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Original Research Article

Formulation and evaluation of nano-ethogel of silver sulfadiazine for treatment of topical burns

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ABSTRACT

Introduction: The present study deals with the formulation of ethosomal suspension containing silver sulfadiazine, followed by its incorporation into a hydrogel, leading to the formulation of a novel vesicular nano-ethogel of silver sulfadiazine for the treatment of topical burns.
Materials and Methods: Silver Sulfadiazine ethosomes were prepared by the hot method suggested by Elka Touitou. This ethosomal suspension was loaded into hydrogel made of Carbopol 934 in a ratio of 1:1. Carbopol 934 was chosen as a gelling agent as it do not cause any sort of skin irritation. The nanoethosomal formulations containing SSD were evaluated for their physical appearance, pH, spreadability, viscosity, extrudability, drug content.
Result and Discussions: In vitro drug release studies were performed for five hours and it was observed that the formulation F4 had the maximum amount of drug released within duration of five hours i.e. 76.80%. The complete study wrap up that this ethosomal approach of silver sulfadiazine incorporated into a hydrogel provides an advance sustained and targeted delivery of silver sulfadiazine.

1. Introduction

Nanotechnology, often abbreviated as nanotech is referred to as imaging, designing, modeling, formulation, characterization, and application of structures by controlled modification of size and shape at the nanometer scale (1nm to 100nm), thereby, producing system with novel properties. Particles formulated in such a manner are termed as nanoparticles. [1]

The ethosomes are vesicular carrier systems consisting of hydroalcoholic or hydro/alcoholic/glycolic phospholipid with relatively high alcoholic concentrations (Figure 1). Main components of ethosomes are phospholipids, ethanol (upto 45%), glycerol and water, which facilitate delivery of high concentration of active ingredients through skin. [2,3]

As ethosomes are soft and malleable vesicles, they serve as potential carriers for drug transportation. Active drug permeation can be enhanced by acclimatizing due to efficacy, safety, and simplicity in their medication.

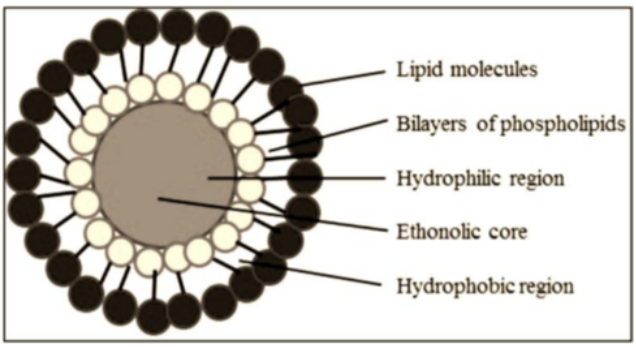

Fig. 1: Structure of ethosome [4]

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Table 1: Composition of ethosomes [5,6]

Classes	Types	Concentration	Uses
Alcohol	Ethanol	20-50%	Efficient permeation enhancer
Other alcohols Glycols	Isopropyl alcohol (IPA) Propylene glycol (PG)	5-20%	In the preparation of ethosomes along with ethanol, efficient permeation enhancers
Phospholipids	Phospholipon 90G, 90H, 80H Lipoid S100, S75,S75-3, E80 Soya phosphatidylcholine (SPC50)	0.5-10%	Vesicle forming agents
Cholesterol	Cholesterol	0.1-1%	Provide vesicular stability and rigidity

Table 1 xemplifies the components of ethosome along with their examples,concentrations and uses.

The advances within the field of nanotechnology have led to the likelihood of converting metallic silver into finer nanoparticles. These nanoparticles are more practical than the first form against microbes. These nano particles have proven to create topical silver treatment more practical and safer. [5–7]

1.1. Silver sulfadiazine (SSD)

Silver Sulfadiazine is a sulfonamide-based topical agent with broad spectrum antibacterial and antifungal activity. The chemical category of silver sulfadiazine is sulfonamides.

Silver sulfadiazine (SSD) is an efficient antibacterial agent approved by the USFDA, which is taken into account as the gold standard treatment in burn injuries. [8–10]

1.2. Mechanism of action of SSD [8–10]

Silver is a biocide, which binds to a broad range of targets. Silver ions bind to nucleophilic amino acids, further sulfhydryl, amino, imidazole, phosphate, and carboxyl groups in proteins, causing protein denaturation and enzyme inhibition. When SSD agent interacts with sodium chloride-containing body fluids, silver ions are released sluggishly and sustainably into wounded areas. Ionized silver atoms catalyze the formation of disulfide bonds resulting in protein structural changes and inactivating thiol-containing enzymes; silver ions may also fitDNA thereby snooping with replication and transcription of bacteria. As a competitive inhibitor of para-aminobenzoic acid (PABA), sulfadiazine inhibits bacterial dihydropteroate synthase, thereby acting in disruption of folic acid metabolism and eventually DNA synthesis.

1.3. Pathophysiology of burns

Burn is defined as an injury causing destruction to the epidermal, dermal or other deeper tissues on exposure to thermal, chemical or electrical agents. [11]

A survey conducted by World Health Organization indicates that in a year approximately 1,80,000 people die due to burns. Therefore, it has been declared as a global public health problem by WHO. [12,13] According to the data of American Burn Association (ABA), there are over 4,50,000 of fatal burn injuries occurring alone in United States. [14]

1.4. Chemical sequences occurring at the time of burn

As a result of burns, proteins in the cells denature and coagulate. The burnt tissues stimulate the release of certain chemicals like histamine, kinin, serotonin and prostaglandin. Leukocytes and platelets adhere to the endothelium and cytotoxic T cells increase, therefore, making the tissue available as an open site for infection. [11,15]

1.5. Injury due to burn occurs in two stages [11,16]

1. Stage- coagulative type necrosis forming in epidermis and tissues
2. Stage- cell lysis as a result of dermal ischemia (with in 24-48hours)

The depth of injury is determined by amount of time period and degree of heat to which it is exposed.

2. Materials and Methods

Silver sulfadiazine was a gift sample from Macsen Drugs, Gudli, Udaipur. Chemicals like soya lecithin, ethanol, ammonia solution (25%), propylene glycol and carbopol 934K were obtained from the laboratory of Bhupal Nobles College of Pharmacy, Udaipur. All chemical solvents were of analytical grade and used without further purifications.

3. Preformulation Studies

3.1. Melting point determination

The melting point of the sample is done to check the purity of the sample. Melting point is defined as the temperature

at which a solid substance transits its state from solid to liquid.[17] Melting point of silver sulfadiazine was found by using the digital melting point apparatus from Remi Instruments.

3.2. Solubility analysis

Solubility is defined as the ability of a solute to dissolve in a liquid (solvent) to form a homogeneous solution. Factors affecting solubility are; type of solvent used, temperature and pressure.[18]

Solubility analysis was primarily performed in order to find out a suitable solvent to dissolve the API, lipid and excipients used for formulation preparation.

3.3. Partition coefficient of the drug

Partition coefficient is the measure of the lipophilic and hydrophilic nature of a drug substance.It is defined as the extent to which a substance is distributed between two liquid phases, one being the aqueous phase and other being the oily phase. The majorly used phases are water and n-octanol (oil phase) in the ratio 1:1.[19]

$$P\,o/w = \frac{C\,(n-octanol)}{C\,(water)}$$

3.4. Determination of λ_{max} of silver sulfadiazine in 0.05% ammonia solution

Accurately weighed 100mg of silver sulfadiazine was added to a 100 ml volumetric flask. The drug was then shaken using 0.05% ammonia solution and volume was made up to the mark to get a stock solution. From this stock solution, aliquots of 100μg/ml were prepared by further dissolving 10ml of the above solution in 100ml of 0.05% of ammonia solution. The dilution was scanned from 400–200 nm with UV spectrophotometer keeping the 0.05% ammonia solution as blank. The spectrum of absorbance versus wavelength was recorded on UV-spectroscopy and analyzed for absorbance maximum and the highest absorbance was noted.[20]

3.5. Calibration curve of silver sulfadiazine using 0.05% ammonia solution

A 100μg/ml solution of silver sulfadiazine was prepared using 0.05% ammonia solution. This solution of 100μg/ml was used to prepare aliquots of varying concentration viz 2-18 μg/ml respectively. Absorbance of each of the solution was measured at 254nm in UV-spectrophotometer using 0.05% ammonia solution as blank and graph of concentration versus absorbance was plotted. The slope, straight line equation and correlation coefficient were obtained from the calibration curve intercept.

3.6. Preparation of silver sulfadiazine loaded ethosomal suspension

Ethosomal suspension of silver sulfadiazine was prepared based on the hot method suggested by Elka Touitou for the exploitation of ethosomal nanocarriers.

A dilution of silver sulfadiazine was prepared in 25% ammonia solution. Six different formulations i.e. F1, F2, F3, F4, F5 and F* were prepared by changing the concentration of ethanol and propylene glycol, along with the required amount of drug (500μg) by heating the preparation to 40°C followed by mechanical stirring at 400rpm. Lecithin was suspended in required quantity of water for a few hours and was quickly stirred mechanically at 900-1100 rpm and then heated to 40°C so that it was completely bloomed at the time of usage. Lipid phase was added dropwise to ethanol mixture with continuous and closed magnetic stirring at room temperature for 30 min at about 300 rpm to achieve uniform mixing. The formulation was finally sonicated using a probe sonicator (Frontline Sonicator) for about 5-8 min keeping in an ice bath (4°C). A homogenous SSD ethosomal suspension was obtained.[21] The nano-ethosomal formulation was stored in a covered vessel at room temperature, away from light for further experimentation.

Composition of SSD ethosomal formulations is given in Table 2 below.

3.7. Preparation of SSD Loaded Ethosomal Gel (Ethogels)

Hydrogels were prepared by dispersing 1.5% w/w of Carbopol 934 in distilled water. The Carbopol hydrogel was neutralized by addition of triethanolamine dropwise, and then the ethosomal suspension in a ratio of 1:1 (1 part of suspension: 1 part of gel) was added to it at 200 rpm for 5 min to get a homogeneous dispersion.

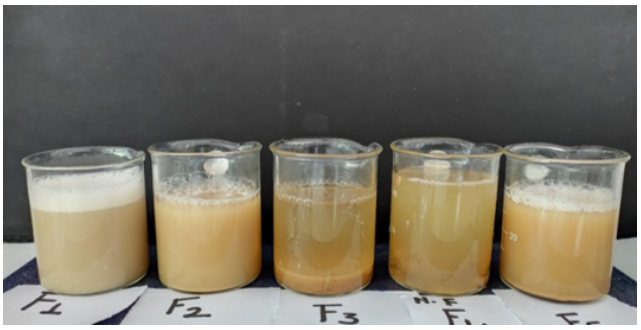

Fig. 2: Silver sulfadiazine loaded ethosomal formulations

Table 2: Composition of different silver sulfadiazine loaded ethosomal formulations

Formulation	Cholesterol (%w/v)	Ethanol (% v/v)	Propylene Glycol (% v/v)	Lecithin (%w/v)	Water (ml)
F1	0.5	20	2	1	26.5
F2	0.5	25	2.5	2	20
F3	0.5	30	3	3	13.5
F4	0.5	35	3.5	4	7
F5	0.5	40	4	5	1.5
F_*	0.5	25	5	6	13.5

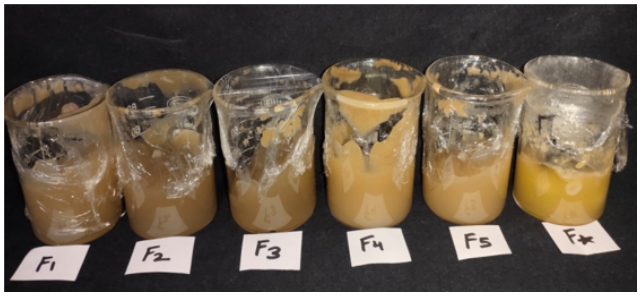

Fig. 3: SSD-loaded ethogels

3.8. Evaluation of prepared SSD-loaded ethogels

3.8.1. Physical appearance

The prepared gel was examined for clarity, colour, homogeneity, odour, feel upon application (greasiness, grittiness) and texture.

3.8.2. Viscosity

The viscosity of the prepared gel was carried out using a Brookfield viscometer using T-bar spindle (spindle#4). The speed of 3 rpm was maintained for spindle rotation and the values were measured when the gel level was stabilized.

Viscosity (mPa.S) = dial reading x factor

3.8.3. pH:[22]

A solution of 1gm of gel was prepared by dissolving in 30ml distilled water. The pH of the ethosomal gel was determined by the use of a digital pH meter.

3.8.4. Spreadability[23,24]

The parallel plate method was used to evaluate spreading behavior using an in-house spreadability testing apparatus that consisted of two smooth glass slides to hold the gel samples tied to a pre weighed volumetric flask. Excess of the gel sample was spread on the surface of the lower slide, then the upper slide was used to cover the sample and a 100 g weight was used to compress the sample between the two slides for 5min to obtain a layer of uniform thickness.

The time (in seconds) required for the upper slide to move away to the edge of the lower slide and the weight required was recorded and spreadability was calculated using to the following equation-

$$S = \frac{M}{T} x\ L$$

Where, S is the spreadability (gm.cm/sec), M is the mass placed on the pan, L is the length of the slide (cm), and T is the time (in seconds) required to move the upper slide.

3.8.5. Extrudability[23]

The extrudability is defined as the amount of formulation that can be ejected from a collapsible tube. The test was performed using a clean aluminum collapsible tube (20 g capacity) with a tip opening diameter of 1 cm. The extrudability was evaluated in by measuring the weight of gel sample ejected from the tube opening upon pressing with fingers, while holding the tube in hands.

3.9. Content uniformity and drug content

The drug content of the prepared gels were conducted by dissolving accurately weighed quantity of 1g gel in 100 ml volumetric flask and volume was made up to 100 ml with 0.05% ammonia as a solvent. The contents were magnetically stirred for 2-3 hours. The contents were filtered followed by making appropriate dilutions. The prepared dilutions were analyzed spectrophotometrically using an UV spectrophotometer at a maximum wavelength of 254nm.

3.10. In vitro drug release

The in vitro drug release studies from prepared SSD ethosomes were performed using dialysis bag diffusion technique.

0.5ml of each prepared SSD ethosomal formulation was filled into the diffusion bag and bag was precisely tied with threads at both the ends and suspended in a beaker which was filled with phosphate buffer solution (PBS) at pH 7.4. The prepared model was stirred with the help of a magnetic stirrer (Remi Equipments, India) at 50 rpm. Samples were withdrawn from the receiver medium at time intervals of 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 hours and then were replaced with equal volumes of fresh PBS. The pH was mandatorily maintained to 7.4 every time. The amount of drug released in buffer was determined using a UV-Vis

spectrophotometer at 254 nm, keeping PBS as blank.

3.11. Stability study

Ethosomal gel formulations were stored in well closed glass beakers under the following conditions and testing was performed at the specified time points:

Room temperature at 25±°C: analysis was performed after the 14^{th} and 28^{th} days of storage.

Refrigerated temperature at 4±2°C: analysis was done after the 14^{th} and 28^{th} days of storage.

4. Results and Discussion

4.1. Identification of pure drug

4.1.1. Melting point determination

Melting point of silver sulfadiazine was determined to be 284°C. It was observed that Silver Sulfadiazine's melting point falls in line with USP standard therefore, it confirms that the drug is free of any impurities.

4.1.2. Solubility analysis

Silver sulfadiazine is insoluble in distilled water, slightly soluble in acetone, practically insoluble in alcohol, chloroform, ether and is freely soluble in 30% ammonia.

4.1.3. Partition coefficient

The Log P of Silver Sulfadiazine was found to be around 2.1 indicating that the drug is highly lipophilic in nature.

4.1.4. Particle size of pure SSD

Particle size was determined using Malvern Zetasizer and was found that all the particles have an average size range lying between 0.1 to 12 μm. The graph obtained is depicted in Figure 4.

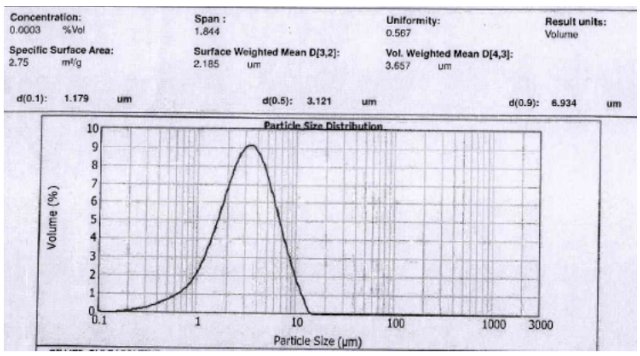

Fig. 4: Particlesize distribution curve of pure silver sulfadiazine

4.1.5. Determination of λ_{max}

The absorbance spectrum of pure Silver sulfadiazine was scanned using a double beam UV spectrophotometer (Shimadzu 1900) in the range 400nm-200nm with concentration of 100 μg/ml in 0.05% ammonia solution. The maximum absorption was obtained at 254 nm.

4.1.6. Standard calibration curve of silver sulfadiazine

The calibration curve of Silver Sulfadiazine was obtained by using the 2-18μg/ml concentration of Silver Sulfadiazine in 0.05% ammonia solution. The absorbance was measured at 254nm. The calibration curve which was plotted was linear in the range of 2-18μg/ ml at λ_{max} 254nm. The correlation coefficient was found to be 0.996. The calibration curve is depicted in Table 3 and Figure 5.

Table 3: Silver sulfadiazine calibration curve (λ_{max} = 254 nm)

S. No.	Concentration (μg/ml)	Absorbance
1.	2	0.136
2.	4	0.19
3.	6	0.29
4.	8	0.393
5.	10	0.479
6.	12	0.556
7.	14	0.622
8.	16	0.718
9.	18	0.785

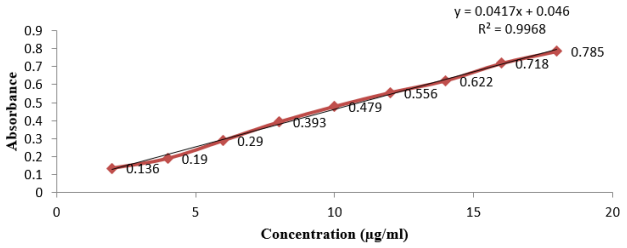

Fig. 5: Calibration curve for silver sulfadiazine

Table 4: Result of regression analysis of UV Method

Statistical Parameters	Results
λ_{max}	254nm
Regression equation (y = mx + c)	0.041x + 0.046
Slope (m)	0.041
Intercept (c)	0.046
Correlation coefficient (R^2)	0.996

4.2. Evaluation of prepared SSD-loaded ethogels

4.2.1. Physical appearance, pH, viscosity, spreadability and extrudability of the prepared gel

All the prepared formulations were homogenous in appearance and smooth in texture. The pH of all was found to be in range of 6.7-7.2, which suit the skin pH indicating the skin compatibility.

Table 5: Physicalappearance, ph, viscosity, spreadability and extrudability of the prepared gel

Formulation	Appearance	pH	Viscosity (mPa.S)	Extrudability (gm)	Spreadability (gm.cm/sec)
F1	Light brown ,Homogenous	6.7	24,000	0.5	7.67
F2	Mud brown, Homogenous	7.0	26,000	0.5	7.63
F3	Mud brown, Homogenous	6.8	38,000	1.3	6.84
F4	Light brown, Homogenous	6.4	34,000	1.8	10.11
F5	Light brown, Homogenous	6.7	43,000	1.6	14.13
F*	Light brown, Homogenous	7.2	29,000	2.2	10.30

Table 6: Percentage drug content of SSD loaded topical ethogels

S. No.	Formulation Code	Drug Content (%)
1.	F1	46.44
2.	F2	48.24
3.	F3	53.30
4.	F4	81.64
5.	F5	74.59
6.	F_*	70.34

Table 7: In Vitro drug release (%) of different formulations of SSD ethosomes

Time (hr)	F1	F2	F3	F4	F5	F_*
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
0.5	6.14±0.92	8.90±0.010	11.93±0.041	14.55±0.204	16.20±0.05	16.18±0.096
1	8.70±0.39	13.64±0.05	15.80±0.96	26.54±0.13	28.53±0.154	22.23±0.041
1.5	11.45±0.285	20.71±0.204	23.23±0.041	34.19±0.53	31.70±.067	27.61±0.204
2	16.92±0.35	28.19±0.72	29.35±0.05	44.65±0.267	36.75±0.020	32.04±0.13
2.5	23.83±0.041	31.70±.067	35.44±0.228	52.14±0.92	40.95±1.02	38.10±0.678
3	27.61±0.204	36.75±0.020	41.74±0.03	60.72±0.336	48.52±0.86	44.65±0.267
3.5	32.04±0.13	40.95±1.02	45.35±0.04	65.84±0.204	56.98±0.852	51.14±0.72
4	37.80±0.204	46.13±0.327	52.14±0.92	69.43±0.92	60.72±0.336	57.52±0.67
5	48.23±0.285	53.52±0.231	60.72±0.336	76.80±0.204	71.54±0.204	65.84±0.204

Table 8: Stability studies of SSD loaded nano-ethogel

	Parameters	F1	F2	F3	F4	F5	F_*
2 Weeks	Appearance	Light Brown	Muddy Brown	Muddy Brown	Light Brown	Light Brown	Light Brown
	pH	6.7	7.0	6.8	6.4	6.7	7.2
	Viscosity	24,000	26,000	38,000	34,000	43,000	29,000
	Spreadability	7.67	7.63	6.84	10.11	14.13	10.3
	Extrudability	0.5	0.5	1.3	1.8	1.6	2.2
	% Drug content	46.44	48.2	53.3	81.64	74.59	70.34
1 Month	Appearance	Light Brown	Greenish Brown	Greenish Brown	Light Brown	Light Brown	Light Brown
	pH	6.7	9.2	8.8	6.4	6.7	7.2
	Viscosity	24,000	26,000	38,000	34,000	43,000	29,000
	% Drug content	46.44	44.90	51.6	81.64	74.59	70.34

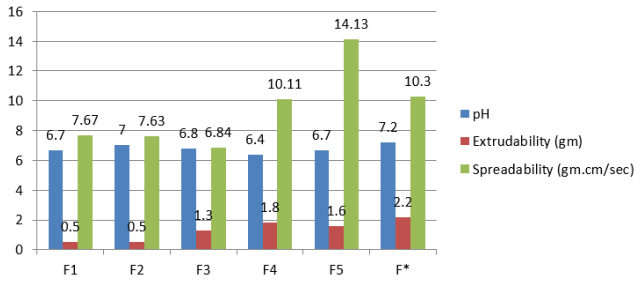

Fig. 6: pH, extrudability and spreadability of the prepared gel

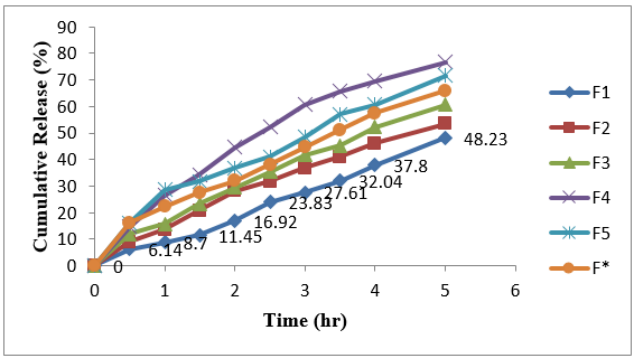

Fig. 7: In Vitro drug release (%) of different formulations of SSD ethosomes

4.2.2. Drug content

The drug content of SSD loaded topical ethogels was found to be maximum in formulation F4 i.e. 81.64%. The percentage drug content of formulations F4, F5 and F_* was found to be satisfactory. Hence, the method adopted for gel formulations was found to be suitable.

The percentage drug content of SSD loaded topical ethogels is tabulated in Table 7.

4.2.3. In vitro drug release

Release of SSD from different ethosomal formulations was estimated by using UV spectrophotometer at 254nm using PBS at pH 7.4. The drug release at different time intervals is shown in Table 8. The study revealed that the drug release from SSD ethosomes can be ranked in following descending order F4>F5>F_*. The results can be concluded that with increasing concentration of ethanol the drug release increases, which could be due to increased fluidity of the bilayer membrane.

4.2.4. Stability studies

The stability studies of SSD loaded topical ethogels were performed at room temperature and refrigerated temperature after two weeks and one month of storage. The results are depicted in Table 8.

5. Summary and Conclusion

The main objective of the study was to develop and characterize a "Silver Sulfadiazine Loaded Ethosomal Gel for Treatment of Topical Burns".

In the present work, ethosomal suspensions of silver sulfadiazine were formulated by using varied concentrations of ethanol, lecithin, and propylene glycol. Theses SSD suspensions were further loaded into the hydrogel made up of Carbopol 934 in the ration of 1:1. SSD entrapped in ethosomal vesicles enhances their skin permeability and allows the drug to be delivered to the targeted site in a controlled release fashion.

The % drug content and the in vitro drug release studies revealed that formulation F4 showed the maximum amount of drug release within five hours. Hence, from all the preparations prepared, F4 was chosen to be the best one.

According to the findings, it can be concluded that that SSD ethogels can prove to be an effective and more efficient system for burn treatments than compared to the traditional SSD creams and ointments that are commercially available.

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7. Abbreviations

SSD: Silver sulfadiazine;, API: Active Pharmaceutical Ingredient;, USFDA: United States Food and Drug Administration;, WHO: World Health Organization;, COA: Certificate of Analysis.

8. Source of Funding

None.

9. Conflict of Interest

The authors declare no conflicts of interest.

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