Preparation and Evaluation of Diclofenac Sodium Loaded Liposomal Hydrogel in the Treatment of Rheumatoid Arthritis

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ABSTRACT

In the present research, it was proposed to provide topical delivery of diclofenac sodium. Diclofenac sodium will be encapsulate in liposome and further loaded into a hydrogel and delivered through topical route. The lipid film hydration approach was used to create diclofenac sodium liposomes, which were then characterised by vesicle size, zeta potential, and entrapment effectiveness. The pH of the generated liposomal gels was within the permissible range of 7.0-7.2. The spreadability of the gels was assessed using slip and drag characteristics and was found to be between 10.45 and 12.32 gm.cm/sec. F1, F2, and F3 spreadabilities were determined to be $10.45\pm0.075, 12.32\pm0.042$ and 11.75 ± 0.049 gm.cm/sec, respectively. The viscosities for F1, F2, and F3 were determined to be 1870 ± 25 cps, 1895 ± 33 cps, and 1875 ± 21 cps, respectively. The percentage of cumulative medication (diclofenac sodium) released from F1, F2, and F3 liposomal gel formulations was $98.15\%\pm17$, $98.72\%\pm2.4$ and $96.27\%\pm2.7$ respectively.

Keywords: Liposomal hydrogel; Diclofenac sodium; Entrapment efficiency; Rheumatoid arthritis; Spreadability; Lipid film; Zeta potential.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory condition that mainly impacts the joints. Warm, swollen, and painful joints are frequently the outcome. After resting, pain and soreness frequently get worse. The wrist and hands are usually involved, and the same joints are frequently involved on both sides of the body. In addition to the blood and nerves, the illness may also impact the skin, eyes, lungs, heart, and nerves. As a result, it's possible for low red blood cell counts, inflammation around the heart and lungs, and other complications to occur. Fever and decreased energy are other potential symptoms. In many cases, symptoms develop progressively over weeks or months [1,2,3].

A study that found that RA affects between 2 and 3% of adults also found that women have more than twice the likelihood of developing the condition than do males. According to the World Health Organization (WHO), this disease is most prevalent in women and has a prevalence of 0.3% to 1% [4,5].

NSAID's are frequently used to treat the symptoms of other rheumatic illnesses that are characterised by persistent musculoskeletal pain and a variety of acute pain symptoms. Due to NSAID's potent anti-inflammatory and analgesic properties, they are frequently used in rheumatism in addition to being used to treat osteoarthritis and inflammatory arthritis [6].

Topical drug administration is a localised method of delivering medication through the epidermis, vagina, rectal, and ophthalmic cavities. The primary path of topical drug delivery is through the skin, one of the most easily available organs on the human body for topical administration. Topically applied medications can have systemic, localized, or surface impacts. Because of its medicinal qualities, such as its emollient, soothing, or protective

action, the base may occasionally be used on its own. However, a lot of topical preparations have therapeutically effective components that are dispersed or dissolved in the base [7,8].

Polymeric hydrogels are hydrophilic 3D polymer networks with the ability to incorporate a lot of water, much like body tissues do. This characteristic makes hydrogels suitable materials for pharmaceutical and medical applications, as they can enclose therapeutic molecules and shield them from quick degradation.

In comparison to other traditional formulations like creams, ointments, and gels, liposomal hydrogels have a few advantages. They increase drug retention in the skin, resulting in greater drug concentrations in the skin, while also reducing drug absorption throughout the body. Additionally, liposomal hydrogels transport sufficient amounts of medicines for therapeutic effectiveness while acting as a drug depot and providing continuous localised drug delivery [10].
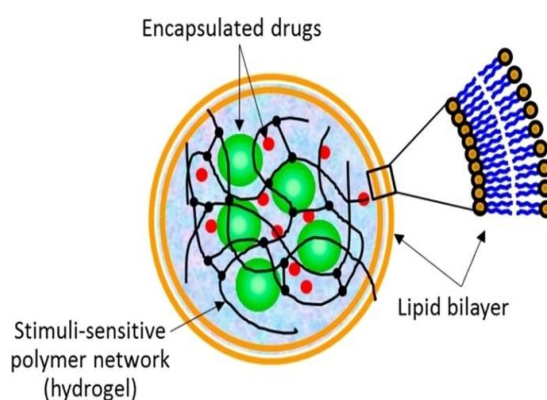

Figure 1. Liposomal hydrogel [11]

1.1. Study Objectives

The following are the main objectives of this study. (i) To develop liposomal gel-based formulation for the useful and effective treatment in Rheumatoid Arthritis. (ii) To increase drug retention in the skin, resulting in higher drug concentrations in the skin. (iii) The lipid film hydration method will be used to create diclofenac sodium liposomes. (iv) Liposomes should have a mean size of 100-200 nm. (v) The Spreadability, viscosity and pH should be in the permissible range.

2. Material and methods

2.1. Materials

Diclofenac sodium, soya phosphatidyl choline from S.D.fine chemicals, Mumbai, cholesterol from Qualigens chemicals, Mumbai, carbopol 934 from S.D.fine chemicals, Mumbai, ethyl paraben, propyl paraben and propylene glycol from Loba chemicals Mumbai [12,13].

2.2. Method

The thin-film hydration technique was used to create the liposomal hydrogel. The liposome was prepared by taking soyabean phosphatidylcholine as phospholipid, cholesterol. Then the drug loaded liposomes was incorporate in to hydrogel by taking Carbopol 934 as gelling agent, propylene glycol as a solvent, methyl paraben, ethyl paraben as preservative.

2.2.1. Preparation of liposome loaded with diclofenac sodium

The liposomes were prepared by thin-film hydration method by using rotatory evaporator. The phospholipid and cholesterol were taken in the ratio of 7:3 and was dissolved in absolute ethanol 10 ml by vortexing and sonication. The organic solution was poured in to the RBF and placed for evaporation by fitted through rotatory evaporator under vacuum condition at 110 RPM and 40 degree Celsius temperature. After the formation of film the drug which was added in the milli-q water was added in to the film for the hydration of film for preparation of proliposomes [14,15].

Table 1. Ingredients used in the formulation of liposomes

S.No.	Ingredients	Description
1.	Soya phosphatidylcholine	70 mg
2.	Cholesterol	30 mg
3.	Diclofenac sodium	50 mg
4.	RPM	110 RPM
5.	Temperature	40

2.2.2. Preparation of Carbopol gel base

Carbopol 934 (0.5 g) was weighed and dispersed in 100ml distilled water with gentle stirring for 24 hours to yield 0.5% gel. Later, 2 ml of glycerine was added to the gel to keep it consistent. The gel also contains preservatives (methyl paraben and propyl paraben). Similarly, Carbopol gels at 1% and 2% were made [16].

Table 2. Formulation code of liposomal hydrogel

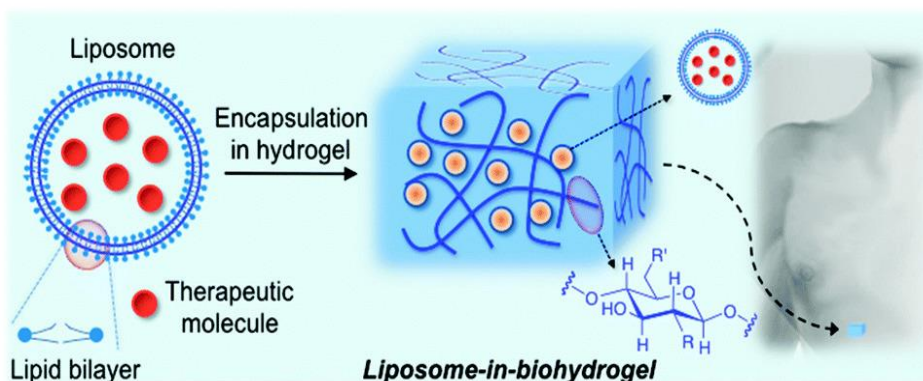| S.No.	Ingredients	Formulation code		
		F1	F2	F3
1	Liposomal diclofenac sodium	3ml	3ml	3ml
2	Carbopol 934	0.25g	0.5g	1g
3	Propylparaben	0.01g	0.01g	0.01g
4	Methylparaben	0.05g	0.05g	0.05g
5	Glycerine	2ml	2ml	2ml
6	Distilled water (qs)	50ml	50ml	50ml

Figure 2. Preparation of liposomal hydrogel [17]

3. Evaluation of prepared diclofenac sodium loaded liposomal hydrogel

3.1. Physical examination

The prepared diclofenac sodium loaded hydrogel formulation was inspected visually for its colour, appearance and consistency [18].

3.2. Determination of pH

50 gm of each gel formulation were weighed and transferred to a 10ml beaker, where the pH was calculated using a digital pH metre. To treat skin infections, the pH of the topical gel formulation should be between 3 and 9 [19].

3.3. Spreadibility test

The spreadability of liposomal gel composition was assessed using the gels' slip and drag properties. Two glass slides were used in a modified and built apparatus, with the bottom of each slide coupled to a wooden plate and the top of each slide connected by a hook to a balance. S=ml/t, where S is the spreadability, m is the weight in the pan attached to the higher slide, t is the amount of time needed to move a specific distance, and l is the actual distance gone, was used to determine the spreadability. For practical reasons, the mass, length, and 't' were all kept constant. Each formulation's spreadability was assessed three times, and the average results are displayed.

3.4. Viscosity test

The viscosity of gels was measured with a Brookfield viscometer. The gel viscosity was determined using Spindle No. 6. During the process, the variables that affect viscosity, such as temperature, pressure, and sample size, were kept constant. The reading for torque was consistently greater than 10%. The viscosity was calculated by averaging five observations made at 10 rpm over a period of 60 seconds [20].

3.5. Drug content

Diclofenac sodium-loaded liposomal hydrogel (100mg) was transferred to a 10 ml volumetric flask, which was then filled to capacity with PBS (pH 7.4). Utilising Whatmann filter paper, the resulting solution was purified. The volume was raised to 10 ml by adding 1 ml of filtrate to a 10 ml volumetric flask and using the same buffer. The absorbance of the sample solutions at 303 nm was measured, and the concentration of pharmaceuticals in the sample solution was calculated using the absorbance values [21].

3.6. Spreadability

Spreadability was determined using a modified device. The spreadability of the gels was assessed using slip and drag characteristics and was found to be in the 10.45-12.32gms. cm/sec range. Because very high and very low Spreadability values suggest that applying the gel to the location is challenging (Table 3), the gels should have optimal Spreadability [22].

3.7. Measurement of viscosity

The viscosity (in cps) of the produced gel formulation was measured using a Brookfield viscometer. The spindle no. 6 was set to 10 revolutions per minute. The formulation's torque% was close to 10%. The viscosity was

calculated by averaging 60 seconds of data at 6 to 10 rpm. The gels' viscosity increases as polymer concentration increases. The increase in bonds between polymer molecules that occurs as polymer concentration rises causes a hard, dense, and compact mass to form. This hardness is related to the fact that gels with high polymer concentrations contain less liquid than gels with low polymer concentrations; in other words, the higher the polymer concentration, the more shear force is required to generate a particular rate of shear [23].

3.8. Drug content analysis

The drug content of several liposomal hydrogel formulations was estimated, and the findings are shown in Table 3. The drug content determination further revealed that the drug was dispersed consistently throughout the gel. The viscosity and spreadability measurements show that the formulations are capable of supporting the liposomal formulation. Furthermore, the F2 formulation has an optimal viscosity that allows it to be spread uniformly across the skin and retain contact with the skin for a longer amount of time, resulting in maximal therapeutic benefit. Furthermore, the pH of the formulations indicates that they are in the range of 7.0 to 7.2, indicating that they are safe for application to the skin and will not cause irritation or harmful effects [24].

3.9. Stability studies

The optimised formulation of diclofenac sodium-loaded liposomal hydrogel was subjected to accelerated stability tests at 41°C, room temperature (25°C), and humidity 60% RH (Relative humidity). The prepared formulation was kept in screw-capped amber glass bottles. After 7, 14, 21, and 28 days of storage under specified conditions, samples were analysed for vesicle size and drug content [25].

4. Result and discussion

4.1. Effect of storage temperature on vesicle size

After 7, 14, 21, and 28 days, the vesicle size of the formulations held at 41°C and 25°C was evaluated using a Zetasizer.

4.2. Effect of storage temperature on drug content

The drug content of both formulations was evaluated after storage for a defined period of time of 7, 14, 21, and 28 days. As previously discussed, the drug content of liposome gel was measured spectrophotometrically [26].

4.3. Evaluation of prepared diclofenac sodium loaded liposomal hydrogel

Physical appearance, pH, spreadability, viscosity, and in-vitro drug release experiments were used to evaluate liposomal gels.

4.4. Physical examination

The diclofenac sodium-loaded liposomal hydrogel was discovered to be cream yellow in colour and semi solid and creamy in substance [27].

4.5. Determination of pH

The pH of the transdermal drug delivery method is critical. A digital pH metre was used to determine the pH. The pH values of the generated liposomal gels were within acceptable limits, and the pH study diclofenac sodium

loaded liposomal hydrogel formulation results show that all formulations are suitable for skin delivery. The pH values of the produced drug-loaded liposomal hydrogel ranged between 7.0 and 7.2.

Table 3. Results of diclofenac sodium loaded liposomal gel formulation

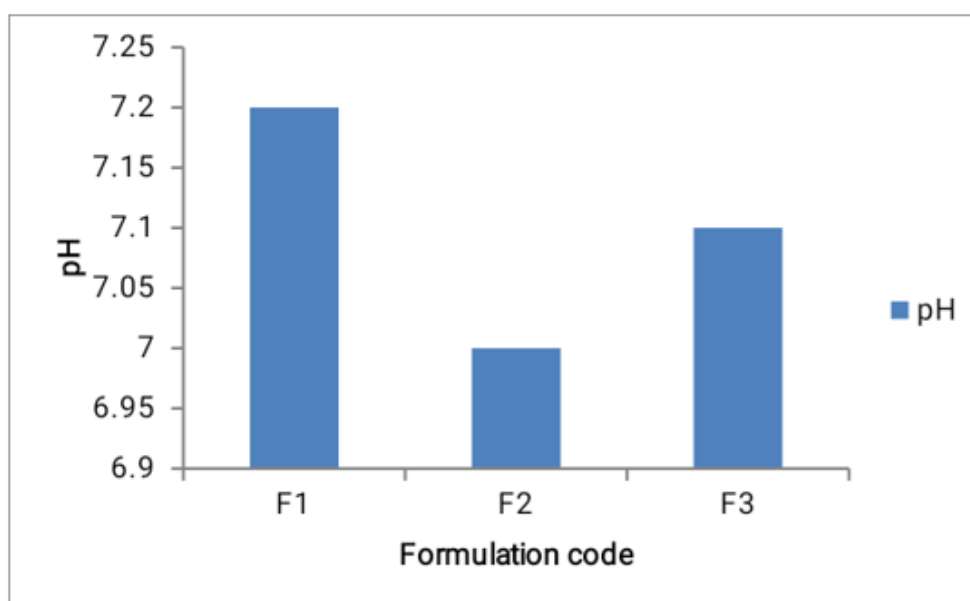| S.No.	Formulation batch	pH	Spredabiility (gm.cm/sec)	Viscosity(cps)	% Drugcontent
1.	F1	7.2±0.024	10.45±0.075	1870±25	95.25±2.24
2.	F2	7.0±0.035	12.32±0.042	1895±33	98.15±1.28
3.	F3	7.1±0.045	11.75±0.049	1875±21	97.75±2.12

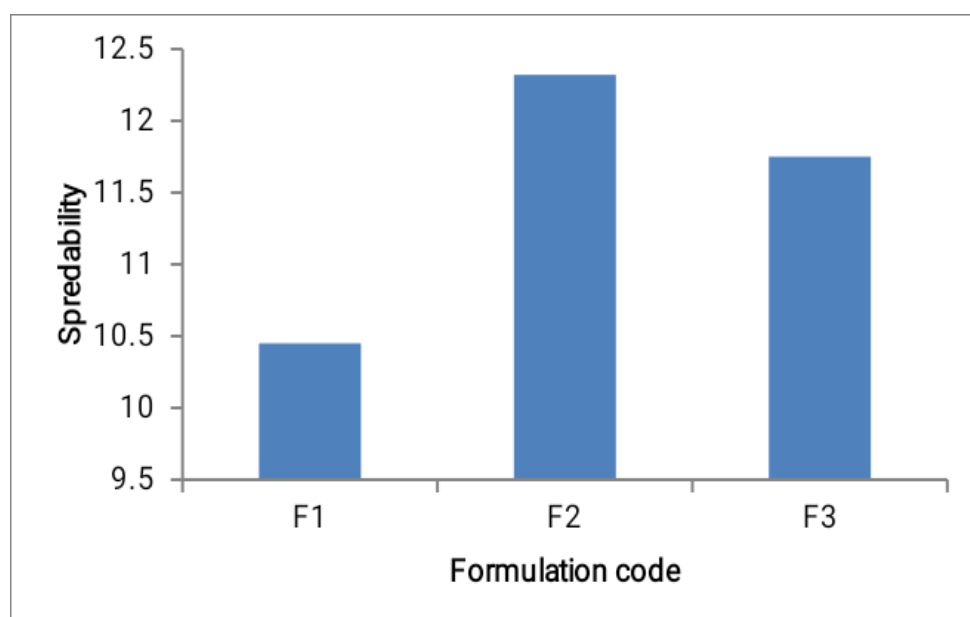**Figure 3.** pH of liposomal formulations
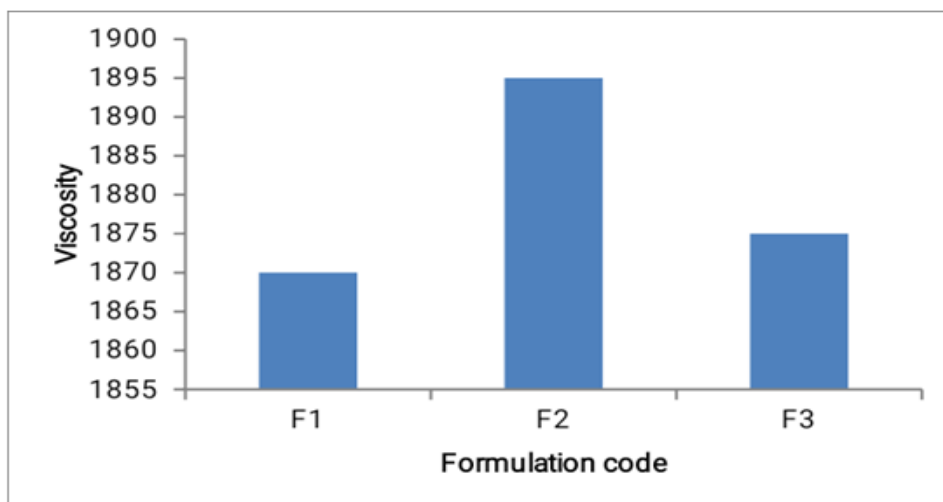

Figure 4. Spreadability of liposomal formulations

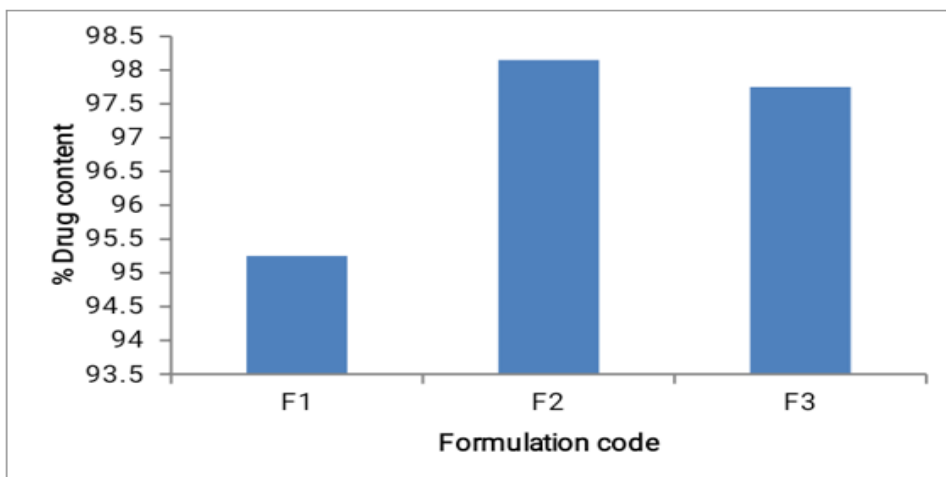**Figure 5.** Viscosity of liposomal formulations

Figure 6. Drug content of liposomal formulations

4.6. In-vitro drug release study

The liposomal gels (F1, F2, and F3) were studied in vitro for 12 hours using a modified Franz diffusion cell with a dialysis membrane in phosphate buffer pH 7.4. Table 4 and Figure 7 summarise the results of diffusion studies. UV spectrophotometry at 303nm was used to assess the rate of gel release from liposome formulation.

Table 4. In-vitro drug release of liposomal hydrogel formulation

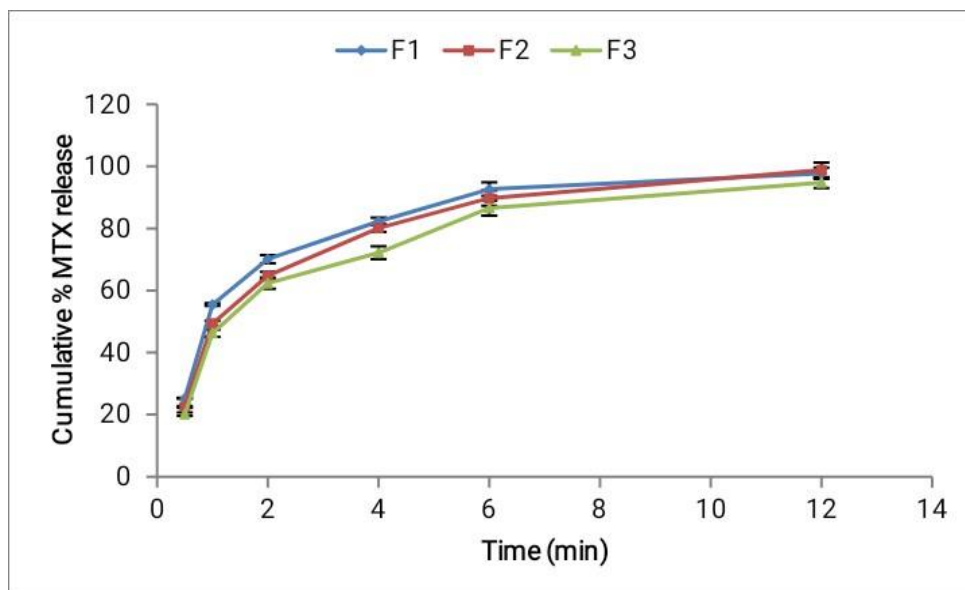| Time (hrs)	Cumulative % drug release		
	F1	F2	F3
0.5	27.35±0.15	25.53±0.26	20.13±0.47
1	54.35±0.25	49.22±0.87	47.23±1.3
2	69.13±1.32	68.74±1.18	60.24±1.7
4	83.67±1.25	82.13±2.3	75.15±2.3
6	93.55±2.2	89.37±2.4	88.54±2.2
12	98.15±17	98.72±2.4	96.27±2.7

Figure 7. Cumulative % drug release from liposomal hydrogel formulations

The drug was discovered to be released from liposomal gel in the following order: F2>F1>F3. The greatest drug release rate was observed in the case of F2 liposomal gel formulation in a drug release study. Based on the results, F2 was chosen as the optimal gel formulation in terms of drug release and other qualities such as viscosity and spreadability.

4.7. Result of stability studies

Stability studies for optimised formulations were conducted over a four-week period at $4.0\pm1^{o}C$ and $25\pm1^{o}C$. There was no significant difference in the physical appearance, vesicle size, or percentage medication content of the liposomal gel F2. Table 5 shows that no noticeable changes in the appearance of the gel formulation were detected at the end of the storage period.

According to the data, there was a little decrease in % drug content at ambient temperature and freezing temperature, which is insignificant, and an increase in vesicle size was found for the optimised batch at $25\pm1^{o}C$. The results indicate that maintaining the liposomal product in refrigerated conditions minimises liposomal gel stability issues, and so the best suited temperature for liposomal gel is $4.0\pm1^{o}C$.

Table 5. Effect of storage temperature on the vesicle size of drug loadedliposomal gel F2

Time	Average Vesicle Size (nm)	
(Days)	$4.0\pm1^{o}C$	$25 \pm 1^{o}C$
0	163.33	165.45
7	176.39	179.80
14	161.43	182.98
21	154.56	187.58
28	167.34	198.67

Table 6. Effect of storage temperature on the % drug content

Time	% Drug Content	
(Days)	4.0±1ºC	25 ± 1ºC
0	96.29±0.02	91.74±0.23
7	89.54±0.16	88.22±0.13
14	79.47±0.21	98.13±0.54
21	98.41±0.23	97.65±0.78
28	88.75±0.17	86.83±0.37

5. Summary and Conclusion

The diclofenac sodium-loaded liposomes are used to create the gel. The lipid film hydration approach was used to create diclofenac sodium liposomes, which were then characterised by vesicle size, zeta potential, and entrapment effectiveness. The TEM analysis revealed that the liposomes are small, spherical vesicles, but there is some variance in size distribution in the TEM image. Liposomes have a mean size of 100-200 nm, according to TEM.

Following that, three distinct concentration ranges. Carbopol gel bases (F1, F2, and F3) with concentrations of 5%, 1%, and 2% were produced. pH, spreadability, viscosity, and in-vitro drug release tests were performed on liposomal gels. A digital pH metre was used to determine the pH. The pH of the generated liposomal gels was within the permissible range of 7.0-7.2. The spreadability of the gels was assessed using slip and drag characteristics and was found to be between 10.45 and 12.32 gms/cm sec. F1, F2, and F3 spreadabilities were determined to be 10.45 0.075, 12.320.042, and 11.750.049, respectively. The viscosities for F1, F2, and F3 were determined to be 187025 cps, 189533 cps, and 187521 cps, respectively.

Liposomal gels (F1, F2, and F3) were studied in vitro in phosphate buffers pH 7.4 for 12 hours using a modified Franz diffusion cell with dialysis membrane. After 12 hours, the percentage of cumulative medication (diclofenac sodium) released from F1, F2, and F3 liposomal gel formulations was 98.15±17, 98.72±2.4 and 96.27±2.7 respectively. The medication was discovered to be released from liposomal gel in the following order: F2>F1>F3. The greatest drug release rate was observed in the case of F2 liposomal gel formulation in a drug release study. F2 was chosen as the optimised gel formulation based on the results.

Stability studies for optimised formulations were conducted over a four-week period at 4.0±1ºC and 25ºC. There was no significant difference in the physical appearance, vesicle size, or percentage medication content of the liposomal gel F2. Stability experiments for Liposomal gel show that the developed formulation is more stable at freezing temperatures than at room temperatures.

In summary, it can be concluded that liposomal gel has proven to be an efficient carrier for transdermal drug delivery of therapeutic molecules. The new liposomal gel-based formulation may be highly useful in the effective treatment of RA. However, clinical correlation and more conclusive study may be required before the same can be used in the treatment of RA in humans.

6. Future Suggestions

(i) This novel method can be developed to overcome the drug limitations such as poor solubility, absorption, and miscibility with lipoidal cell membrane.

(ii) It will be utilized to encapsulated wide range of bioactive compounds in Pharmaceutical, cosmetic and food industry.

(iii) Hydrogels by nature of transparency can be used to promote the monitoring of wound healing.

(iv) Liposome products can be used in anticancer and antifungal therapy and for the prophylaxis of diseases.

Declarations

Source of Funding

This study has not received any funds from any organization.

Conflict of Interest

The authors declare that they have no conflict of interest.

Consent for Publication

The authors declare that they consented to the publication of this study.

Authors' Contribution

All the authors took part in data collection, literature review, analysis, and manuscript writing.

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