owing to the lower concentration (i.e. cross-linking) of xanthan gum 1%, and lower surface tension due to the higher percentage of emulsifiers 5% and a lower percentage of oil phase represented by liquid paraffin 5% ⁽³⁴⁾.

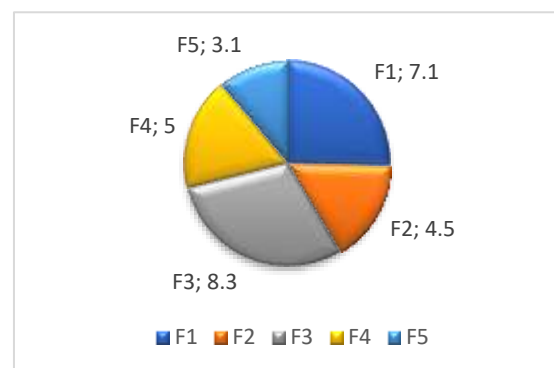


Figure 3. Spreadability of the prepared loxoprofen sodium emulgels as mean of three measurements expressed in cm at 25°C ± 0.5°C

In-vitro release of loxoprofen sodium from the prepared emulgels

The result of the *in-vitro* release of loxoprofen sodium from the prepared emulgels were depicted below in Figure 4. A significantly ($p < 0.05$) higher extent of drug release after 6 h was observed in F3 emulgel with an average % drug release of 94.81 ± 1.30 followed by $F1 > F4 > F2 > F5$ having $78.04 \pm 1.94 > 75.04 \pm 1.93 > 72.10 \pm 1.03 > 69.06 \pm 1.07$ % of drug release, respectively. The result might be again attributed to the higher percent of surfactant mixture (5%) and lower concentration of liquid paraffin (5%) and gelling agent (xanthan gum 1%) in F3 compared to other formulas, which increased the hydrophilic property, and facilitated the penetration of the surrounding medium and the diffusion of the drug from the emulgel preparation (35).

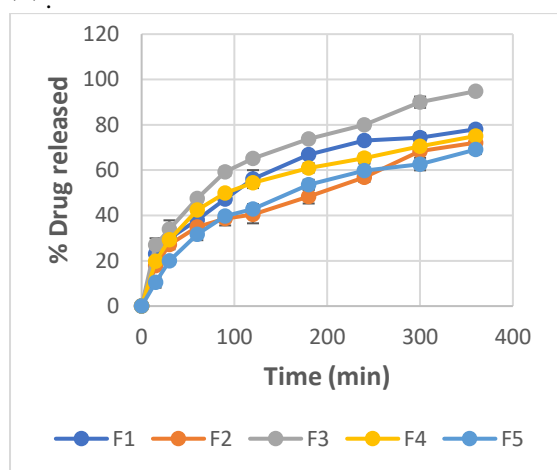


Figure 4. Comparative In-vitro release profile of the prepared loxoprofen emulgels at $37 \pm 0.5^\circ\text{C}$ (Results are expressed as mean \pm SD, $n=3$).

From the previous evaluation, F3 Emulgel was selected as the optimum formula with (99.37 ± 1.22 loxoprofen) content, higher extent of drug release after 6 h (94.81 ± 1.30) and higher spreadability (8.3 ± 0.1) with lower viscosity, in addition to its good homogeneity, consistency and accepted color and pH (6.33 ± 0.85).

Skin irritation & stability results of F3

The optimum emulgel formula F3 caused no skin lesion or irritation for any of the 15 volunteers. These results indicated its safety for human application. Furthermore, stability results are shown in Table 3. The optimum emulgel formula F3 showed no significant change in the consistency, drug content and pH at both temperature (4 and 25°C) demonstrating good stability at different temperatures of the selected emulgel formula.

FTIR spectra

To determine the compatibility between loxoprofen and xanthan gum, the FTIR spectrum of each one in addition to their physical mixture was illustrated below in Figure 5. The pure drug spectrum showed all the characteristic peaks of loxoprofen represented by the prominent peaks at 1728 cm^{-1} and 1730 cm^{-1} owing to the carbonyl stretching of the cyclopentane and carboxylic acid, respectively. Furthermore, the peak on 3086 cm^{-1} was attributed to the C-H stretching band of the aromatic ring, while the CH_2 stretching vibration was observed on 2870 cm^{-1} . Finally, the peak at 1410 cm^{-1} was due to C-H bending. Results of the physical mixture showed no obvious change or shift in the pure drug's characteristic peaks, indicating the compatibility between the two excipients (36, 37).

Table 3. Stability results of the optimum loxoprofen emulgel

Emulgel parameter		At $4 \pm 2^\circ\text{C}$	At $25 \pm 2^\circ\text{C}$
1 st month	Consistency	Excellent	Excellent
	% Drug content	98.17 ± 1.20	98.12 ± 1.07
	pH	6.3 ± 0.75	6.3 ± 1.24
2 nd month	Consistency	Excellent	Excellent
	% Drug content	98.26 ± 1.52	98.22 ± 1.07
	pH	6.2 ± 0.71	6.2 ± 0.48
3 rd month	Consistency	Excellent	Excellent
	% Drug content	98.40 ± 1.20	98.02 ± 1.43
	pH	6.3 ± 0.94	6.2 ± 1.18

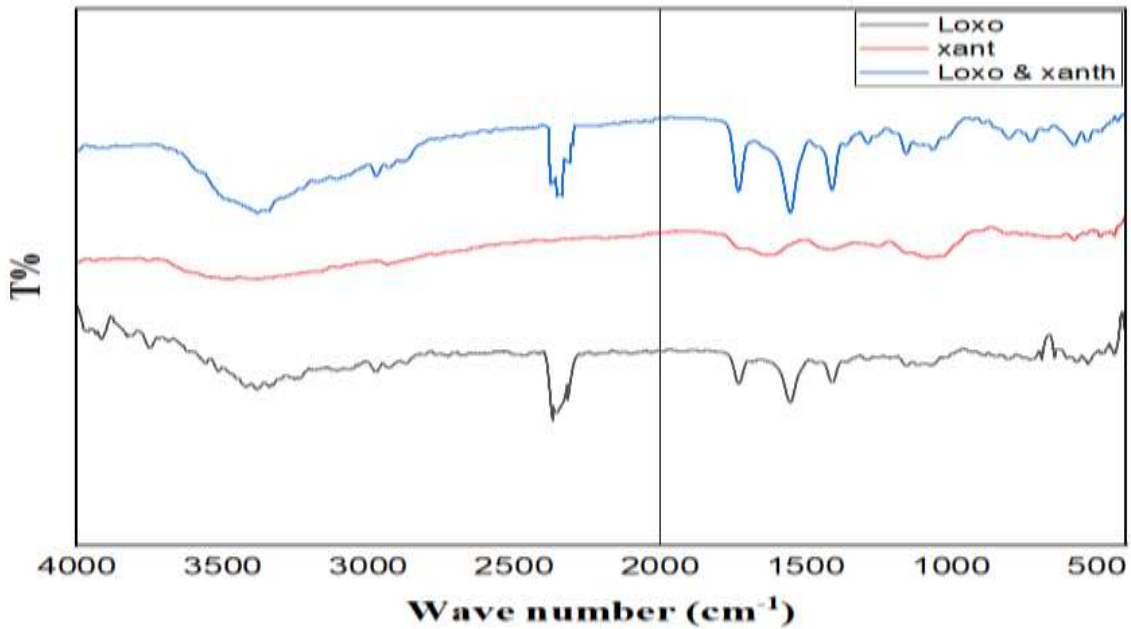


Figure 5. FTIR spectral analysis of the optimum loxoprofen sodium emulgel (F3)

To predict the exact mechanism of drug release, the optimum formula (F3) dissolution results were fitted to the zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations, as illustrated in table 4. The data showed clearly that the release of loxoprofen obeyed zero-order kinetics owing to its higher value of coefficient of determination R^2

(0.9773) compared to other models, with a non-Fickian (anomalous) diffusion ($n= 0.6395$). These results strongly suggested that, the rearrangement and swelling of the polymeric chain took place slowly along with the diffusion process which gave a time-dependent anomalous effect ^(38, 39).

Table 4. Kinetic analysis data of the optimum formula (F3) of loxoprofen sodium emulgel

Formula	Mathematical model of drug release kinetics						Korsmeyer-Peppas	
	Zero-order		First-Order		Higuchi		K_{kp}	n
	K_0	R^2	K_1	R^2	K_H	R^2		
F3	0.0093	0.9773	0.0073	0.9209	0.0044	0.8443	7.925013	0.6395

Comparative In-vitro release analysis

The *in-vitro* release profile of the selected loxoprofen emulgel F3 was compared to that of the marketed loxoprofen gel (Loxonin®) in Figure 6. A statistically significant difference ($p<0.05\%$) were observed in the rate of the drug release between the two loxoprofen preparations, with Loxonin® gel exhibited a higher release rate of $95.45\pm1.76\%$ after 2 h compared to the formulated loxoprofen emulgel F3 which displays a slower rate of drug release $94.81\pm1.38\%$ which extends up to 6 h. after application.

This result demonstrated the effectiveness of the prepared emulgel preparation to extend the period of drug release for a prolonged period, improving patient acceptance and adherence ⁽³⁷⁾.

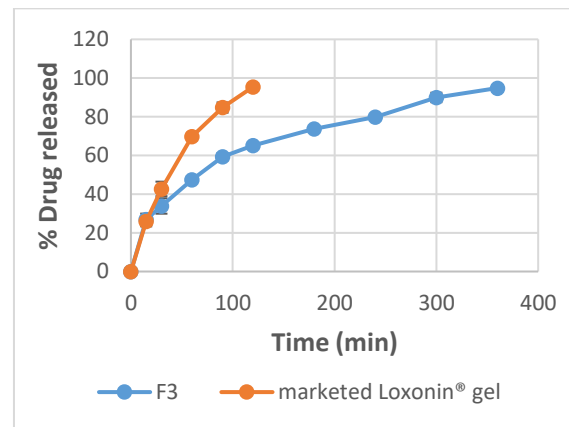


Figure 6. Comparative in-vitro release profile of the optimum loxoprofen emulgels F3 and marketed loxoprofen gel (Loxonin®) at $37\pm0.5^\circ\text{C}$ (Results are expressed as mean \pm SD, $n=3$).

Conclusion

This study developed a topical loxoprofen sodium emulgel (F3) using 5% liquid paraffin, 5% surfactant mixture (tween 80/span 80), and 1% xanthan gum as a gelling agent, that proved to achieve prolonged release of loxoprofen (up to 6 h compared to the marketed loxoprofen gel (loxonin®), an effect which reduces application frequency and gives better patient compliance.

Acknowledgements

The authors appreciate Al-Farahidi university for supporting this work.

Conflicts of Interest

The authors declare there are no conflicts of interest.

Funding

The researchers did not receive any financial support from any agencies.

Ethics statements

It is an in-vitro study and does not require ethics statements.

Author Contribution

The authors contributed to the manuscript equally.

References

1. Tanaji DN. Emulgel: A comprehensive review for topical delivery of hydrophobic drugs. *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm.* 2018;12(02).
2. Yadav SK, Mishra MK, Tiwari A, Shukla A. Emulgel: a new approach for enhanced topical drug delivery. *Int J Curr Pharm Res.* 2016;9(1):15-9.
3. Joshi B, Singh G, Rana AC, Saini S, Singla V. Emulgel: a comprehensive review on the recent advances in topical drug delivery. *Int Res J Pharm.* 2011;2(11):66-70.
4. Ashara K, Soniwala M, Shah K. Emulgel: A novel drug delivery system. *Journal of Pakistan Association of Dermatologists.* 2016;26(3):244-9.
5. Sah SK, Badola A, Nayak BK. Emulgel: Magnifying the application of topical drug delivery. *Indian Journal of Pharmaceutical and Biological Research.* 2017;5(01):25-33.
6. Singh RP, Parpani S, Narke R, Chavan R. Emulgel: A recent approach for topical drug delivery system. *Asian Journal of Pharmaceutical Research and Development.* 2014:112-23.
7. Joseph J, Pa D GBJ, R Pr TN, Carla B. EMULGEL: A novel trend in topical drug delivery system. *World Journal of Pharmaceutical and Medical Research.* 2017;3(4):35-9.
8. Hardenia A, Jayronia S, Jain S. Emulgel: An emergent tool in topical drug delivery. *International journal of pharmaceutical sciences and research.* 2014;5(5):1653.
9. Haneefa KPM, Easo S, Hafsa PV, Mohanta GP, Nayar C. Emulgel: An advanced review. *Journal of pharmaceutical sciences and research.* 2013;5(12):254.
10. Kumar D, Singh J, Antil M, Kumar V. Emulgel-novel topical drug delivery system-a comprehensive review. *International journal of pharmaceutical sciences and research.* 2016;7(12):4733.
11. Budavari S. *The Merk Index, An encyclopedia of chemicals, drugs and biologicals, USA; Merk & Co. Inc; 2006.*
12. *The Japanese pharmacopoeia XIV Part II, 899-956, 2001.*
13. Paudel S, Shrestha A, Cho P, Shrestha R, Kim Y, Lee T, et al. Assessing Drug Interaction and Pharmacokinetics of Loxoprofen in Mice Treated with CYP3A Modulators. *Pharmaceutics.* 2019;11(9):479.
14. Venkatesan P, Manavalan R, Valliappan K. Preparation and evaluation of sustained release loxoprofen loaded microspheres. *Journal of basic and clinical pharmacy.* 2011;2(3):159.
15. Greig SL, Garnock-Jones KP. Loxoprofen: A review in pain and inflammation. *Clinical drug investigation.* 2016;36(9):771-81.
16. Sweetman SC. *Martindale: the complete drug reference: Pharmaceutical press London; 2009.*
17. Sawamura R, Kazui M, Kurihara A, Izumi T. Pharmacokinetics of loxoprofen and its active metabolite after dermal application of loxoprofen gel to rats. *Die Pharmazie-An International Journal of Pharmaceutical Sciences.* 2015;70(2):74-80.
18. Taylor KMG, Aulton ME. *Aulton's pharmaceutics E-Book: The design and manufacture of medicines: Elsevier Health Sciences; 2021.*
19. Khullar R, Kumar D, Seth N, Saini S. Formulation and evaluation of mefenamic acid emulgel for topical delivery. *Saudi pharmaceutical journal.* 2012;20(1):63-7.
20. Patil SS, Phutane KR, Adnaik RS, Mohite SK, Magdum CS. Novel cosmeceutical herbal emulgel for skin care. *World journal of pharmacy and pharmaceutical sciences.* 2014;3(4):801-11.
21. Kumar V, Mahant S, Rao R, Nanda S. Emulgel based topical delivery system for loratadine. *ADMET and DMPK.* 2014;2(4):254-71.
22. Sah SK, Badola A, Mukhopadhyay S. Development and evaluation of tioconazole loaded emulgel. *Int J Appl Pharm.* 2017;9:83-90.
23. Zaman M, Sarfraz RM, Adnan S, Mahmood A, Hanif M, Qureshi J, et al. Development and in-vitro evaluation of once daily tablet dosage

- form of loxoprofen sodium. Tropical Journal of Pharmaceutical Research. 2015;14(9):1557-63.
24. Shivhare UD, Jain KB, Mathur VB, Bhusari KP, Roy AA. FORMULATION DEVELOPMENT AND EVALUATION OF DICLOFENAC SODIUM GEL USING WATER SOLUBLE POLYACRYLAMIDE POLYMER. Digest journal of nanomaterials & biostructures (DJNB). 2009;4(2).
 25. Jamadar MJ, Shaikh RH. Preparation and evaluation of herbal gel formulation. Journal of Pharmaceutical Research and Education. 2017;1(2):201-24.
 26. Varma VNSK, Maheshwari PV, Navya M, Reddy SC, Shivakumar HG, Gowda DV. Calcipotriol delivery into the skin as emulgel for effective permeation. Saudi Pharmaceutical Journal. 2014;22(6):591-9.
 27. Ramteke KH, Dighe PA, Kharat AR, Patil SV. Mathematical models of drug dissolution: a review. Sch Acad J Pharm. 2014;3(5):388-96.
 28. Viswanath DS, Ghosh TK, Prasad DHL, Dutt NVK, Rani KY. Viscosity of liquids: theory, estimation, experiment, and data: Springer Science & Business Media; 2007.
 29. Gandhi SV, Nilgar NM, Bhalekar MR. Formulation and evaluation of phytoconstituents emulgel for the treatment of varicose veins. Ejpms. 2018;5(7):432-9.
 30. Khalil YI, Khasraghi AH, Mohammed EJ. Preparation and evaluation of physical and rheological properties of clotrimazole emulgel. Iraqi Journal of Pharmaceutical Sciences (P-ISSN: 1683-3597, E-ISSN: 2521-3512). 2011;20(2):19-27.
 31. Sun JH, Zhang FS, Wu YW, Liu GL, Li XN, Su HM, et al., editors. Overview of emulsified viscosity reducer for enhancing heavy oil recovery. IOP conference series 2019: ,3(1),1-6.
 32. Dłużewska E, Stabiecka A, Maszewska M. Effect of oil phase concentration on rheological properties and stability of beverage emulsion. Acta scientiarum polonorum technologia alimentaria. 2006;5(2):147-56.
 33. Kar M, Chourasiya Y, Maheshwari R, Tekade RK. Current developments in excipient science: implication of quantitative selection of each excipient in product development. Basic Fundamentals of Drug Delivery: Elsevier; 2019. p. 29-83.
 34. Jelvehgari M, Rashidi MR. Adhesive and spreading properties of pharmaceutical gel composed of cellulose polymer. Jundishapur journal of natural pharmaceutical Products. 2007;2(1):45-58.
 35. Jain A, Gautam SP, Gupta Y, Khambete H, Jain S. Development and characterization of ketoconazole emulgel for topical drug delivery. Der Chemica Sinica. 2010;1(3):221-231.
 36. Farooq M, Shoaib MH, Yousuf RI, Qazi F, Hanif M. Development of extended release loxoprofen sodium multiparticulates using different hydrophobic polymers. Polymer Bulletin. 2019;76(5):2537-58.
 37. Maraie NK, Kadhium HS. Efficacy of Gelling Agents on The In Vitro Release and Physical Properties of Loxoprofen Sodium Gel Containing Ultra Elastic Vesicles. Technology.9(4):671-7.
 38. Peppas NA, Narasimhan B. Mathematical models in drug delivery: How modeling has shaped the way we design new drug delivery systems. Journal of Controlled Release. 2014;190:75-81.
 39. Bruschi ML. Strategies to modify the drug release from pharmaceutical systems Woodhead Publishing; 1st Edition, volume 10, 2015.