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A Study of Light Influence on Silver Sulfadiazine Cream: Causes, Effects, and Solutions

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Heyam Ali[1], Rasha Saad[2*], Ahmed Ahmed[3], and Babiker El-Haj[4]

1 Department of Pharmaceutics and Pharmacy Practice, Dubai Pharmacy college, Dubai, United Arab Emirates

2 Department of Pharmaceutical Chemistry, School of Pharmacy, Management & Science University, Malaysia

3 General surgery-Colorectal department, Nottingham Hospital, United Kingdom,

4 Ajman University of Science and Technology, Shāriqah, United Arab Emirates.

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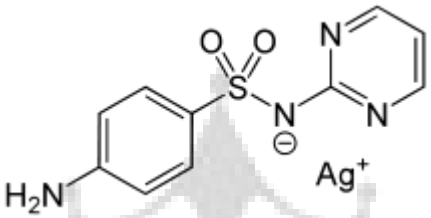
ABSTRACT

Objective: The aim of this research is to identify the possible causes of the color change in silver sulfadiazine cream (SSD) manufactured by Julphar Company packed in plastic container 500 gm, furthermore is to find suitable measures to overcome this problem. Our target in this study is to check the stability of the formula as well as the effect of light and the container in SSD cream. **Methods:** Silver sulfadiazine cream was prepared by following the existing Julphra's standard sterile cream Manufacturing Method. The prepared cream was filled into white plastic container with white cap, black plastic container and black cap & white container with white cap along with aluminum foil liner from inside. Initially, samples were examined visually and were chemically analyzed. Three samples in different containers were kept in normal condition and under exposure to light for three months. The effect of these containers and environmental conditions then observed at weekly interval. **Results:** At the end of our study we found that upon exposure of the SSD to light the color of the cream in the white container was changed to dark, the color of the cream in the white container with white cap along with aluminum foils was not changed remarkably and the color of the cream in the black container remain unchanged and this arises the importance of the packaging components on dosage form stability which shows that faulty packaging of pharmaceutical dosage form can invalidate the most stable formulation. Consequently, it is essential that the choice of container materials for any particular product be made only after a thorough evaluation has been made of the influence of these materials on the stability of the product and of the effectiveness of the container in protecting the product during extended storage under varying environmental condition of temperature humidity, and light. **Conclusion:** Despite the wide range of new burn treatment agents, SSD cream still can be considered as the best typical antibacterial agent of major importance in treatment of the burn patient. The emergent issue of colour change is caused by silver oxidization resulted from exposure to light. This issue can be resolved by the use of light resistance jar. However, it is found by this research that the discoloration issue will not change the therapeutic effect.

1.0: INTRODUCTION

Silver sulfadiazine (INN, or silvadene) is a topical sulfonamide/silver [1] antibacterial used as a topical cream on burns. Evidence regarding its usefulness in burns is poor.[2] Tentative evidence has found that silver sulfadiazine may increase healing times – wounds may take longer to heal if treated with this drug, so it is not recommended by the authors of a Cochrane review.[2] Silver sulfadiazine is typically delivered in a cream or aqueous suspension. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[3]



2.0: MATERIALS AND METHODS

2.1 Equipments and Materials

The active ingredients and the excipients (Julphar Company), the measuring cylinders, beakers, Electronic balance (UniBlock, Shimadzu Corporation, Japan). Petri-dishes, aluminium foils, containers (Julphar Company), thermometer (U.S.A), Water bath (Schutzart Din, Germany). Homogenizer (IKA Labortchnick, Germany)., Mixer (IKA Labortchnick, Germany)., Stirrer (IKA Labortchnick, Germany), PH detector, UV Spectrophotometer (Model: UV 1650PC, Shimadzu, Japan), HPLC (Shimadzu Corporation, Japan).

2.2 Experimental Design

2.2.1 SSD Cream Preparation:

Preparation of 1% SSD Cream and filling 3 plastic jars containers according to the study protocol.

Critical point: cream was protected from direct light at all stages of manufacturing. (Batch size: 2.0 Kg)

Batch Formula:

Material Name	Quantity
1) Silver Sulfadiazine	**20.0 gm**
2) Cetyl Alcohol	**120.0 gm**
3) Glyceryl Monostearate A / S	**160.0 gm**
4) Liquid Paraffin	**160.0 gm**
5) Tween 80	**60.0 gm**
6) Tween 60	**40.0 gm**
7) Propylene Glycol	**300.0 gm**
8) Purified Water	**1160.0 gm**

Justification for use of each ingredient:

- **Cetyl Alcohol:** Coating agent; emulsifying agent; stiffening agent. It is widely used in cosmetics and pharmaceutical formulations such as suppositories, modified-release solid dosage forms, emulsions, lotions, creams, and ointments.
- **Glyceryl Monostearate:** Emollient; emulsifying agent; solubilizing agent; stabilizing agent; sustained-release ingredient; tablet and capsule lubricant. It is used as a nonionic emulsifier, stabilizer, emollient, and plasticizer in a variety of food, pharmaceutical, and cosmetic applications. It acts as an effective stabilizer, that is, as a mutual solvent for polar and nonpolar compounds that may form water-in-oil or oil-in-water emulsions.
- **Mineral Oil (Liquid paraffin):** Emollient; lubricant; oleaginous vehicle; solvent. It is used primarily as an excipient in topical pharmaceutical formulations. It is additionally used in oil-in-water emulsions, as a solvent.
- **(Tween 80, 60) Polysorbates:** Emulsifying agent; nonionic surfactant; solubilizing agent; wetting, dispersing/ suspending agent. Polysorbates are used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical emulsions.

- **Propylene Glycol:** Antimicrobial preservative, disinfectant, humectant, plasticizer, solvent and stabilizer. It has become widely used as a solvent, extractant, and preservative in a variety of parenteral and non parenteral pharmaceutical preparation.

Step-I (For Oil Phase)

Cetyl Alcohol	120.0 gm
Glyceryl Monostearate A / S	160.0 gm
Liquid Paraffin	160.0 gm
Tween 80	60.0 gm
Tween 60	40.0 gm

Take the above material in a beaker, heat to 90^{o}C for 60 minutes while stirring. Cool to 60^{o}C. Maintain the temperature to 60^{o}C – 65^{o}C.

Step-II (for Aqueous Phase)

Purified Water: 1160.0 gm

Take Purified water in a beaker and heat to 90^{o}C for 30 minutes, then cool to 60^{o}C. Maintain temperature to 60^{o}C – 65^{o}C.

Step-III (For Disperse Phase)

Transfer oil phase to the aqueous phase with continuous stirring, temperature 60^{o}C. Homogenise at speed II for 5-10 minutes. Cool to 40^{o}C.

Step-IV (Drug Phase)

Propylene Glycol: 250.0 gm
Silver Sulfadiazine: 20.0 gm

Warm Propylene Glycol to 40^{o}C in water bath in a beaker. Dissolve Silver Sulfadiazine in Propylene Glycol (40 ^{o}C) using homogenizer.

Add drug phase to the disperse phase while mixing at temperature 40^{o}C

Step-V (Rinsing)

Propylene Glycol: 50.0 gm

Rinse the beaker with propylene glycol and add to the disperse phase, mix and homogenize for 10 minutes at temperature 40^{o}C

Step-VI

Cool Cream to 30^{o}C while mixing. Then transfer to the container protecting from direct light.

2.2.2 Specification test (observation):

Description: white, smooth, homogeneous cream in different temperature and different intervals

pH: specification between 4 and 7 at 25 ^{o}C

2.2.3 Silver Sulfadiazine Assay

(1 gm/100 gm) performed by HPLC.

Identification of silver sulfadiazine in silvadiazine 1% cream.

Specification: (NLT 90.0% & NMT 110% of LC).

1. Chromatographic conditions:

Column: Waters, µ-Bondapak C-18, 3.9 × 300 mm or equivalent, Mobile phase: Water: Acetonitrile, 90: 10, Add 0.5 mL of triethylamine (TEA) to 1000 mL of water, adjust the pH to 3 with using phosphoric acid. Use this water for mobile phase preparation, 1.3 Wavelength: 254nm, 1.4 Flow rate: 1.5 mL/min, 1.5 Inj. Volume: 20µL, 1.6 Temperature: Ambient, 1.7 Diluent: Transfer 50 mL of ammonia solution to 500 mL volumetric flask. And complete to volume with water.

2. Preparation of Standard:

Weigh and transfer accurately 50mg of Silver Sulfadiazine reference standard in 100 ml volumetric flask. 2.2 Add about 60 ml of diluent and shake well to dissolve, make up to volume

with diluent and mix well. Dilute 5 ml of this solution to 50 ml with mobile phase and mix well. 2.4 Pass this solution through 0.45 µm filter before injecting to HPLC. This is the working standard preparation having concentration approx. 5mg% of Silver Sulfadiazine.

3. Preparation of Test sample:

Weigh accurately and transfer 2 gm of test cream (equivalent to 20 mg of Silver Sulfadiazine) in a 100 ml beaker, Add 30 ml of ethanol, heat on a water bath to felt, mix well and add 30 ml of diluent and mix well, transfer the content of the beaker to a 100 ml volumetric flask, cool to JO temperature and complete to volume with diluent, 3.4 Dilute 5 ml of this solution to 20 ml with mobile phase and mix well, filter this solution through 0.45 µ filter. This is the test sample preparation having concentration 5mg% of Silver Sulfadiazine.

3.0 EXPERIMENTAL:

4.1 Prepare the mobile phase, set parameters, run mobile phase to stabilize the system, prepare Standard and Test Sample as described in steps 3 and 4, inject 20 µl of each Standard preparation and Test sample preparation until replicate chromatograms of either solutions are identical.

3.2.4 Calculation

Assay Calaulation for Silver Sulfadiazine:

The percentage L.A. of Silver Sulfadiazine in Silvadiazin 1% Cream is calculated by the formula:

$$\text{Silver Sulfadiazine (\% L.A.)} = \frac{PA_T \times Cs \times P}{PA_S \quad C_T}$$

Where,

- PA_T is the peak area of Silver Sulfadiazine peak in test solution.
- PAs is the peak area of SSD peak in standard solution as is the final.
- Cs is the final concentration of Silver Sulfadiazine in standard solution.
- C_T is the final concentration of Silver Sulfadiazine in test solution.
- P is the potency of Silver Sulfadiazine reference standard in % w/w.

3.2.5 Stability Study in different conditions:

The prepared cream was kept in different containers and under specific environmental conditions in order to evaluate the stability as follow:

1) 50 gm cream in white container with white cap closed and kept under light and room temperature.
2) 50 gm cream in white container with white cap and covered it with aluminium foil kept under light and at room temperature.
3) 50 gm cream in black container and black cap closed and kept under light and room temperature.
All the samples were kept for observation and after 7 days, we checked the appearance.

Figure 6. Containers

Figure 7. Foils used as covers

3.2.6 Measuring transmittance of light through the containers

The percentage transmittance of the two containers (black and white) was calculated by cutting off a slide of each one and inserts them to the cell path holder in the UV spectrophotometer (Model: UV 1650PC,Shimadzu).

In the range of 400 – 800nm.

3.2.7 Microbiological tests:

Specification microbial limits as specified in the USP and discussed in the results section of this research.

4.0 RESULTS

The drug content of the formulation was found to be in compliance with the specification, indicating the stability of the drug in the formulations. Initially the three container color of the samples was white to off-white. After 7 days of exposure to light color of the sample in white container was darkened. Color of the sample kept in white with aluminum foil liner (inside) was off-white and the color of the sample kept in black container was not changed and color was white to off-white. (Shown in the attached Figures 8 to 10. Results are presented in the Table: 1).

Transmittance of light through the black container was found less than that the white containers (result presented in Table: 2).

Table: 1 Observation of the samples in different containers on exposure to light.

Description of the containers	Initial color of the samples	Color of the samples after 7 days on exposure to light
White plastic container with white cap	White to off-white	Dark
White container with white cap along with aluminium foil liner (inside)	White to off-white	Off-white to dark
Black plastic container and black cap.	White to off-white	White to off-white

		
Color change with white plastic container and white cap	**White container with white cap along with aluminum foils**	**Black plastic container and black cap.**

Table: 2: Transmittance of light through different containers

Description of the container	Transmittance (400nm-800nm)
White plastic container	0.134%
Black plastic container	0%

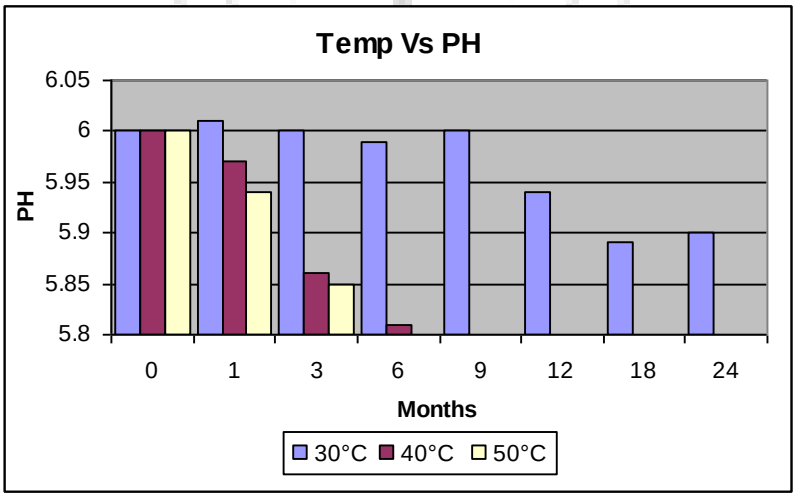
4.1 PH Specification: Between 4.00 and 7.00 at 25°C

(Determined on the supernatant liquid obtained from 1 in 20 mixture of the cream in water).

Storage conditions for SSD

Due to time constraint of our research, we used shelf data about the stability of the SSD when it stored in different temperature and time period.

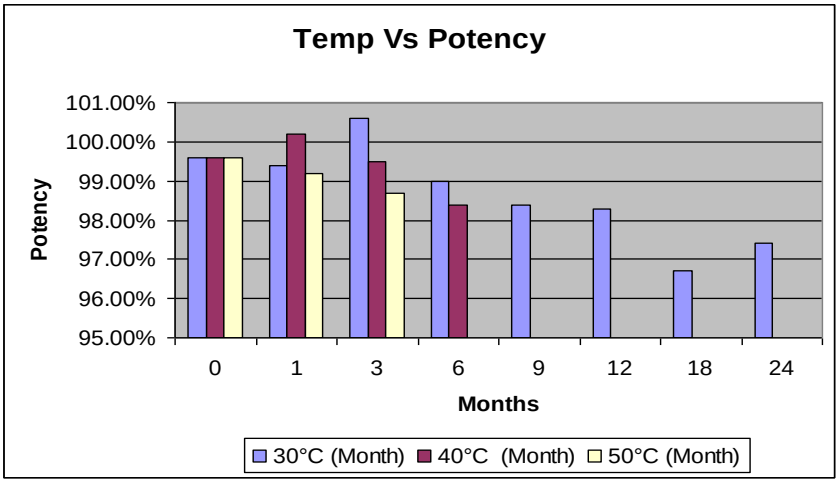
- 30°C Temperature 30°C + 2°C for 24 months
- 40°C Temperature 40°C + 2°C for 6 months
- 50°C Temperature 50°C + 2°C for 3 months



As illustrated in the graph above, pH results of the supernatant liquid obtained from 1 in 20 mixture of the cream in water of all the three SSD containers at three different stations (30°C, 40°C and 50°C) were within the specifications throughout the study period.

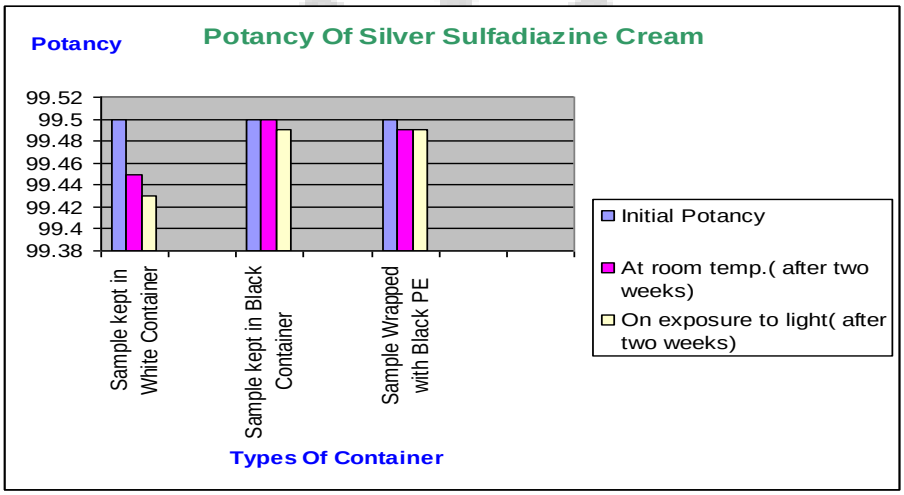
4.2 Silver Sulfadiazine Assay

Specification: (NLT 90.0% & NMT 110.0% of the labeled amount of C10H9AgN4O2S (SSD).

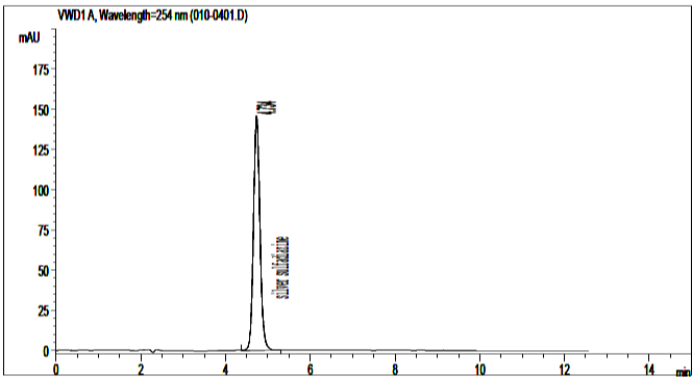


This graph shows the assay results of silver sulfadiazine at 30°C, 40°C and 50°C stations for all three containers were within the specifications throughout the study period.

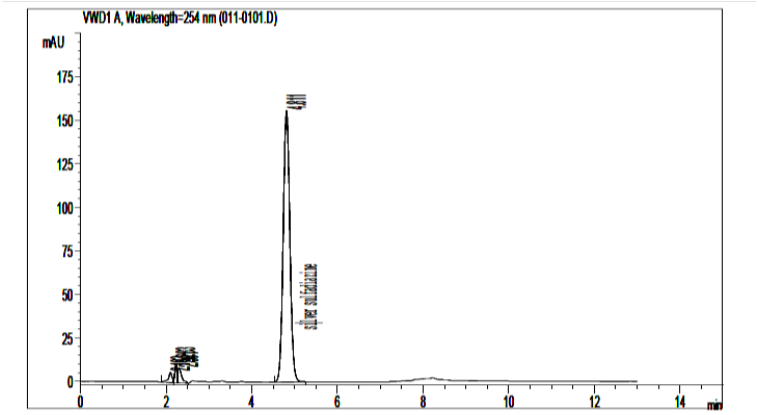
4.3 The effect of the containers on the potency:



Typical Chromatogram of Silver Sulfadiazine Reference Standard



Chromatogram of Silver Sulfadiazine 1% cream of the sample



4.4 Microbial limit tests:

Specifications

Total Aerobic Microbial Count	NMT 23 C.F.U/g	
Total Yeast and Mould Count	NMT 10 C.F.U/g	
Detection of pathogen	*Escherichia coli*	Absent
	Salmonella spp.	Absent
	Staph. aureus	Absent
	Pseudomonas aeruginosa	Absent

Duration (months)	**Total Aerobic Bacterial Count**	**Total Yeast and Mould Count**	**Detection of Pathogen**
Initial (30°C,40°C,50°C)	LT 10 c.f.u/g	LT 10 c.f.u/g	Absent
03 (30°C,40°C,50°C)	LT 10 c.f.u/g	LT 10 c.f.u/g	Absent
06 (30°C,40°C)	LT 10 c.f.u/g	LT 10 c.f.u/g	Absent
12 (30°C)	LT 10 c.f.u/g	LT 10 c.f.u/g	Absent
24 (30°C)	LT 10 c.f.u/g	LT 10 c.f.u/g	Absent

The results of microbial test for the samples stored at 30^{o}C, 40 ^{o}C and 50 ^{o}C for all tree batches were within the specifications throughout the study period.

5.0 DISCUSSION

Lot of the findings of our investigation are noteworthy. For instance, the SSD cream darken in the jar because of the light catalyzed reaction which is a common characteristic of all silver salts. A similar analogy is the oxidation of silverware. The product of this color change reaction is silver oxide that ranges in color from gray to black. Our research shows that silver oxide has rarely been associated with permanent skin discoloration. Additionally, the antimicrobial activity of the product is not substantially diminished because the color change reaction involves such a small amount of the active drug and is largely a surface phenomenon.

Exposure of a drug to irradiation can influence the stability of the formulation, leading to changes in the physicochemical properties of the product. The influence of excipients of frequently used stabilizers is often difficult to predict and, therefore, stability testing of the final preparation is important. The selection of a protective packaging must be based on knowledge about the wavelength causing the instability. Details on drug photoreactivity will also be helpful in order to minimize side-effects and/or optimize drug targeting by developing photoresponsive drug delivery systems. Proper packaging and storage of pharmaceutical products are essential in maintaining product stability and efficacious use. Proper labeling of manufactured products and dispensed prescriptions is also vital to the appropriate use of medication.

Photolabile drugs must be protected from light under every phase, from the preparation to the final use. In particular, the commercialized dosage form must be such that no significant decomposition of the active principle takes place. This can be done either by avoiding the light reaches the preparation, via using an opaque container or by incorporating in the preparation some additive that either absorbs the active light competitively with the drug principle or quenches the photoreaction of the latter (internal protection).

6.0 CONCLUSION

The data and observations collected from this study lead us to considerable support to use of light resistance containers for the SSD in order to prevent colour change. We found that the

colour change is caused by light transmittance to the cream which eventually transform silver layer of the surface to silver oxide. Our study concluded that this colour change has no effect on the therapeutic action of the cream. However, it could lead the end users to loose trust in the effectiveness of this SSD when they see the discoloration layer at the top of the container when they open it. Therefore we recommend black plastic container as a primary packaging material for the SSD or any other photolabile medicines.

Even though this study was limited in many aspects, it can provide valuable insights into the selection of proper and appropriate containers for all photolabile medicines. We also understand that the results of this study are just a small step to a better understanding of the applicability of SSD and a lot of other burn treatment agents.

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