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ROLE OF CARRIERS FOR ENHANCING SOLUBILITY OF SILVER SULFADIAZINE

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ABSTRACT

The present research work was aimed to enhance the solubility of Silver Sulfadiazine by solid dispersion approach. The study was carried out aiming firstly to increase the solubility and thus therapeutic action of silver sulfadiazine by preparing solid dispersions, secondly compare between formulated polyethylene glycol6000, polyvinyl pyrrolidone and mannitol varying the concentration of each polymer ratio of drug to the polymer was(1:1,1:2,1:3) and gelling agent, carbopol934 P(0.5% and 1%) for increasing the solubility using different techniques of solid dispersion formulation and thirdly carry out in-vitro diffusion study of optimized formulations. Solid dispersions of Silver Sulfadiazine were prepared by solvent evaporation method. Maximum Entrapment efficiency was of solid dispersions prepared with PEG 6000(1:2) corresponding to PVP and Mannitol.0.5% gel incorporated with PEG (1:2) showed to have the highest drug content (98.125%).

KEYWORDS: Solid dispersion, silver sulfadiazine, solubility.

INTRODUCTION

For centuries, silver compounds and ions have been extensively used for both hygienic and healing purposes, due to their strong bacterial properties.[1] In the last decade, it has been found that nearly 75% of patients with burns who were autopsied have died of invasive bacterial infections originating in the burn wound.[2] Burn is a coagulative destruction of the part or whole of the skin, and sometimes deeper tissues as well. It is caused by heat which

may be dry as flame or moist as boiling water, tea, milk, etc.[3] Burn injury disrupts the skin's natural protective barrier, which serves to protect the body from invading environmental bacteria. The skin's surface flora changes after burn injury, resulting in the eventual overgrowth of pathogenic organisms. Burn wounds are targets for bacterial colonization and subsequent tissue invasion.[4] The skin area of human beings ranges from 0.25m2 at birth to 1.5-1.9 m^2 in adults. It is the first barrier against entry of microorganisms which regulates heat loss by means of hair and sweat glands, receives stimuli, excretes waste products, protects from injury, ultraviolet light and desiccation.[5]

The term 'solid dispersion' is employed to dosage forms whereby the drug is dispersed in a biologically inert matrix. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion and when exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particle. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size.[6]
The use of topical therapy is essential for the survival of patients with major burns by minimizing the chances of burn wound sepsis in these patients.[7] Silver sulfadiazine is a sulfonamide and is a white or creamy white, odorless or almost odorless crystalline powder, which can become yellow when exposed to light.[8] Silver sulfadiazine is found to have broad spectrum of activity against most microorganisms, particularly the gram negative and has good tolerability by the patient and has low toxicity. It is very slightly soluble in water and having poor bioavailability and comes under the category of class IV of biopharmaceutical classification (BCS) system.[2]

MATERIALS AND METHODS

Materials

Silver sulfadiazine was obtained as a gift sample from Simca Laboratories, Carbopol 934P from Sampada Healthcare Pvt. Ltd. Polyvinyl pyrolidone, mannitol, methyl paraben, propyl paraben, nutrient broth and mannitol salt agar was procured from Himedia Laboratories Pvt. Ltd. Poly ethylene glycol, propylene glycol and sodium hydroxide pellets were purchased from Thermo Fischer Scientific Pvt. Ltd. and potassium dihydrogen orthophosphate and disodium dihydrogen orthophosphate were purchased from Qualigen Fine Chemical.

METHODOLOGY

Preformulation studies

The main goal of preformulation study is to establish physicochemical characteristic of a new drug substance. Preformulation studies of the drug, excipients and their combination were carried out to determine the solubility and melting point and to determine the feasibility, possibility and solubility of the ingredients to develop the formulation.[9]

Solubility Analysis

Solubility analysis was carried out in methanol and ethanol.

Melting point determinations

Melting point of drug was determined by using capillary tube method in which the pure drug was placed in a capillary tube which was fused at one end and placed in a digital melting point apparatus. The temperature was noted down at which the drug started melting.

Calibration Curve

- A stock solution of 1mg/ml of Silver Sulfadiazine was prepared by dissolving approximately about 50 mg of drug in small quantity and volume was made upto 50 ml.
- The stock solution was serially diluted to get solutions in the range of 10-50µg/ml and λ_{max} of the solution was found out.
- The absorbance of the different diluted solutions was measured in a UV-Visible spectrophotometer at 241nm.
- A calibration curve was plotted by taking concentration of solution in X axis and absorbance in Y axis and regression coefficient ‘r’ was calculated.

Preparation of solid dispersion

Only 10% of sulfadiazine is absorbed from the body and problem occurs due to minimal bioavailability of silver sulfadiazine when it is applied to large area burns or lesions so solid dispersions were prepared by using solvent evaporation method in order to change its solubility.

Solvent evaporation method was used to prepare a solid dispersion in which the drug and polymer were dissolved in the solvent (ethanol). Then the solvent was allowed to evaporate at room temperature. The drug and polymers were taken in different proportions (1:1, 1:2 & 1:3).

Preparation of gel base

Various gel formulations were prepared using carbopol934P as gelling agent. Required quantity of gelling agents were weighed and dispersed in a small quantity of distilled water to form a homogenous dispersion and allowed to stand for 1 day. 10% NaOH solution was added to adjust the pH to 7.4 and then propyl paraben and methyl paraben were added as preservatives. Methyl paraben and propyl paraben were weighed and then dissolved in slightly warm propylene glycol and then added to the mixture. Finally, the volume of solution was maintained adding sufficient quantity of water to prepare carbopol gel.

Incorporation of solid dispersion of SSD into gel base

Solid dispersion of SSD was first dissolved with small quantity of ethanol and this mixture was mixed into gel base with continuous stirring with glass rod, the amount of solid dispersions were added into gel, such that the prepared gel has 1%w/w SSD concentration.

Table 1: Formulation matrix of SSD gel using PEG (polyethylene glycol) as polymer.

Concentration	**0.5% Carbopol**			**1% Carbopol**		
Formulations	F1	F2	F3	F4	F5	F6
Silver Sulfadiazine	1%	1%	1%	1%	1%	1%
Carbopol 934 P	0.5 %	0.5%	0.5%	1%	1%	1%
PEG 6000	1%	2%	3%	1%	2%	3%
Propyl Paraben	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Methyl paraben	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
Propylene Glycol	2%	2%	2%	2%	2%	2%
Water	q.s	q.s	q.s	q.s	q.s	q.s
NaOH	q.s	q.s	q.s	q.s	q.s	q.s

Table 2: Formulation matrix of SSD gel using PVP (polyvinyl pyrrolidone) as polymer.

Concentration	**0.5% Carbopol**			**1% Carbopol**		
Formulations	F1	F2	F3	F4	F5	F6
Silver Sulfadiazine	1%	1%	1%	1%	1%	1%
Carbopol 934 P	0.5%	0.5%	0.5%	1%	1%	1%
PVP	1%	2%	3%	1%	2%	3%
Propyl Paraben	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Methyl paraben	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
Propylene Glycol	2%	2%	2%	2%	2%	2%
Water	q.s	q.s	q.s	q.s	q.s	q.s
NaOH	q.s	q.s	q.s	q.s	q.s	q.s

Table 3: Formulation matrix of SSD gel using mannitol as polymer.

Concentration	0.5% Carbopol			1% Carbopol		
Formulations	F1	F2	F3	F4	F5	F6
Silver Sulfadiazine	1%	1%	1%	1%	1%	1%
Carbopol 934 P	0.5%	0.5%	0.5%	1%	1%	1%
Mannitol	1%	2%	3%	1%	2%	3%
Propyl Paraben	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Methyl paraben	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
Propylene Glycol	2%	2%	2%	2%	2%	2%
Water	q.s	q.s	q.s	q.s	q.s	q.s
NaOH	q.s	q.s	q.s	q.s	q.s	q.s

All the quantities are in percentage.

Evaluation of SSD gel[9-11]

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.

PH of the gels

The pH of gel was determined after diluting and dispersing it in distilled water (10% w/v).

Spreadability

One gram of gel was placed between the two glass slides and load of 50g was applied. The time required to slip off the slides was measured and Spreadability was calculated using formula:

$$S = M. L / T$$

Where,

M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides.

Entrapment efficiency (%)

Exactly 1gm gel was completely dispersed in distilled water to make final volume 250 ml by subjecting it to stirring (400 rpm) for 5 min. The dispersion was then filtered. The absorbance of the drug was determined spectrophotometrically at 241 nm. Six batches of each polymer concentration were subjected to this determination. The percent encapsulation efficiency was

determined using the following expression:[9]

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoritical Drug Content}} \times 100$$

Antibacterial studies

111.02 grams of mannitol salt agar was suspended in distilled water and heated to boiling to dissolve the medium completely. Then it was sterilized by autoclaving at 15 lbs (121℃) for 15 minutes. The test organism was taken from the stock medium and swirled in into the test tubes containing sterilized nutrient broth and was allowed for incubation for 4 hours. The test organisms were taken and swabbed on the mannitol salt agar medium in an aseptic condition. The filter paper disc of 0.7 cm diameter were prepared and dipped into the prepared formulations and marketed product and the disc was then placed on the surface of the mannitol salt agar plates and gently pressed down to ensure complete contact of disc with agar surface. Plates were incubated at 37℃ for 24 hrs.

Drug content

Silver sulfadiazine content in gel was measured by dissolving gel in distilled water. Absorbance was measured after suitable dilution at 241 nm in UV spectrophotometer.

In-vitro diffusion studies

The invitro diffusion studies for SSD were conducted in pH 7.4 Phosphate buffer for 12 hours in dialysis membrane having pore size of 2.5 nm. Accurately weighed samples of the gel were added to a dialysis membrane and immersed into the dissolution medium (phosphate buffer 7.4 pH) and temperature was maintained at 37℃.±1℃ and fluid was agitated at 50rpm. 3 ml of dissolution media was withdrawn every one hour and volume withdrawn was replaced with equal quantity of the fluid so as to maintain constant volume. After suitable dilution, the samples withdrawn were analyzed spectrophotometrically at 241 nm.

Drug Release kinetics from diffusion data

In order to describe the kinetics of the release process of drug in the different formulations, models were fitted to dissolution data of all formulations using linear regression analysis. In order to study the exact mechanism of drug release from gel, drug release data were analyzed according to Zero order kinetics, First order kinetics, Higuichi square root equation, and Korsemeyer-Peppas model. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

RESULT AND DISCUSSION

Silver Sulfadiazine (SSD) was found to be soluble in ethanol (95%), alkali hydroxide and acetone and was found to be insoluble in water. The melting point of SSD was found to be 285℃ which was determined by capillary tube method using digital melting point apparatus. It was found that due to solid dispersion drug molecules were dispersed in the matrix, and when exposed to aqueous media, the carrier dissolved and the drug released as fine colloidal particle. The resulting enhanced surface area produced higher dissolution rate and bioavailability of poorly water soluble drugs.[6] The drug content was found to be highest for 0.5%carbopol gel incorporated with PEG(1:2), that is 98.125%. From drug diffusion study the formulation 0.5% PEG (1:2) was found to be better than marketed formulation. The λmax of pure Silver Sulfadiazine was found at 241nm in ethanol. The pH of the gel was found to be in a range of 7.36-7.50 which falls in the range of skin pH. The spreadability of the 0.5% gel was found to be superior to that of 1% gel. The zone of inhibition of marketed product and 0.5%, PEG (1:1) formulation was found to be comparable while the zone of inhibition of other formulations were found to be greater than that of the marketed product.

Calibration curve of SSD

The graph obtained was linear; with regression coefficient 0.986.

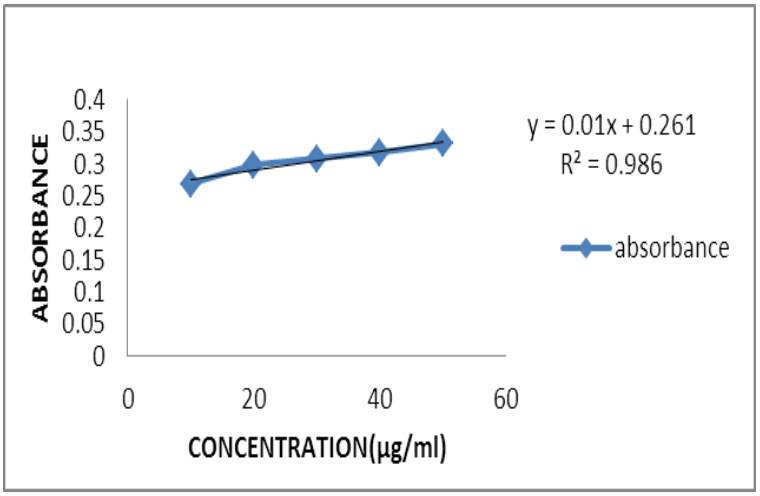


Figure 1: Calibration curve of SSD in ethanol at 241nm.

Entrapment efficiency analysis

Table 5: Table for entrapment efficiency.

Formulation	Entrapment Efficiency (%)	
	0.5% Carbopol	1% Carbopol
PVP (1:1)	7.4875±0.08	6.6125±0.02
PVP (1:2)	8.625±0.07	6.7625±0.01
PVP (1:3)	9.2625±0.05	6.3±0.01
PEG (1:1)	8.9625±0.02(F1)	7.9875±0.05(F4)
PEG (1:2)	9.8125±0.05 (F2)	7.9125±0.05 (F5)
PEG (1:3)	8.25±0.04(F3)	7.4±0.02 (F6)
Mannitol (1:1)	8.15±0.01	7.65±0.04
Mannitol (1:2)	7.625±0.04	7.1125±0.08
Mannitol (1:3)	8.0375±0.02	7.75±0.03

Here, PEG showed the highest entrapment.

Evaluation of SSD gel containing solid dispersion of PEG

Physical evaluation

Table 6: Table for physical evaluation of gel.

PEG (0.5%)			
Test	**F1**	**F2**	**F3**
Spreadability	Easy	Easy	Easy
Washability	Washable	Washable	Washable
Homogeneity	Yes	Yes	Yes
Colour	White	White	White
Odour	No	No	No
Phase separation	No	No	No
Feel upon application	Smooth	Smooth	Smooth
Test	F4	F5	F6
Spreadability	Easy	Easy	Easy
Washability	Washable	washable	Washable
Homogeneity	Yes	Yes	Yes
Colour	White	White	White
Odour	No	No	No
Phase separation	No	No	No
Feel upon application	Smooth	Smooth	Smooth

PH studies of gel

Table 7: Table showing PH of gel formulation.

Formulation	PH
F1	7.48
F2	7.36
F3	7.50
F4	7.44
F5	7.45
F6	7.48

Spreadability studies of the gel

Table 8: Table showing the spreadability of gel.

Formulation		Spreadability g.cm/sec)
F1	0.5%	23.79
F2		23..38
F3		23
F4	1%	17
F5		17.25
F6		17.73

Spreadability was found to be highest for F1 formulation of 0.5%

In-vitro releases studies of formulations

Table 9: Iv-vitro releases studies of F1, F2 & F3 formulations.

Time(hrs)	%Cumulative Drug Release (CDR)		
	F1	F2	F3
0	0	0	0
1	24.66	27.75	22.92
2	33.32	35.79	28.71
3	42.0	45.86	33.53
4	46.5	51.43	35.25
5	47.36	52.07	37.5
6	55.93	52.93	38.36
7	58.18	56.25	42.43
8	58.82	62.46	44.35

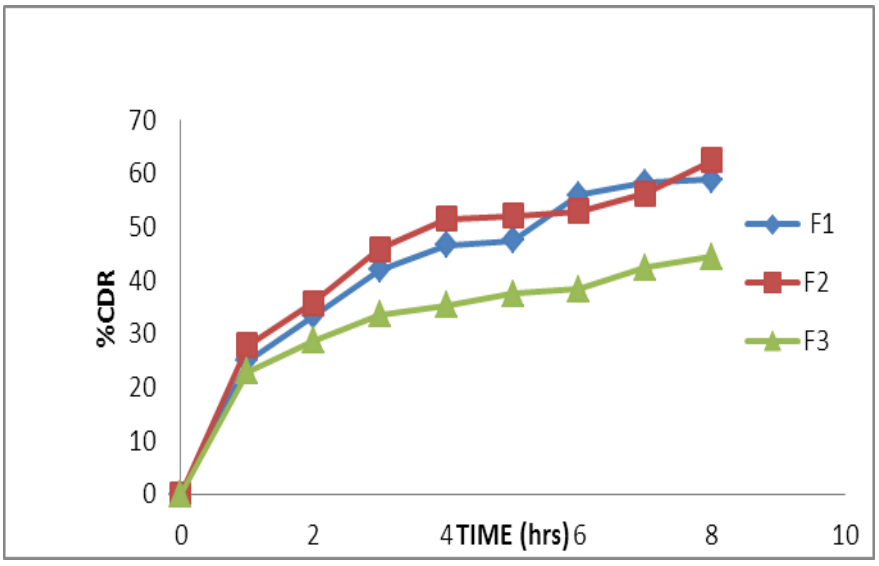


Figure 2: In-vitro releases of F1, F2 & F3 formulations.

Table 10: In-vitro releases studies of f4, f5 & f6 formulations.

Time(hrs)	%Cumulative Drug Release(CDR)		
	F4	F5	F6
0	0	0	0
1	19.93	21.21	21.96
2	28.61	29.25	27.53
3	33.96	33.0	33.10
4	35.78	35.03	33.53
5	37.61	38.57	34.28
6	44.14	39.10	36.32
7	46.61	47.35	44.14
8	47.46	51.96	46.61
9	57.85	54.85	52.71

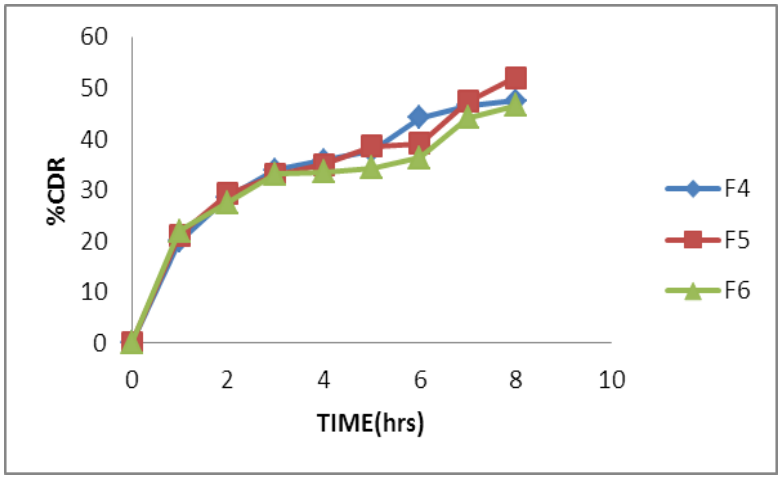


Figure 3: In-vitro releases of formulations F4, F5 & F6.

In-vitro releases studies of marketed product

Table 11: In-vitro releases studies of marketed product compared to optimized formulation.

Time (hrs)	%Cumulative Drug Release	
	Marketed Product	Optimized Formualtion (0.5% PEG (1:2))
0	0	0
1	14.78	35.78
2	16.39	45.85
3	23.89	51.43
4	24.0	52.07
5	24.75	52.93
6	45.0	56.25
7	45.32	62.46
8	45.64	70.82

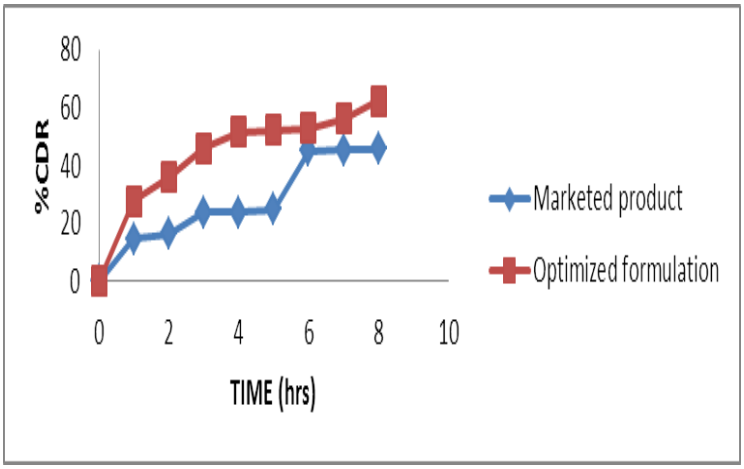


Figure 4: In-vitro releases studies of marketed product compared to optimized formulation.

Release kinetics

Table 12: Release kinetics data of formulation F1-F6.

Formulations code	Zero order	First order	Higuichi	Korsmeyer-Peppas	Best Fit
	R2	R2	R2	R2	
F1	0.940	0.884	0.978	0.986	Korsmeyer-Peppas Release
F2	0.897	0.839	0.95	0.967	
F3	0.950	0.904	0.982	0.989	
F4	0.846	0.880	0.977	0.982	
F5	0.860	0.929	0.948	0.960	
F6	0.933	0.916	0.924	0.936	

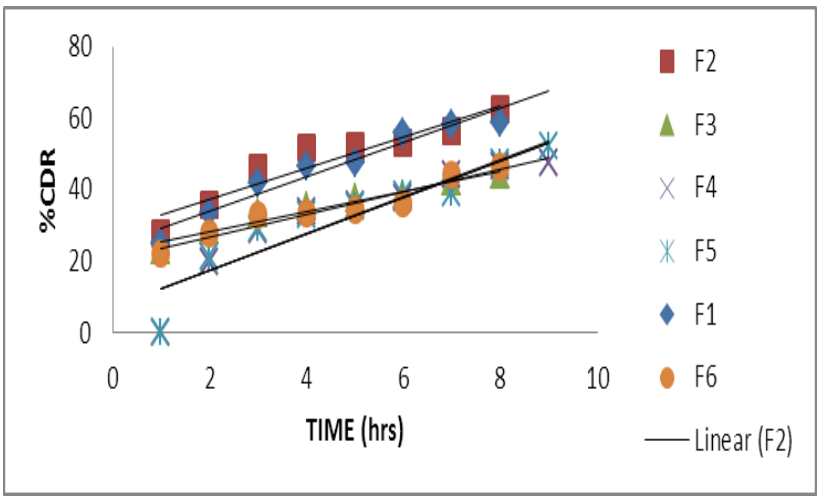


Figure 5: Release kinetics data of formulation F1-F6 (Zero order model).

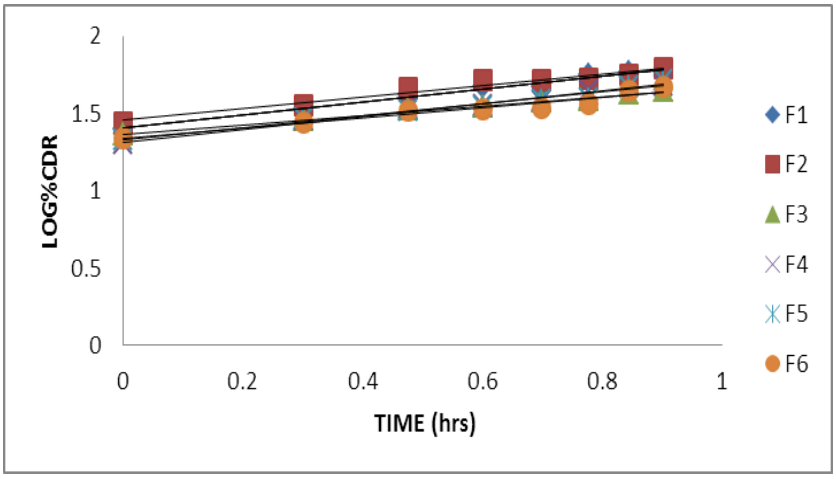


Figure 6: Release kinetics data of formulation F1-F6 (First order model).

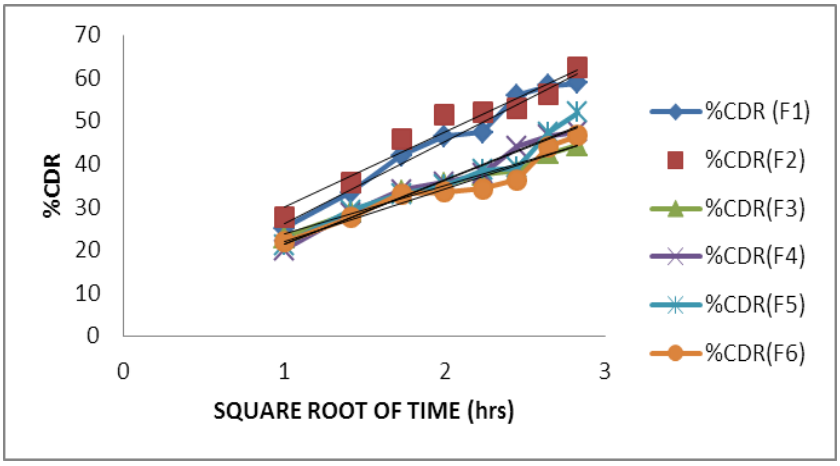


Figure 7: Release kinetics data of formulation F1-F6 (Higuchi model).

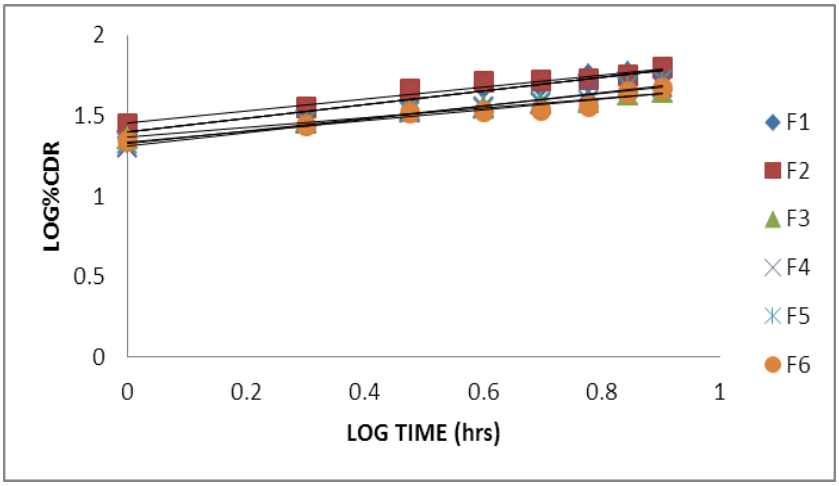
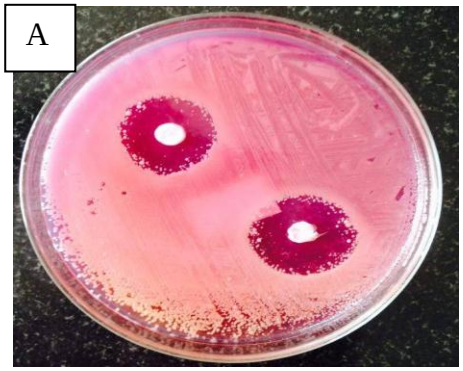


Figure 8: Release kinetics data of formulation F1-F6 (Korsmeyer-Peppas model).

Antibacterial studies

Table 13: Table showing zone of inhibition of marketed product and prepared formulations.

Formulations		Zone of Inhibition(cm)
Marketed Product		2.25
0.5%	1:1	2
	1:2	2.85
	1:3	2.75
1%	1:1	3.4
	1:2	3.5
	1:3	3



A: Marketed Product- ZOI:2.25cm

Figure 9: Figure showing zone of inhibition of marketed product.

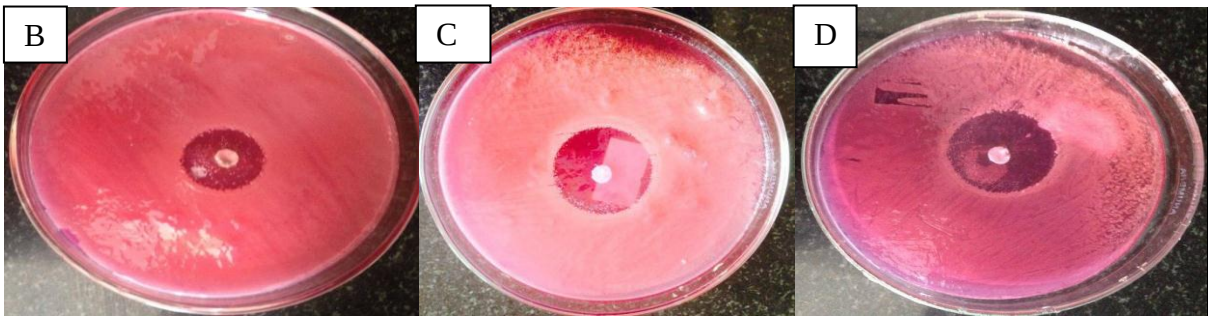


Figure 10: Figure showing zone of inhibition of F1, F2 & F3.

B: PEG 0.5% 1:1 -ZOI:2cm

C: PEG 0.5% 1:2 -ZOI:2.85cm

D: PEG 0.5 % 1:3 -ZOI:2.75cm

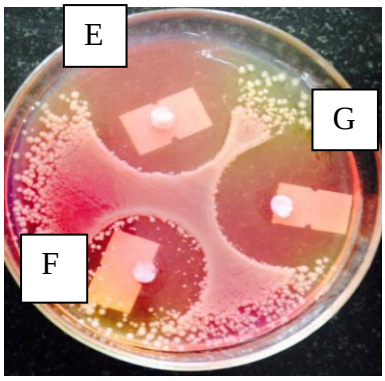


Figure 13: Figure showing zone of inhibition of F4, F5 & F6.

E = PEG 1% 1:1 –ZOI: 3.4cm

F= PEG 1% 1:2 –ZOI: 3.5cm

G= PEG 1% 1:3 –ZOI: 3cm

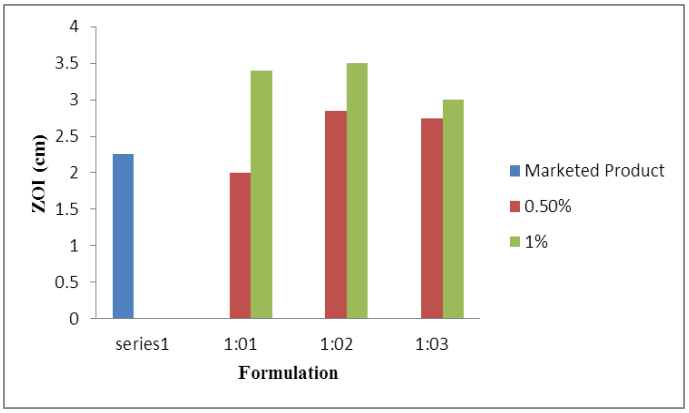


Figure 14: Figure showing Zone of Inhibition.

CONCLUSION

- Solid dispersion approach is proved to be one of the effective method in enhancing solubility of poorly water soluble silver sulfadiazine. The approach of using solid dispersion in enhancing the solubility of SSD gel was rigorously used in this study.
- Silver Sulfadiazine showed maximum absorption at 241nm in ethanol. The value of regression coefficient was found to be 0.986, which showed linear relationship between concentration and absorbance. Thus, it can be concluded that, Beer's law was obeyed.
- Still validated protocol & stability data need to be justified for commercialization.

RECOMMENDATION

- Manufacturing, Stability and scale up issues should be taken in consideration for commercialization.

- Since limitation of our study is permeability. The further work should be carried out to increase the permeability of SSD by using DMSO solid dispersion.

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