

Formulation And Evaluation Of Silver Sulfadiazine Cubosomes For Management Of Burns

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Abstract: -

Silver sulfadiazine (SSD) is widely used for its antimicrobial properties, particularly in the treatment of burns and wounds. However, its efficacy can be enhanced by developing novel delivery systems. This abstract explores the formulation and characterization of cubosomes loaded with silver sulfadiazine. Cubosomes, nanostructured lipid carriers with a cubic liquid crystalline phase, provide a stable, biocompatible platform for drug delivery, enhancing the controlled release and bioavailability of SSD. The study investigates the preparation method of SSD-loaded cubosomes, evaluates their physicochemical properties, particle size and entrapment efficiency. The results demonstrate that cubosome-encapsulated SSD exhibits higher entrapment efficiency and suggesting its potential as an innovative treatment for infected wounds and burns.

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Introduction: -

The skin, composed of proteins, serves as a protective barrier that shields the body from external elements, regulates temperature, and prevents fluid loss. When a burn occurs, this barrier is compromised, and immediate medical attention is essential. Burns can result from various causes, including flames, radiation, electricity, and chemical exposure. According to the World Health Organization (WHO), "A burn is an injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction, or contact with chemicals." WHO reports that globally, fires alone cause approximately 265,000 deaths annually, with even more fatalities stemming from scalds, electrical burns, and other types of burns. In India, around 7 million people experience burn injuries each year, leading to 140,000 deaths and 240,000 cases of disability. The main objective of burn treatment and management is to prevent infection and promote healing with minimal scarring. [1, 2, 3]

Silver sulfadiazine (SSD) is one of the most commonly used topical treatments for burns and is widely recognized as an effective antibacterial agent. It is included in the World Health Organization's List of Essential Medicines, highlighting its importance in basic healthcare. SSD combines the antimicrobial properties of silver with the antibacterial effects of sulfadiazine. Silver is effective against a broad spectrum of Gram-negative and Gram-positive bacteria, has antifungal properties, and exhibits strong anti-inflammatory effects. Its antibacterial action is primarily due to its ability to interact with thiol groups

in bacterial respiratory enzymes, disrupt structural proteins, and inhibit DNA replication. [4, 5]

However, the current forms of SSD, available as creams, ointments, and pastes, have several drawbacks. These include wrinkling of the skin, allergic reactions, wound dryness, slow healing, lack of natural skin regeneration, difficulty in washing off, and the formation of an adhesive pseudoeschar that may impede drug penetration. Additionally, the heavy metals in SSD can be toxic to fibroblasts and keratinocytes. In vitro studies have shown that SSD can be cytotoxic, though its toxicity can be reduced by controlling its release from the dosage form. [6, 7]

One promising solution to these issues is the development of novel drug delivery systems, such as cubosomes. Cubosomes are nanoscale structures formed by dispersing bicontinuous cubic liquid crystalline phases. These self-assembled nanostructures are designed to control drug release, a recent trend in drug delivery. In the pharmaceutical field, lipid-based systems like bicontinuous cubic liquid crystalline phases offer significant potential as drug carriers. Cubic-phase nanoparticles, or cubosomes, retain the unique properties of the bulk cubic phase while exhibiting much lower viscosity, making them an attractive option for improving the delivery of SSD. [8, 9, 10]

Material and methods: -

Silver sulfadiazine was purchased by SRL Pvt. Ltd. Taloja. GMO was purchased by Chemdyes Corporation, Rajkot. Poloxamer 407 was supplied as a gratis sample by BASF chemical company (Mumbai).

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Polyvinyl alcohol, carbopol 934, Triethanolamine were obtained from Loba chemie Pvt Ltd. All other reagents used were of analytical grade.

Preformulation study: -

Identification: -

Determination of Melting Point: - Melting point of drug (silver sulfadiazine) was determined by melting point apparatus. [11]

Solubility study: - Solubility study of drug was determined in different solvent using equilibrium method. [12]

FTIR Spectroscopy: -

Physical Mixture: - IR spectral study of pure drug and physical mixture of drug along with excipients were analysed and compared with the reference spectrum of silver sulfadiazine. [13]

λ max determination of drug: - λ max of pure drug determined by the UV spectroscopy. 100mg drug was weighed accurately and transferred into 100ml volumetric flask. Then the drug dissolved using 0.05% ammonia solution and volume was makeup up to 100ml with the phosphate buffer 6.8. Then aliquot of 100 μ g/ml concentration was prepared from the stock solution. Then this solution scanned 400-200nm using blank solution. The spectrum of wavelength versus absorbance was recorded on UV- spectroscopy and λ max was determined. [14]

Calibration curve of drug: - From the stock solution, aliquots of 0.3, 0.6, 0.9, 1.2 and 1.5ml were transferred to 10ml volumetric flask and diluted up to the mark using phosphate buffer 6.8 to obtain a concentration of 3-15 μ g/ml. Absorbance of each solution were measured at 254nm in UV- spectrophotometer. [14]

Method of Preparation: -

Cubosomes dispersion were prepared on the basis of emulsification of monoglyceride/ surfactant mixture in water. The composition of various formulation is presented in table- 1.

Firstly, GMO melted at 70°C on a water bath and poloxamer 407 and PVA were dissolved in distilled water at 70°C on water bath separately. Then the molten mixture was added dropwise into aqueous solution of Poloxamer 407 at the same temperature under magnetic stirrer at 1500 rpm for 15min and then on mechanical stirrer at 1500 rpm for 2h. The dispersion was allowed to cool at room temperature. After emulsification, the dispersion was subjected to ultra- sonication at 5 pulses on and 2 pulse off for 15min. Cubosomal dispersions were stored at room temperature. [8, 9]

Table 1: - Formulation of silver sulfadiazine loaded cubosomes

Formulat ion code	Silver Sulfadiaz ine (mg)	GM O (%)	Poloxa mer 407 (%)	Wat er up to (ml)
CF1	100	25	1.25	100
CF2	100	15	0.5	100
CF3	100	15	2	100
CF4	100	5	1.25	100

Evaluation: -

Entrapment efficiency: - entrapment efficiency of drug was determined by dialysis bag method. Where the formulations placed and dialyzed against 100ml of phosphate buffer 6.8 for 2hr at 100-200 rpm. Then the dialysis content was analysed spectrophotometrically at 254nm. [15]

Entrapment efficiency

$$\frac{\text{Total drug concentration} - \text{Free drug concentration}}{\text{Total drug concentration}} \times 100$$

Particle size and zeta potential: - Particle size and zeta potential were determined by using Malvern Nano- ZS. All the formulation of silver sulfadiazine cubosomes were analyzed for particle size and zeta potential. [16]

Visual examination of cubosomal dispersion: - The initial stability of Cubosomal dispersions were assessed visually through observation of the samples after sonication. A well-dispersed sample contained no visible aggregates and shows milky white consistency. In contrast, poorly dispersed samples were largely transparent systems with visible aggregates of lipid. The visual assessment was used as an initial screen to rapidly exclude very poor dispersions from further study.

Optical Microscopy: - All Cubosomal formulations were viewed under light microscope. The Cubosomal dispersion suitably diluted with water and then this diluted solution was deposited on slide and observed under magnification of x400 by using light microscope. [17]

Result and Discussion: -

Determination of Melting Point: -

Melting point of the sample silver sulfadiazine was determined 282°C-285°C which was reported in the literature, this indicates the purity of the drug sample.

Melting Point	Reported	Observed
Silver Sulfadiazine	282-285°C	281-285°C

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Solubility study: - Solubility of silver sulfadiazine in different solvent were reported in table :3.

S. No.	Solvent	Solubility
1	Ammonia solution	Freely soluble
2	Water	Insoluble
3	Octanol	Slightly soluble
4	Acetone	Slightly soluble
5	Chloroform	Practically insoluble
6	Alcohol	Practically insoluble

FTIR Spectroscopy: -

FTIR spectrum of silver sulfadiazine and its physical mixture with poloxamer 407 were recorded by using FTIR and shown in the figure: - 1 and 2. and it is compared with the standard of silver sulfadiazine shown in table: 4.

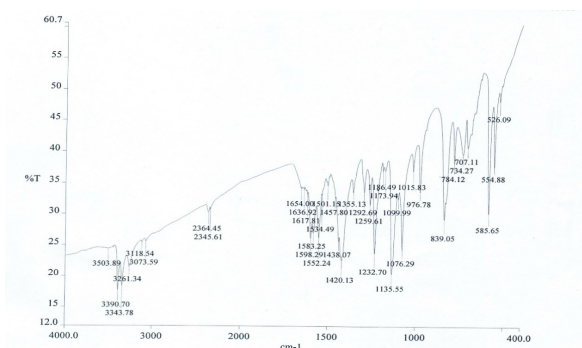


Figure 1: - FTIR spectra of silver sulfadiazine

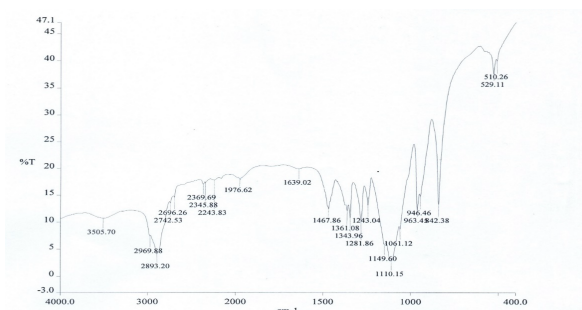


Figure 2: - FTIR spectra of Poloxamer 407

Characteristic Peak of SSD	Wavenumber (cm ⁻¹)	
	SSD Sample	SSD + Poloxamer 407
N-H Stretching	3390.70	3391.86
C-N stretching	1232	1233.26
C=C Stretching	1654	1664.43
C-S stretching	784, 736	784.33, 733.79
S=O stretching	1076	1076.90
C-H Stretching	1438, 1420	1420.20, 1438.20

λmax determination of drug: -

The absorbance spectrum of drug (Silver sulfadiazine) was scanned between 400 to 200nm on UV spectrophotometer. The maximum absorbance was at 254nm with concentration of drug was 100 µg/ml in ammonia solution.

Calibration curve of Drug: - the absorbance of silver sulfadiazine was measured at 254nm which was ranging from 3-15µg/ml. The correlation coefficient was found to be 0.995. the calibration curve was showed in table: 5 and Figure:3.

Concentration in micro gram per ml	Abs.
0	0
3	0.198
6	0.363
9	0.507
12	0.67
15	0.894

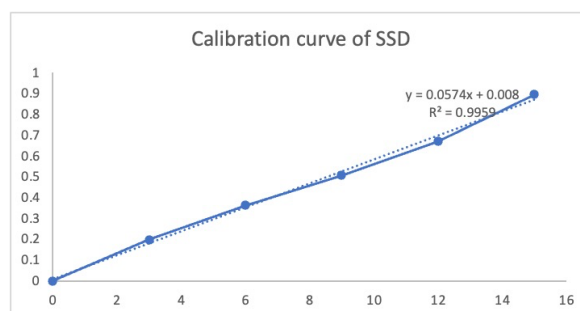


Figure 3: - Calibration curve of silver sulfadiazine

Evaluation: -

Entrapment efficiency: -

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The percentage of drug entrapment efficiency of formulated formulations are listed in table:6.

Particle size and Zeta potential: - Particle size of the formulations (CF1-CF4) is listed in table: 6.

Table 6: - %EE, Particle size, Zeta potential and Polydispersity Index of formulations				
Formulation code	Entrapment efficiency	Particle size	Zeta potential	Polydispersity Index
CF1	74.4	227.3	-21.5	0.378
CF2	87.28	280.2	-14.6	0.537
CF3	90.94	139.8	-21.9	0.247
CF4	84.23	133.6	-26.7	0.212

Visual examination of cubosomal dispersion: -

The initial stability of cubosomal dispersions were assessed visually by physical observation of sample. There is no phase separation were observed in batch CF1-CF4 formulations.

Optical microscopy: -

The batches of cubosomal dispersions were observed under light microscope at x40. And that indicate the cubosomes were well separated from each other. The photomicrograph shown in Figure: 4-7.

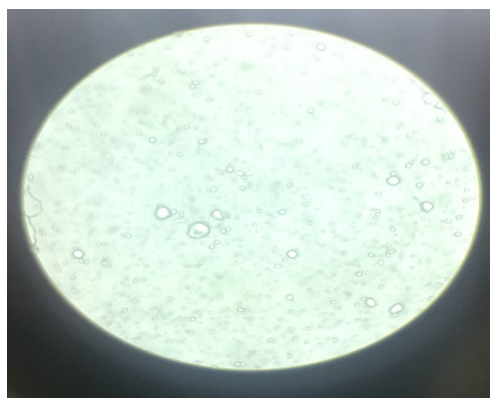


Figure 4: - CF 1



Figure 5: - CF2

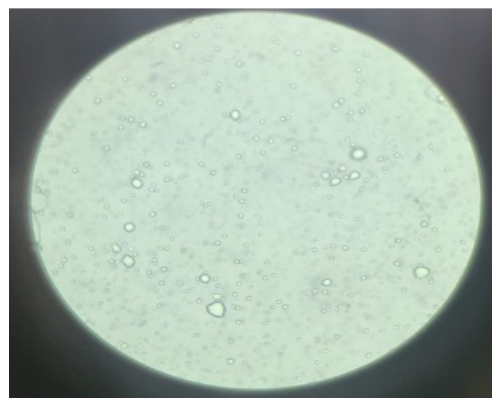


Figure 6: - CF3

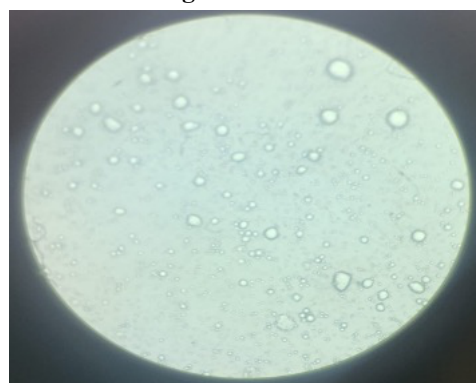


Figure 7 - CF4

Summary

The present study focused on the preformulation, preparation, and evaluation of silver sulfadiazine-loaded cubosomes. Preformulation studies were conducted to determine the physicochemical properties of the drug. The melting point of silver sulfadiazine was found to be 281–285 °C, which closely matches the reported value (282–285 °C), indicating the purity of the drug.

The solubility study showed that silver sulfadiazine is freely soluble in ammonia solution, insoluble in water, and slightly soluble in solvents such as octanol and acetone, while being practically insoluble in chloroform and alcohol.

FTIR spectroscopy was used to analyze the compatibility between the drug and excipients such as poloxamer 407. The characteristic peaks of the drug were retained in the physical mixture, indicating no significant interaction between the drug and excipients. The λ_{max} of silver sulfadiazine was determined using UV spectrophotometry and found to be 254 nm. A calibration curve in the concentration range of 3–15 $\mu\text{g/ml}$ showed good linearity with a correlation coefficient of 0.995, confirming the reliability of the analytical method.

Cubosomal formulations (CF1–CF4) were prepared using the emulsification method with glyceryl monooleate (GMO) and poloxamer 407. The

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formulations were evaluated for entrapment efficiency, particle size, zeta potential, and polydispersity index. Entrapment efficiency ranged from 74.4% to 90.94%, with CF3 showing the highest efficiency. Particle size ranged between 133.6 nm and 280.2 nm, indicating nanosized dispersions. Zeta potential values ranged from -14.6 to -26.7 mV, suggesting acceptable stability.

Visual examination showed no phase separation, and optical microscopy confirmed well-separated cubosomal structures with uniform dispersion.

Conclusion

The study successfully developed silver sulfadiazine-loaded cubosomal formulations using the emulsification technique. Preformulation studies confirmed the purity of the drug and compatibility with excipients. Among all formulations, CF3 showed the best performance with highest entrapment efficiency, smaller particle size, and good stability. The results indicate that cubosomes are a promising carrier system for the delivery of silver sulfadiazine, potentially improving its stability and therapeutic effectiveness.

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