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Research Article

DESIGN, DEVELOPMENT AND EVALUATION OF LIPID BASED TOPICAL FORMULATIONS OF SILVER SULFADIAZINE FOR TREATMENT OF BURNS AND WOUNDS

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ABSTRACT

The aim of this research was to develop a novel lipid based film forming gel based on polymer and to investigate its potential as slow-release wound healing vehicle. The lipid based is composed of water soluble gel with model drug (Silver Sulfadiazine) and an egg oil, which acted as a remove scars. The morphology, rheology, mechanical properties, in-vitro drug release profiles were investigated. A smooth film layers was produced. The characterization results showed that film has superior mechanical and rheological properties than the ointment and cream. The lipid based gel treating low suppurating wounds and suitable for slow release application on wound surfaces. The lipid based gel also provided a significant higher healing rate in-vivo, with well-formed epidermis with faster granulation tissue formation when compared to the controls. In conclusions, a novel polymer-based lipid film gel was developed and results suggested that they can be exploited as slow-release wound dressings.

Keywords: Wound healings, slow release, silver sulfadiazine and film gel

INTRODUCTION

Wound healing is defined as body's replacement injured tissues with living tissues. It is a dynamic and intricate process which involve multiple cellular and matrix components act together to restore the integrity of injured tissue. The primary goals of wound care are rapid wound closure and leave minimal or aesthetically acceptable scar. Wound management is important in providing optimum healing milieu for wound healing [1,2]. Depending on the severity of the wound, the desirable wound dressing may therefore serve among the purposes of (a) to provide moisture and occlusion, (b) protection from infections and contamination, (c) debridement, and (d) easy application and removal avoiding dressing-related trauma [3, 4, 5]. Occasionally, drug-loaded wound dressings are used to treat wound locally such as anti-infections due to secondary infection or for pain control, especially in chronic wounds [6]. Various wound care products are available in the wound care management market and they are targeted towards the treatment of both acute and chronic wounds [5]. Among the modern wound dressings, dressings cast from hydrogels, have been developed and uses as the first major advances in moist wound management. Wound healing is promoted by dressings that maintain a moist environment. The formation of gel allows excess fluid to escape without permitting wound desiccation.

Hydroxy Propyl Methyl Cellulose (HPMC), a natural polymer, is used in the fabrication of hydrocolloid film wound dressings due to its biocompatibility, biodegradation and excellent film forming properties. HPMC is a water-soluble. The various degree of cross-linking will reduce significantly the hydrogels swelling in the presence of the water, causing the release of drugs within the matrices will be delayed. As a result, HPMC is often being exploited as a drug controlled release vehicle in drug delivery systems. As wound dressings HPMC gels can retain and create a moist environment around the wound to promote wound healing [7].

In this study, a lipid-based film formulation was developed and investigated for its potential as slow-release wound healing vehicle. A model drug (Silver Sulfadiazine) was loaded in lipid and dispersed in HPMC. Silver Sulfadiazine was chosen because it is used as an effective topical antimicrobial. The aim of this research was to develop a novel lipid based film forming gel to characterize rheological and mechanical properties. The surface and cross-sectional morphology was examined *in-vitro* drug release was conducted using Franz diffusion cells. The key focus for such formulations with SSD would intend to prevent infection, decrease fluid imbalance, promote re-epithelialisation, and reduce the occurrence of pain and scar tissue in case of mild to severe burns and wounds.

MATERIALS AND METHODS

Materials

Silver Sulfadiazine (purity 99%) was procured from Cipla pharmaceutical, Mumbai and Egg oil from VAV Life Science Pvt. Ltd. Mumbai, India. Hydroxy Propyl Methyl Cellulose (grade 1) (AR), Buffer Solution pH-7 (LR), Chloroform (LR), Di-methyl Sulphoxide (LR), Buffer Solution pH-4 (LR), Dichloromethane (AR) was purchased from Central Drug House (P) Ltd. New Delhi, India. Hydroxy Propyl Methyl Cellulose (grade 2)(LR) was purchased from E. Merck Ltd., Mumbai, India. Tween 80 (LR), Methyl paraben sodium (LR), Ammonia(25%) solution (LR), Polyethylene Glycol(PEG_S)- 200 (LR), Benzyl Alcohol (LR), Glycerin (LR), Sodium Benzoate (LR), Triethanolamine (LR), Propylene Glycol (LR) was purchased from Thomas baker (chemicals) Pvt. Ltd. Mumbai, India. Carbopol 980 NF (LR) was obtained from Lubrizol and Octanol (AR) from Finar Reagent, Ahemdabad, India. All other chemicals and solvents were of analytical reagent grade.

Methods

Preformulation Studies

Preformulation studies of the drug, excipients and their combination were carried out to determined the solubility, partition coefficient, Infra red spectroscopy etc. were carried out to determined the feasibility, possibility and solubility or the ingredients to develop the formulation and to determined compatibility.

Partition Coefficient Determination

Partition Coefficient was determined in n-octanol and water. Two solvents were mutually saturated before use, by shaking them together in equal volumes, for 24 h at 37°C or ambient temperature. With pure Silver Sulfadiazine after centrifugation at 2000 rpm for 20 min, the n-octanol layer was pipetted out. A stock solution of drug was prepared in water. The drug stock solution (2 mL) and

saturated octanol (13 mL) were taken in a 25 mL conical flask that was capped tightly and shaken on a platform shaker for 24 h at 37° C at 80 horizontal stocks. The two liquids were than separated and analyzed for SSD content using the standard plot in distilled water. The partition/distribution coefficient was calculated according to the equation

$$PC = \frac{Co}{Cw} X \frac{Vw}{Vo} \qquad \text{Equation (1)}$$

Where,

C_o stands for concentration in oil phase

C_w stands for concentration in aqueous phase

V_w stands for volume of aqueous phase

V_o stands for volume of oil phase

Formulation Development

The codes and composition of various gels prepared in the study are provided in table 2.1.

Method of preparation

The Silver sulphadiazine lipo-gels were formulated using different grades of polymers and different ratio of drug: lipids 1:1, 1:2 and 1:5. Unloaded gels were prepared in the same way except that Silver sulphadiazine was not added into the formulations. To formulate the gels, Silver sulphadiazine (1% w/w) was dispersed in known quantity of lipid in a beaker and mixed with Tween 80 and stirred until a viscous paste was obtained and stirring continuously followed by ultra-sonication for 20 min. This homogenous solution was obtained that was the lipoidal solution identified as solution 'A'.

In yet another beaker, measured volume of purified water was taken to which weighed quantities of Sodium Benzoate and Tween 80 were added and dissolved. To this solution, required quantity of polymer was added using mechanical stirrer. A thick, viscous gel was formed that was identified as solution 'B'. To this viscous gel B, all the contents of solution A were added as using mechanical stirrer into the vortex formed in solution. The mixture was stirred for 25 min. followed by this, propylene Glycol, Poly ethylene glycol-200, Poly Ethylene Oxide (303), Ethanol was added into the formed gel. The total weight of the formulation was made up to 100 gm with purified water. Finally the pH of the gels was adjusted. The gels were kept in vacuum desiccators at room temperature to remove entrapped air over night. The final gel was filled in lacquered aluminum tubes and stored at room temperature.

Table 2.1: Composition of gels prepared in the investigation

Ingredients	Formulation code & Quantities (%)								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
Silver Sulphadiazine	1	1	1	1	1	1	1	1	1
Lipids	5	5	2	5	1	1	2	2	1
HPMC 15000 cps	-	-	-	2	-	-	-	2	2
Carbomer	2	-	2	-	2	-	-	-	-
HPMC 4000 cps	-	2	-	-	-	2	2	-	-
Tween 80	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Poly ethylene glycol-200	2	2	2	2	2	2	2	2	2
Propylene Glycol	5	5	5	5	5	5	5	5	5
Sodium Benzoate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Glycerin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Poly Ethylene Oxide(303)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Ethanol	10	10	10	10	10	10	10	10	10
Purified Water (up to)	100	100	100	100	100	100	100	100	100

Evaluation Parameters for the prepared formulation
Visual appearance

The prepared gels were visually inspected for clarity, color and transparency.

Presence of particulate matter (grittiness)

The prepared gels were evaluated for the presence of any particles. Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness.

pH of the gels

The pH of gel was determined after diluting and dispersing it in distilled water (10% w/v). All the measurements were made in triplicate and mean calculated.

Determination of Vesicle Size

Optical microscopy was used for the determination of the vesicle size of the prepared formulation. The parameters observed were particle size, shape and presence of aggregates.

Rheology of Gels

Rheological studies of different formulations were performed at ambient temprature using a physical (MC-1) rheometer. The diameter of plate was 20.05 mm and cone angle was 1°. The interpolate diameter was 0.052 mm and truncation was 0.05'. Rheograms were produced in duplicate by gradually increasing the shear stress. The shear stress value was increased automatically by the instrument to a maximum value of 500 Pa over a period of 30 s.

The relationship between shear stress and shear rate of each formulation was determined using Power law described in equation 2.

$$\tau = k \gamma^{n}$$

Equation-2

All rheological analyses were performed in duplicate. Rheograms of optimized formulations by design was statistically evaluated by three way analysis of variance (ANOVA).

***in-vitro* Permeation Studies**

This study was performed using Franz diffusion cell assembly. The jacketed cell embodied two limb reservoirs that involve a donor compartment, receptor compartment and a sampling port. The area of donor compartment exposed to receptor compartment, *i.e.* diffusion cross sectional area is 3.142 cm2, and the total capacity of the receptor compartment is 30 ml. The receptor medium is stirred throughout the study at 500 rpm employing a magnetic stirrer. The temperature of the receptor medium is maintained at 32±20C by circulating hot water in the outer jacket of cell employing a thermostatic water circulator. The release study carried out using diffusion membrane cut off range between 10000 to 14000Da.
Prior to permeation experiment, membrane was clamped into donor and the receptor compartment of the jacketed vertical Franz diffusion cell. The receptor compartment was filled with distilled water pH 7.0. Silver sulphadiazine lipo-gel was applied on the

membrane at the donor cell of franz diffusion assembly having 1 gm drug. The donor chamber and sampling port were covered by para-film to prevent evaporation during the study. Aliquots of 1ml are withdrawn periodically and replaced with equal volume of the receptor medium to maintain the receptor phase volume at constant level. Samples are suitable diluted and analyses for Silver sulphadiazine in UV spectroscopy at λmax 241 nm

Treatment of dialysis tubing

Dialysis tubing was treated before permeation studies as per procedure recommended by the supplier. The tubing was washed with running water for 3-4 h. to remove glycerin. The sulphur compounds were removed by treating the tubing with 0.3% w/v solution of sodium sulphide at 80° C for one minute. The tubing was subsequently washed with hot water (60°C) for two minutes, followed by acidification with a 0.2% v/v solution of sulphuric acid. Finally the tubing was rinsed with hot water to remove the acid. The treated tubing was kept in PBS 7.4 and refrigerated till use. Before use, the tubing was washed with distilled water and was cut open to expose maximum surface area

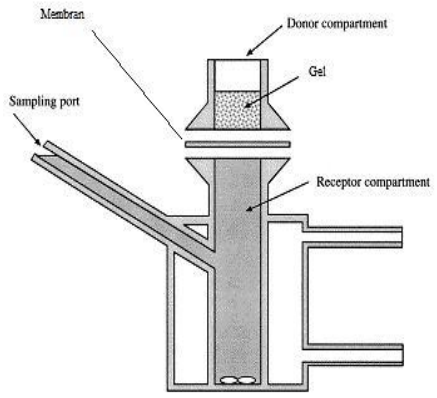

Figure 3.1: Franz diffusion cell

Drug loading and entrapment efficiency

Exactly 0.1g gel was completely dispersed in distilled water to make final volume 100 ml (0.1% w/v) by subjecting it to stirring (400 rpm) for 5 min. The dispersion was than filtered to remove the undissolved residue. Exactly 1 ml of the filtrate was diluted to 5 ml and absorbance was measured at 241 nm. An unloaded gel was also subjected to a similar determination to observe the effect of excipients on the absorbance. Using the standard curve of Silver sulphadiazine in ammonia solution, the drug content in gel was finally estimated. Three batches of each polymer concentration were subjected to this determination. The percent encapsulation efficiency was determined using the following expression:

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Conformational stability of SSD in formulation by FTIR

The conformational stability of SSD was determined by means of Fourier Transform Infra Red (FTIR) spectroscopy. The FTIR spectra of all formulations were obtained in the frequency range of 500 – 4000 cm^{-1} and they were compared with FTIR spectra of pure SSD to assess any changes occurring to SSD on being formulated into a polymer solution.

Stability Testing

Physical stability testing

The selected lipo-gel formulations were visually inspected everyday for seven weeks for any change in physical appearance of gels *i.e.*, color, turbidity, odor etc.

Chemical stability testing

All the lipo- gels were subjected to stability studies by keeping them at accelerated conditions of temperature and humidity (40°C, 75% RH) for a period of 6 months. Zero time samples were used as controls. Lipo-gels packed in tubes as well as in plastic bottles were subjected to stability studies. Samples withdrawn at predetermined intervals (0, 1, 2 and 3 months) were analyzed for various performance parameters *i.e.*, pH, rheology, microbial growth and drug content. Gels that failed in accelerated stability studies were stored at a temperature of 8-15°C (in a refrigerator). Samples from these gels were withdrawn at predetermined intervals (0, 1, 2 and 3 months) and analyzed for above mentioned performance parameters. These gels were also subjected to freeze-thaw study. In this study, samples were kept in refrigerator for 2 days followed by room temperature for two days. Five cycles were carried out and at the end, the performance parameters were determined.

Containers for formulation

According to USP XXII, containers including the closures for gels should not interact physically or chemically with the preparation in a manner to alter the strength of purity beyond the official requirements under ordinary or customary conditions of handling, shipment, storage, sale and use. Two types of containers were used in the study. Plastic bottles with wide mouth (3 cm diameter) and lacquered aluminum collapsible tubes were selected for the storage of gels. Aluminum collapsible tubes (20 g) were first washed with flowing tap water. They were subsequently washed with very mild detergent and again held under tap water to remove the detergent solution. They were then washed with purified water and dried in oven. Plastic closures were washed with tap water and with mild detergent solution. Later, they were thoroughly washed with purified water and dried at 40°C. Gels were filled in lacquered tubes and tubes were subsequently crimped.

The aluminum collapsible tubes were tested for compliance with freedom from leakage and metal particles, as below:

Freedom from Leakage

Aluminum collapsible tubes (n=8) filled with the gel were placed in a horizontal position on a sheet of absorbent blotting paper in an oven maintained at 60 ± 3°C for 8 h. After 8 h tubes were observed for leakage.

Freedom from metal particles

Aluminum collapsible tubes (n=8) filled with the gel were selected randomly. Smears of gels were prepared on glass slide and observed under microscope.

RESULT AND DISCUSSION

Preformulation Studies

Physical characterization

Table No. 3.1: Physical characterization of Silver Sulfadiazine

Characteristic	Result
Colour	White
Odour	Odourless
Texture	Fine powder

Solubility Study

Silver Sulfadiazine pH-Solubility Profile

The solubility profile of Silver Sulfadiazine measured in various solvent. The lowest value for solubility 0.11mg/100ml was obtained in the water and the highest value of about 5.6 x 10^3mg/100ml was obtained in Nitric acid.

Table no. 3.2: Solubility Behaviour of Pure Silver Sulfadiazine Drug

Solvent	Solubility (mg/100ml)
Water	0.11
DMSO	35.6
10% ammonia solution	2.2 x10^3
Nitric acid	5.6 x 10^3

CONCLUSION

From the above results solubility shown in table 3.2 indicates that Silver Sulfadiazine is insoluble in water and highest solubility seen in 10% ammonia solution and Nitric acid.

Partition coefficient of Silver Sulfadiazine

In order to assess the permeation of the drug, partition coefficient was determined at different pH.

The log P value for a compound is the logarithm (base 10) of the partition coefficient (P), which is defined as the ratio of the compound's organic (oil) to aqueous phase concentrations. The log P of a compound is constant for a given specific pair of aqueous and organic solvents. For example, a drug with a measured log P equal to 1 indicates that its concentration is at a 10:1 ratio in organic to aqueous phase. The drug is hydrophobic and requires dissolution in an organic solvent. In contrast a drug with a log P value equal to –1 indicates that the concentration is at a 1:10 ratio in organic to aqueous phase. This indicates that the drug is hydrophilic. A drug with a log P equal to 0 partitions at 1:1 ratio in organic to aqueous phase. The log P values of SSD with octanol/water system were found to be about 1, indicative of highly hydrophobic nature of SSD.

The partition studies were performed in triplicate to ensure accuracy and reproducibility. The data obtained is shown in Table 3.3. Results obtained were comparable with literature reports.

Table 3.3: Log P determination of SSD

Conc. in water (mg/mL)	Conc. in octanol (mg/mL)	P	Log p
2.18	8.93	4.09	0.611

Evaluation of Silver Sulfadiazine Gel

***in-Vitro* Permeability Release**

All the 9 formulations were subjected for the in vitro Permeability studies using Franz diffusion cell. The samples were withdrawn at ifferent time intervals and analyzed at 241 nm. Percentage Cumulative drug release was calculated on the basis of mean amount of silver sulfadiazine present in the respective gel. The results obtained in the in vitro drug release for the formulations B1 to B9 are tabulated in Table 3.4 The plots are shown in Figure no. 3.1 for % cumulative drug release Vs time.

Table 3.4: In-Vitro release Profile of silver sulfadiazine gel Formulations (B1 to B9)

Time (hrs.)	% Cumulative drug release (Mean ± SD) n= 3								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
0	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.50	9.59±0.55	10.69±0.85	5.57±0.69	8.56±0.48	2.39±0.43	13.65±0.34	9.60±1.58	15.25±0.12	8.59±0.36
1	13.21±0.38	37.89±0.28	21.98±0.84	16.98±0.24	5.62±0.21	26.48±0.51	15.49±2.01	19.87±0.98	21.65±0.56
2	18.82±0.47	45.69±0.91	32.16±0.79	26.15±0.84	9.23±0.39	38.45±0.65	25.45±1.87	32.45±1.25	45.58±0.64
4	23.23±0.28	67.87±0.72	36.66±1.06	55.26±0.53	15.23±0.45	56.98±0.21	41.84±1.25	45.89±0.43	51.29±0.23
6	29.26±0.62	74.26±1.03	42.15±0.37	79.32±0.38	22.02±0.72	76.56±0.54	58.95±0.87	65.28±0.22	71.51±0.48
8	38.36±0.58	89.78±0.95	52.26±1.02	98.78±0.31	27.71±0.49	92.35±0.48	75.88±0.41	79.25±2.22	85.65±0.89

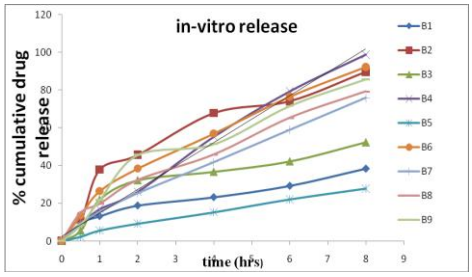

Figure 3.1: *In-vitro* Release Profile of Silver Sulfadiazine gel from Formulation batches (B1 To B9)

The results are shown in Figure 3.1 indicate that the formulation, B4 which was prepared by the HPMC (2%) and lipid (5%) with silver sulphadiazine showed good drug release after 8 hrs. Thus, the formulation (B4) has better result as comparison to others formulations.

The mean % release of all formulation is presented in Table-3.4. The smallest mean % release of 27% was observed from Lipid based of Silver Sulfadiazine formulation B5 where as maximum % release was obtained as 98 % for B4 formulation. This indicates that at higher lipid concentration, the retention of gel is increased. So, the B4 formulation has 98.78% release

Visual appearance

All the nine hydrogels containing SSD were dispersed and found to be transparent and uniform in consistency.

Figure: 3.2: gel base formulation of HPMC 4000cps, carbopol and HPMC 15000cps

Presence of particulate matter

All the nine formulations were evaluated microscopically for the presence of particulate matter. No appreciable particulate was seen in B7, B8 and B9 formulation under microscope. Hence, the gel formulations fulfilled the requirement of freedom from particulate matter.

Vesicle size

The vesicle size of the prepared three batches of optimized formulation B7 was measured using optical microscopy as described above. The particles were found to be spherical, vesicular, multi lamellar and none aggregated. Particle size range from 20 to 400 µm. figure no. depicts a representative micrograph of optimized formulation. The results of vesicle size are shown in Table 3.5.

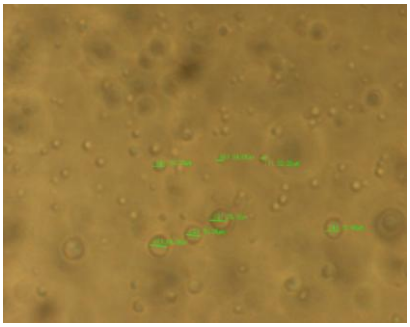

Figure 3.3: Vesicles of Silver Sulfadiazine observed in optimized formulation

Table 3.5: Vesicle size of the optimized formulation

Batch No.	Vesicle Size (µm)
1	84.38
2	70.26
3	78.10
Mean	**77.58±7.07**

The mean vesicle sizes of all formulation are range in 45 µm to 159 µm Formulation with same HPMC (15000cps) and sonicated at same time shows increase in vesicle size with respect to increase in lipid concentration. Though with decrease in lipid concentration the vesicular size also decreased, so the B4 formulation mean vesicle size is 77.58 µm

Drug loading and entrapment efficiency

Table 3.6 shows percent drug loaded and entrapment efficiency of optimized formulation. The optimized formulation offered good entrapment efficiency (89±0.66) and drug loading (6.15±0.66). The drug loading was based on polymer weight or total solid content of the formulation. The high entrapment efficiency of the particles may be attributed to the high polymer: drug ratio (1:1 in the present case), molecular weight of polymer, hydrophilicity of the polymer, viscosity of polymer and type of organic solvent used. High polymer content and high molecular weight of the polymer in the optimized formulations increase the viscosity of the formulation and exert pronounced molecular weight dependent attraction forces between polymer and lipid.

Table 3.6: Drug loading and entrapment efficiency of

S. No.	Drug Loading (%) (n=3)	Entrapment Efficiency (%) (n=3)
1	6.04	86
2	6.26	93
3	6.17	90
mean	6.15±0.66	89±0.66

3.2.6 *In-vitro* release of Optimized formulation

The optimized formulation was prepared and their release study through cellophane membrane was studied. The optimized formulation showed near to 75% release in 8 hr. The release profile of optimized formulation is showed in **Table 3.7** and graph is showed in Figure 3.4.

Table 3.7: Release profile of Optimized formulation

Time (Hr)	% Release
0.00	0.0000
0.50	8.56±0.48
1.0	16.98±0.24
2.0	26.15±0.84
4.0	55.26±0.53
6.0	79.32±0.38
8.0	98.78±0.31

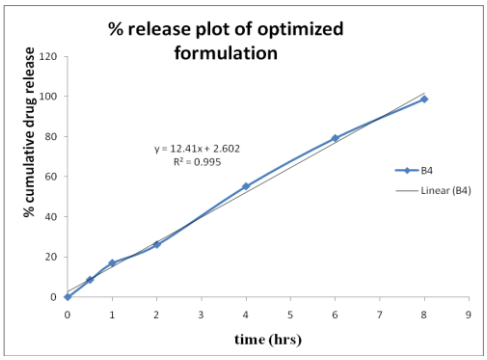

Figure 3.4: Release plot of optimized formulation

Drug Release Kinetics Studies

The drug release data of Silver Sulfadiazine were fitted to models representing zero order, first order, Higuchi's, Hixson-crowell and Korsmeyer's equation kinetics to know the release mechanisms. The data were processed for regression analysis using MS EXCEL statistical function. The results are shown in Table 3.8.

Table 3.8: Equation of line and r² values after fitting the release data to various models

Model	Formulation No.B4	
Zero order	y = -8.674x + 96.92	R^2 = 0.988
First order	y =12.41x +2.602	R^2 = 0.995
Higuchi	y = 15.29x - 5.741	R^2 = 0.946
Hixon-Crowell	y = 0.187x + 0.009	R^2 = 0.973
Peppas	y = 0.315x - 1.020	R^2 = 0.985

It was found that the in vitro drug release of optimize batch B4 was best explained by First order as the plots showed the highest linearity (R^2 = 0.995).

Rheology

The rheology of the optimized formulation was measured. In the optimized formulation increasing the concentration of the polymer significantly increased the consistency. Increased consistency was ascribed to enhanced polymeric entanglements, thereby increasing the resistance to deformation. The formulations exhibited pseudoplastic flow; however no evidence of thixotropy was evident. Representative rheograms for optimized formulations are shown in figures 3.5 respectively. Application of the power law model to the rheological properties of each formulation enabled the calculation of the consistency (k) and flow index (n). The values of flow index (n) were found to be less than the optimized formulation confirming the shear thinning behavior of the gel. The same is also confirmed from viscosity *vs.* shear rate graphs**.**

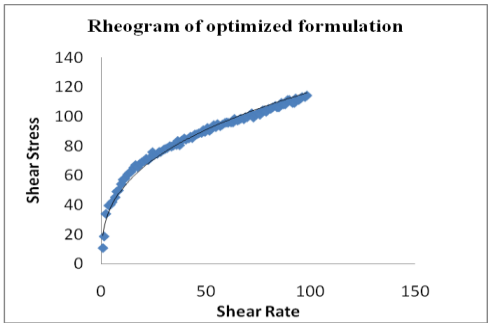

Figure 3.5: Rheogram of optimized formulation depicting power law

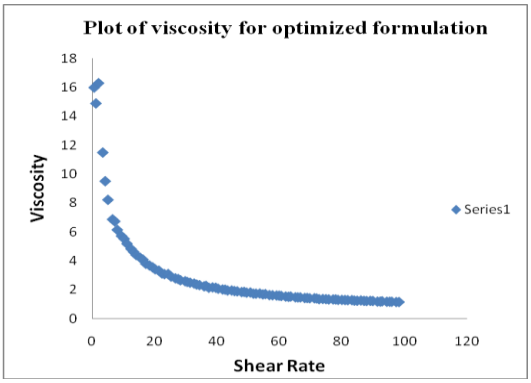

Figure 3.6: Plot of Viscosity *vs.* Shear rate for optimized formulation

These figure 3.6 indicate that the viscosity of the system decreases with increase in shear rate. The formulation did not break even at shear rate of 500 indicating good gel strength. The values of flow index for optimized formulation was highest. High flow index reflects the mobility of the gel from the container. The values of consistency index for optimized formulation was found to be higher

Infra-Red Spectroscopy

The conformational stability of SSD was determined by means of Fourier Transform Infra Red (FTIR) spectroscopy. The FTIR spectra of all formulations were obtained in the frequency range of 500 – 4000 cm^{-1}. In Figure 3.7 the Infra red spectroscopy of Silver Sulfadiazine and in Figure 3.8 Infra red spectroscopy of Silver Sulfadiazine and HPMC gel are present and following peaks are interpret with Silver Sulfadiazine pure drug structure.

Stability Testing

Physical Stability

The optimized formulation was visually inspected for everyday for first week and then was inspected at intervals of 1, 2 and 3 months respectively. The optimized formulation does not show any appreciable change in gel clarity and color ratifying physical stability of prepared optimized formulations. Further, no obnoxious odor was perceptible from formulation. However, the consistency of the optimized formulation was altered.

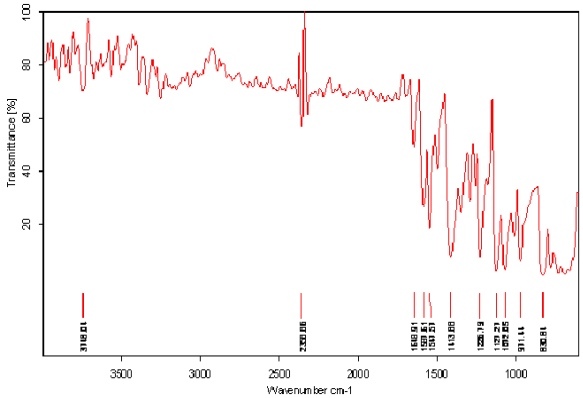

Figure 3.7: Infra red spectroscopy of Silver Sulfadiazine

Accelerated Stability Studies

The optimized formulation was found to be stable at room temperature and at accelerated conditions (40oC+2oC, 75%+5%RH). Even after exposure to heat and humidity, not much change was observed in pH of the gels Table 3.10. All other parameters were also observed to be comparable. The optimized formulation was then stored in refrigerator (8 to 15 ⍰ C) and all the performance parameters were found to be comparable at each time point of the study. The results of freeze thaw study have been compiled in Table 3.11. The optimized formulation will be stable during that period

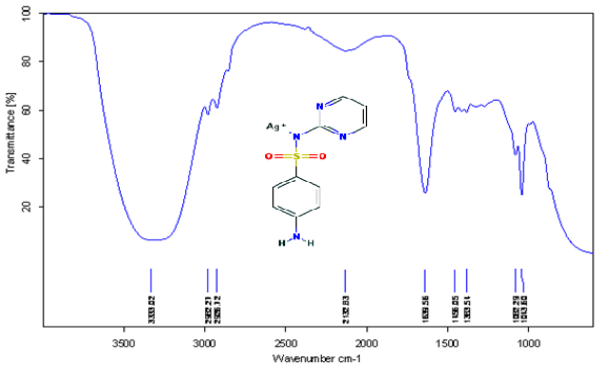

Figure 3.8: Infra red spectroscopy of Silver Sulfadiazine and HPMC gel

Functional Groups which are present in SSD are interpret with SSD+HPMC gel and following functional group in table- 3.9

Table-3.9: Interpretation of FT-IR spectra of Silver Sulfadiazine+Hpmc gel

Functional Group	Pure drug	(HPMC + drug) gel
C-H Stretch asymm.	2950-3000 cm^{-1}	2982 cm^{-1}
N-H Stretch (Amines)	3500-3300 cm^{-1}	3333 cm^{-1}
$S=O_2$	≈1050 cm^{-1}	1040cm^{-1}
C-N Stretch (Aryl)	1390-1250 cm^{-1}	1383cm^{-1}
N-H Bend (Amines)	1640-1500cm^{-1}	1639 cm^{-1}

Table 3.10: various parameters noted in accelerated stability testing

Gels ⇒ Factors ⇒	Optimized formulation		
	pH	Microb. growth	Drug content (%)
Zero	7.0	None	98.68±0.25
1 month	7.0	None	98.61±0.39
2 month	7.0	None	98.64±0.21
3 month	7.0	None	98.57±0.65

Table 3.11: Results of Freeze Thaw studies conducted on optimized formulation

Gels ⇒ Factors ⇒	Optimized formulation		
	pH	Microb. growth	Drug content (%)
Zero	7.0	None	98.70±1.2
1 month	7.0	None	98.61±0.41
2 month	7.0	None	98.67±0.12
3 month	7.0	None	98.65±0.26

SUMMARY & CONCLUSION

The formulation was selected as a lipo-structured carrier to deliver the Silver Sulfadiazine into systemic circulation through topical application. The evaluation of the formulation is dependent upon accurate results obtained by analytical method used during the study. Lipo-structured of Silver Sulfadiazine formulation were prepared with the lipid and hydrophilic polymers. All these polymers are generally recommended as safe by FDA. The formulation was optimized by using vesicle size, in-vitro permeability and rheology.. Different literature review was selected. Through this the effect of lipid and polymer on the response i.e. vesicle size, viscosity and % release studied.

It was found that the increase in lipid concentration decrease the viscosity but it also increases the size of the vesicle. Viscosity was found to be decrease with the increase in the lipid and drug concentration. The optimized formulation has the minimum vesicle size and enough viscosity. The % release of the optimized formulation was also found to be 98% in 8 hr. The lipo-structured based Silver Sulfadiazine formulation was prepared with good spread ability, strength, and extrusion from the container. The drug content of the formulations was found to be within the limits. Increasing the concentration of the polymer significantly increased the consistency. The formulation exhibited pseudo plastic flow with no thixotropy. The values of flow index (n) were found to be less of the optimized formulation confirming the shear thinning behaviour of the gel.

The optimized formulation was found to be stable at accelerated stability conditions. Even after exposure to heat and humidity, no significant change was observed in the content uniformity, pH, clarity, and rheological properties of the gels. All other parameters were also observed to be comparable. When these gels were stored in refrigerator (8 to 15 °C), all the performance parameters were found to be comparable at each time point of the study. It could be concluded from freeze thaw study that optimized formulation was stable if they are stored in refrigerator. However, the formulation can be kept at room temperature for short periods of time if taken out for application.

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