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Effects of Humactents and Oleogeneous Base in the Photostabilization of Secnidazole Emulgels

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Abstract: This investigation aims to study the formulation of emulgel preparations of secnidazole (SZ, The variables in the composition of the oleaginous phase (liquid paraffin and castor oil) and humectants (propylene glycol and glycerol) and the physical and rheological properties like homogeneity, spreadability, and extrudability were studied. Variations in the viscosity of SZ emulgels were observed due to changes in formulations. The viscosity was central to the stability of the SZ emulgel preparations. SZ is a photosensitive drug, and irradiation formed its primary photodegraded product 2,4-(N-2-hydroxypropyl) diaza-3-methyl-1-nitro-1,5-dione. SZ has been subjected to photolysis by irradiation, and the clear first-order rate constant, kobs, for the degradation of SZ has been determined. The values of kobs (2.79-5.12 × 10^{-2} min^{-1}) have decreased with the increase in viscosity (20085-29985 cP) of emulgel preparations. The ratio of stabilization is in the range of 2.31-4.22. It is concluded that increasing the viscosity of pharmaceutical preparations may enhance the photostability of light-sensitive drugs.

Keywords: secnidazole, emulgel, viscosity, kinetics, photostabilization.

保湿剂和油性碱对塞克硝唑乳胶光稳定作用的影响

摘要：本研究旨在研究塞克硝唑乳膠製劑的配方。研究了含油相（液體石蠟和蓖麻油）和保濕劑（丙二醇和甘油）的組成變量以及均勻性、鋪展性和可擠出性等物理和流變特性。由於配方的變化，觀察到塞克硝唑乳膠粘度的變化。粘度對塞克硝唑乳膠製劑的穩定性至關重要。塞克硝唑是一種光敏性藥物，輻照形成其主要光降解產物 2,4-(N-2-羥丙基)迪亞扎-3-甲基-1-硝基-1,5-二酮。塞克硝唑已通過輻照進行光解，並確定了塞克硝唑降解的明確一級速率常數球棒。球棒(2.79-5.12 × 10-2 分鐘-1) 的值隨著乳膠製劑粘度(20085-29985 厘泊)的增加而降低。穩定比在 2.31-4.22 範圍內。結論是增加藥物製劑的粘度可能會增強光敏藥物的

光穩定性。

关键词：塞克硝唑，乳膠，粘度，動力學，光穩定。

1. Introduction

Emulgel is one of the most appealing semisolid dosage forms. It has dual controlled release systems like emulgels and emulsions, which are directly applied at the site of action and produce an extended period of action at the site of application [1]. The use of high molecular weight polymers like hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, carboxymethyl cellulose, carbopol 940, carbopol 934 and xanthine gum are usually preferred as gelling agents. Castor oil, liquid paraffin, clove oil, sesame oil, soybean oil are mainly used for the oleaginous phase and penetration enhancers in semisolid preparations [2]. Glycerin, polyethylene glycol, propylene glycol and ethylene glycol are used as humectant, to keep the preparation moist [3]. The formulation possesses high viscosity, spreadability, homogeneity with filming abilities at low concentrations of polymers [4].

Secnidazole (SZ) (an anti-infective) (Fig. 1) belongs to the nitroimidazole. It is chemically known as (RS)-1-(2-methyl-5- nitroimidazole-1yl) propane-2-ol [5]. SZ is sparingly soluble in water [6]. It is used for treating amebiasis, giardiasis, trichomoniasis, and bacterial vaginosis. SZ is a broad spectrum antibiotic and possesses efficacy against protozoa [7]. UV-visible spectrophotometer was by many researchers for the quantitative and qualitative analysis of SZ [8-11]. The major advantage of this technique is to provide rapid result, high selectivity, accuracy, precision, and sensitivity with the degradation products of drugs [12, 13]. The major suitability of UV-visible spectrometry is the rapid quantitative analysis of pure SZ and its degradation [14].

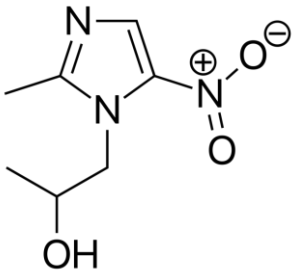

Fig. 1 Chemical structure of SZ

The main objective of this investigation was to formulate a stable SZ emulgel. Moreover, the stability-like photostability was also carried out for the assay of SZ in emulgel formulations and in aqueous preparations. However, the effect of different oleaginous phases and humectants on the stability of SZ in emulgel is still not determined. The work includes the rate constant of photolysis (kobs) of pure SZ solution (5 × 10–5 M) at different pH acidic (4.0), neutral (7.0) and alkaline (9.0).

2. Materials and Methods

2.1. Materials

Secnidazole (SZ) (98%) was gifted from Nabi-Qasim Industries Private Limited, Karachi, Pakistan with assigned purity. Carbopol 934 used as the gelling agent, mineral oil, castor oil, glycerol (85%), propylene glycol (≥99%), citric acid (monohydrate), sodium citrate dehydrates, methanol, hydrochloric acid (HCl), potassium chloride (KCl), potassium hydroxide (KOH), sodium hydroxide (NaOH), methylparaben sodium (MP), and propylparaben sodium (PP) were purchased from Merck & Co. Whitehouse Station, NJ, USA. The SZ solutions and emulgels were prepared using freshly boiled de-ionized water.

2.2. SZ Emulgel Formulations

Carbopol 934 was selected as the gelling agent to prepare the gel matrix formulation [15]. Carbopol 934 was dispersed in hot distilled water with continuous stirring and adds methylparaben and propylparaben, then allowed to cool overnight. SZ (1% w/w) was added to the gel preparation and add glycerol and propyleneglycol to SZ gel.

Castor oil and liquid paraffin (mineral oil) were used as an oleaginous phase for SZ emulgel formulations. The oleaginous phase (castor oil or liquid paraffin) was added in SZ gel preparations to prepare (w/o) emulgel. Finally, a homogenizer homogenized the emulgels. The pH of the formulation was adjusted with citric acid buffer. The formulation and role of ingredients in SZ emulgel in this study are given in Table 1.

Table 1 Ingredients of formulations of SZ emulgel

Ingredients	**% *w/w***	**Role of Ingredients**
Secnidazole	1	Active pharmaceutical ingredient
Carbopol 934	2.5	Gelling agent
Mineral oil and castor oil	5-7.5	Oleaginous phase
Glycerol, and propylene glycol	5-7.5	Humectant
Salt of methylparabens and propyl parabens	0.2 and 0.04	Preservative (antimicrobial)
Citric acid	0.3	Antioxidant/ Buffer
Sodium citrate dehydrate	0.6	Buffer
De-ionized water	Q.S	Vehicle

2.3. Measurements of pH

A digital pH meter with a glass electrode (model CP501; sensitivity 0.01 pH units, Emlenton, Poland) measured the pH of the emulgel formulations. Buffer tablets of pH = 4.0, 7.0 and 9.0 standardized the pH meter. The pH electrode was immersed directly in the emulgel to determine the pH adjusted to pH = 5.0.

2.4. Rheological Properties of SZ Emulgels

The effect of the oleaginous phase (castor oil and mineral oil) and humectants (glycerol and propylene) on the rheological properties like viscosity, homogeneity, spreadability, extrudability, physical appearance and of SZ emulgel were assayed.

2.5. Viscosity Measurements

The viscosity of SZ formulated emulgels were assayed by rotational viscometer (Brookfield Engineering Laboratories Inc. (Model LVDV-E., USA). The different formulations of SZ emulgel were taken in a 250 ml beaker and its pivot was dipped into the emulgel. The viscosity of the emulgel was analyzed by a spindle number 5 for 1 min at 25°C at different angular speeds and measured 3 times to exclude the variability and determine the mean viscosity [16].

2.6. Physical Appearance

The physical stability-like change in color, homogeneity and consistency and phase separation of SZ emulgel were visually observed.

2.7. Spreadability Test

The spreadability was determined by the wooden block and glass slide method. In this apparatus, emulgel present between 2 slides with a certain load, when the upper movable slide separates completely from the fixed slide time noted [1].

$$S = \frac{\text{Weight} \times \text{Length of slide}}{\text{Time taken for complete separation}} \times 100 \quad (1)$$

2.8. Extrudability Test (Tube Test)

The extrudability test is a primary test to determine the pressure force required to extrude the emulgel from a collapsible aluminum tube. It can be determined by the weight required to extrude 0.5 cm ribbon of emulgel in 10 sec. from the lacquered packaging tube.

2.9. Light Intensity Measurements

Potassium ferrioxalate actinometry was used to investigate the intensity of the irradiation source and a value of 1.20 ± 0.11 × 1017 quanta s^{-1} was obtained previously by [17].

2.10. Photolysis of SZ

1 g of different formulations of SZ emulgel was uniformly placed on 5 small glass slabs. These slabs occurred at a distance of 30 cm in a dark chamber with a constant temperature and humidity (25 ± 2°C/60 % RH) and illuminated by a Philips HPLN 125-W high-pressure mercury vapor fluorescent lamp. After 30 min of light exposure, each sample of emulgels was removed for the qualitative and quantitative estimation.

2.11. Thin Layer Chromatography

The photosensitizer preparations of SZ emulgels were extracted with KOH (0.1 M) with methanol (10:90 v/v) and subjected to TLC using precoated silica emulgel 60 F 254 as the stationary phase (E. Merck). This helps in the determination of SZ and its photodegraded product. The spots were determined under UV light (209 nm) [18].

2.12. Accelerated Stability Studies

The formulated SZ emulgels were packed and sealed in aluminum tubes. These tubes are placed at 40 ± 2°C/ 5% ±5% RH for 3 months in the stability chamber. The withdrawn samples were pH, physical appearance, SZ content and their rheological properties were evaluated every 15 days.

2.13. Assay of SZ

A UV spectrometric method was used to assay SZ in aqueous solution and in different emulgel formulations. The measurements of absorbance and spectra were assayed on a Shimadzu UV-visible spectrometer (UV-1800), using matched quartz cells of 10 mm in path length. The baseline was corrected before assay by the built-in baseline memory at the initializing period with an auto-zero adjustment by a one-touch operation.

The pure SZ solution and different formulations of SZ emulgel weighed 1g was diluted in 50 ml of HCl-KCl buffer (0.001 N) solution (pH=2.0) and poured in a 250 ml separating funnel. Chloroform was added in the funnel and vigorously shacked for extracting lipid components. The aqueous extracted layer of SZ was separated and added to KOH (0.1 N) at pH=9.0 for the quantitative and qualitative assay of SZ by UV-visible spectrometry. The same process was repeated with photolyzed aqueous preparation and emulgel formulations of SZ for the qualitative and quantitative assay of SZ and its photodegraded product (2,4-(N-2-hydroxypropyl) diaza-3-methyl-1-nitro-1,5-dione,

3. Results

3.1. Formulation of SZ Emulgel

The formulation composition of SZ (1%, w/w) emulgel is given in Table 2. The quantities of carbopol, methylparaben and propylparaben, citrate buffer were used as constant. In this study, the effect of mineral oil and castor oil as an oleaginous phase and glycerol and propylene glycol used as humectants in the

formulation of emulgel preparation. The change in formulations was used to determine the stability of SZ in emulgel preparations (Table 2).

Table 2 Formulation composition of SZ emulgel*

Formulations	SZ (1% *w/w*)	CP-934 Gel	LP	CO	PG	GL	MP	PP	Citrate Buffer
Pure SZ		-	-	-	-	-	-	-	-
EG 01	1	48	4.48	-	6.25	-	0.2	0.04	0.6
EG 02	1	48	6.25	-	8.02	-	0.2	0.04	0.6
EG 03	1	48	6.25	-	4.48	-	0.2	0.04	0.6
EG 04	1	48	7.50	-	5.00	-	0.2	0.04	0.6
EG 05	1	48	8.02	-	6.25	-	0.2	0.04	0.6
EG 06	1	48	5.00	-	7.50	-	0.2	0.04	0.6
EG 07	1	48	5.00	-	5.00	-	0.2	0.04	0.6
EG 08	1	48	7.50	-	7.50	-	0.2	0.04	0.6
EG 09	1	48	6.25	-	6.25	6.25	0.2	0.04	0.6
EG 10	1	48	-	4.48	-	6.25	0.2	0.04	0.6
EG 11	1	48	-	6.25	-	8.02	0.2	0.04	0.6
EG 12	1	48	-	6.25	-	4.48	0.2	0.04	0.6
EG 13	1	48	-	7.50	-	5	0.2	0.04	0.6
EG 14	1	48	-	8.02	-	6.25	0.2	0.04	0.6
EG 15	1	48	-	5.00	-	7.5	0.2	0.04	0.6
EG 16	1	48	-	5.00	-	5	0.2	0.04	0.6
EG 17	1	48	-	7.50	-	7.5	0.2	0.04	0.6
EG 18	1	48	-	6.25	-	6.25	0.2	0.04	0.6

* QS to produce 100 g by water † CP-934 (Carbopol-934); LP (liquid paraffin); PG (propyleneglycol); GL (glycerol); MP (methylparaben); PP (propylyparaben)

3.2. Rhelogical Properties of SZ Emulgels

The rheological parameters like spreadability, extrudability, viscosity, physical appearance of the different formulations of SZ emulgels have been evaluated (Table 3).

Table 3 Viscosity, spreadability and extrudability of SZ emulgel preparation

Emulgel Code	Viscosity (cp)	Spreadability (cm/sec)	Extrudability
EG 01	23955	5.9	+++
EG 02	21395	4.2	++
EG 03	22085	4.9	++
EG 04	21038	3.9	+
EG 05	20385	3.8	+
EG 06	21345	4.1	++
EG 07	21987	4.6	++
EG 08	20085	3.6	+
EG 09	21325	4.0	+
EG 10	29985	9.2	+++
EG 11	28330	7.5	+++
EG 12	29380	8.5	+++
EG 13	28214	7.3	+++
EG 14	28753	7.9	+++
EG 15	28444	7.7	+++
EG 16	29242	8.3	+++
EG 17	28000	7.1	+++
EG 18	26989	6.4	+++

3.3. Photodegradation of SZ

Light mainly influences the rate of photolysis of the photolabile drugs [19]. SZ is sensitive to light and photolyzed in the presence of visible and UV light [20]. The UV irradiation has high energy content, thus, increases the photolytic degradation of SZ. The different concentrations of oleaginous phase and humectants may affect the clear first-order rate constant (k_{obs}) for the photolysis of SZ in emulgel formulations compared to aqueous preparation (Table 4).

Table 4 Clear first-order rate constant (kobs) for the photolysis of SZ and stabilization ratio*

Emulgel Code	$k_{obs} \times 10^2$ (min^{-1}) ± SD	t_{90} (~min)	Stabilization Ratio
Pure Solution	11.81 ± 0.008	8.89	-
EG 01	3.90 ± 0.012	26.92	3.03
EG 02	4.21 ± 0.017	25.00	2.81
EG 03	4.05 ± 0.013	26.25	2.95
EG 04	4.41 ± 0.019	23.86	2.68
EG 05	4.49 ± 0.018	23.34	2.63
EG 06	4.19 ± 0.015	25.06	2.82
EG 07	4.15 ± 0.011	25.31	2.85
EG 08	5.12 ± 0.017	20.51	2.31
EG 09	4.18 ± 0.017	25.12	2.83
EG 10	2.79 ± 0.014	37.50	4.22
EG 11	3.55 ± 0.012	29.58	3.33
EG 12	2.99 ± 0.011	35.12	3.95
EG 13	3.72 ± 0.013	28.38	3.19
EG 14	3.33 ± 0.013	31.53	3.55
EG 15	3.45 ± 0.010	30.43	3.42
EG 16	3.08 ± 0.012	33.87	3.81
EG 17	3.61 ± 0.009	29.08	3.27
EG 18	3.83 ± 0.012	27.63	3.11

* The value of k_{obs} for the photodegradation of SZ in aqueous solution

3.4. Analysis of SZ and Its Photoproducts

A standard curve of absorbance against the concentration of SZ within the range 0.5-5.0 M × 10^{-5}) has formed a linearity with least-squares regression equation (R^2 = 0.998) (Fig. 2). The peak (λ_{max}) of pure SZ solution has been observed in spectra at 311 (a), 320 (b), 277 (c) and 313 nm in neutral pH (7.0), alkaline (KOH, 9.0), acidic (HCl, 4.0) and alkaline methanol (KOH, 9.0) pH (Fig. 3). The light was exposed to pure SZ solution and different formulations of SZ emulgel at a time interval of 30 min for 150 min. A constant loss was in the peak of SZ in pure aqueous solution and emulgel formulations in acidic (HCl, 4.0), neutral (7.0) and alkaline (KOH, 9.0) and alkaline methanolic solution (KOH, 9.0) pH medium after the exposure to light. Furthermore, the peak of the SZ photodegraded product (2,4-(N-2-hydroxypropyl) diaza-3-methyl-1-nitro-1,5-dione) was not observed at acidic pH (4.0) alkaline methanol solution (9.0) and neutral pH (7.0) (Fig. 3). The photodegraded product of SZ was found in non-methanolic alkaline medium at pH (9.0). A gradual loss in the peak of SZ from 318 nm to 310 nm with an increase in the peak at 209 nm has been observed in spectra with an isosbestic point at 295 nm (Fig. 4).

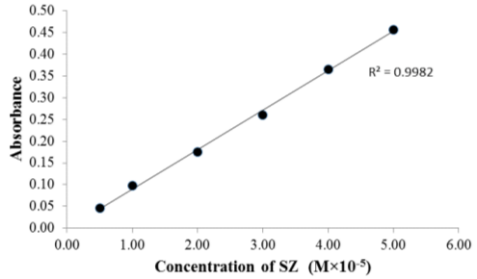

Fig. 2 Linearity plot of absorbance against the concentration of SZ

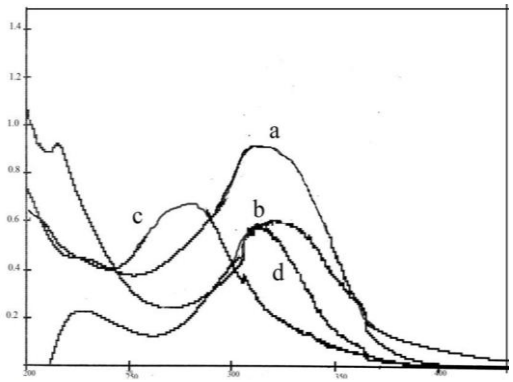

Fig. 3 Photolyzed aqueous SZ in different media: (a) neutral (b) alkaline (c) acidic (d) alkaline methanol

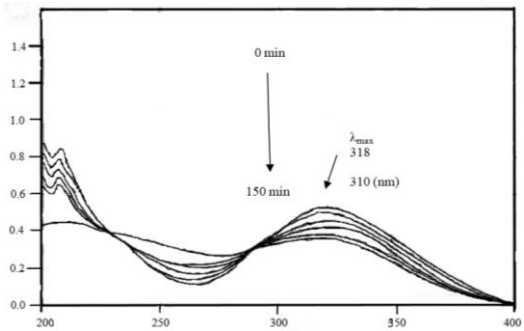

Fig. 4 Absorption spectra of photolyzed SZ emulgel formulation (EG 10) in citrate buffer (pH 9.0)

3.5. Accelerated Stability Studies of SZ Emulgels

The accelerated stability studies of different formulations of SZ emulgel were studied for 3 months at 40 ± 2°C at 75.5% RH. All the formulations of SZ emulgel were found to be smooth, homogenous, viscous and milky-like preparations (Fig. 5). The drug content (SZ) was also calculated (Table 5).

Fig. 5 Physical texture of SZ emulgel formulation (EG 10) after 3 months

Table 5 Validation of SZ in aqueous and emulgel preparations

Compound	Aqueous Solution	Emulgel Preparation
λ_{max} nm	320	318
Molar absorptivity (ϵ) M^{-1} cm^{-1}	9.52×10^3	
Linearity [a]		
Concentration range ($M\times10^5$)	5-15	100-500
Slope	0.951 ± 0.014	
Intercept	0.025	
SD of Slope	± 0.03	
SE of Slope	0.970	
Recovery range (%)	98.4–101.4	
Accuracy (%)± SD	99.4 ± 0.28	
RSD (%)	1.18	
LOD[d] ($M\times10^6$)	1.018	
LOQ[e] ($M\times10^6$)	3.278	

Notes: RSD - relative standard deviation; LOD - limit of detection; LOQ - limit of quantification; SE - standard error, [a] the mean of five determinations

4. Discussion

4.1. Formulation of SZ Emulgel

The gelling agent carbopol 934 was used to formulate the emulgel. Carbopol 934 was used to increase the sustain release action of SZ from the emulgels. The duration of action of pilocarpine hydrogels made of carbopol in ophthalmic preparation was enhanced with thermal stability [21]. The matrix of carbopol hydrogel was not destroyed at high temperature. [22] observed the better stability and release profile of carbopol against hydroxypropyl methylcellulose in metronidazole emulgel.

Castor oil reduces inflammation and relieves pain. Castor oil moisturizer the skin and reduced the irritation and itching. It also possessed antibacterial activity [23]. Mainly liquid paraffin is preferred in the formulation of topical emulgel preparations [24]. In this study, liquid paraffin and castor oil were included as an oleaginous phase to formulate SZ emulgels. The main disadvantage of minerals and castor oil is to produce a laxative effect in oral preparations [1]. Castor oil has been found to be safer as compared to liquid paraffin with the least skin irritation and for the stable formulation of emulgels. Furthermore, castor oil also increased the permeability of the drug. [25] found an increase in the permeability of flurbiprofen in emulgel without penetration enhancers. The penetration of flurbiprofen in emulgel was directly related to the concentration of castor oil.

Glycerol and propylene glycol were used as humectants. They are also used as co-solvents in aqueous media [26]. Glycerol and propylene glycol have produced its effect on the viscosity of emulgel. Glycerol is also used as an emulsifier, whereas, propylene glycol acts as a penetration enhancer [27]. Glycerol increases the dispersion of ibuprofen with an

increase in the crystallization of the drug due to higher concentration of ibuprofen [28].

All formulations of SZ emulgel were opaque in appearance. The formulations of emulgel were consistent in appearance after proper mixing. The emulgel formulations were found stable with no phase separation and creaming. Furthermore, no signs of grittiness or gritty particles were noticed after applying them on the hands. Thus, it indicated a uniform mixing and homogenization of all ingredients in the emulgel formulations. Similarly, indomethacin [29], metronidazole [30], tioconazole [31], solanum lycopersicum-derived lycopene [32], ketoconazole [33], ibuprofen [28], ofloxacin [34] and Annona squamosa L extracts [35] formulations of emulgel has shown a white color with better homogeneity, which also impact on the viscosity and spreadability.

4.2. Accelerated Stability of SZ Emulgels

All SZ formulations of emulgel were shown stability in accelerated stability studies with a negligible change in viscosity. Carbopol is mechanically stable after long-term storage [36]. It has been documented that SZ is stable against hydrolytic degradation [20]. SZ is also stable to dry heat but destabilized in the presence of oxygen and possesses oxidative stress [37]. Several studies investigated the accelerated stability testing of different drugs and extracts formulated in emulgel preparations like metronidazole [30], indomethacin [29], tioconazole (31), Solanum lycopersicum derived lycopene [32] and extracts of Annona squamosa L. [35].

The pH values of SZ emulgel formulations have not changed significantly during the time of accelerated stability studies. The use of citrate buffer has played a major role in the stabilization of SZ emulgel formulations. Citric acid is hydrophilic and possesses antimicrobial properties. Moreover, it is also used as an antioxidant [38]. [39] found an increase in the stability of flucloxacillin in citrate buffer solution. Similarly, [40] observed the highest stability of protein in citrate buffer even at temperature at 40°C. Citric acid has been used as a buffer and as an antioxidant. Thus, the oxidative degradation of SZ in emulgel formulations was found to be negligible. Accelerated stability testing of vaginal emulgel was conducted for the delivery of IQP-0528 (pyrimidinedione analog) and observed negligible change in viscosity with no effect in the change in the release profile of the drug in carbopol emulgel [36]. The formulations of SZ emulgel containing castor oil have been found to be stable and homogeneity with no segregation in the oleaginous phase. Castor oil mainly consists of mono-saturated fatty acids where double bonds activate the oxidation reaction. It has been noted oxidation reaction of castor oil has been reduced compared to the induction of oxidation by a faster process [41]. [42] observed significant stability of castor oil-based nanoemulsion for 6 months. There was no significant change in the mean droplet size at 37^{o}C. The change in pH was observed due to the liberation of free fatty acid from castor oil. The main drawback in the formulation of castor oil-based nanoemulsion did not contain any buffering agent to stabilize the pH of the nanoemulsion preparation. The strong matrix system in gels stabilized the phases of emulgels and avoided the chances of creaming. [32] also found the stability of emulgel formulation containing liquid paraffin with no creaming and phase separation for 3 months. A centrifugation test confirmed the accelerated stability of the emulgel formulation.

4.3. Photolysis of SZ

The photolysis of SZ mainly occurred due to photooxidation [43]. The rate of photolysis of SZ was the least found in EG 10 and EG 08 formulation, respectively (Fig. 6). The viscosity of emulgel preparations played a key role in the photooxidation of SZ in the emulgel formulations. The increase in the viscosity of emulgel formulations has reduced the rate constant (kobs) of the photolysis of SZ. Thus, the formulations of SZ emulgel containing glycerol have shown more photostability compared to propylene glycol. The penetration of oxygen was minimized due to the viscosity of the glycerol. The viscosity is decreased by increasing in temperature that may leads to phase separation, coalescence and creaming. Emulgels are stable at higher temperature due to strong matrix system allow to produce a stable and safe drug delivery system [32].

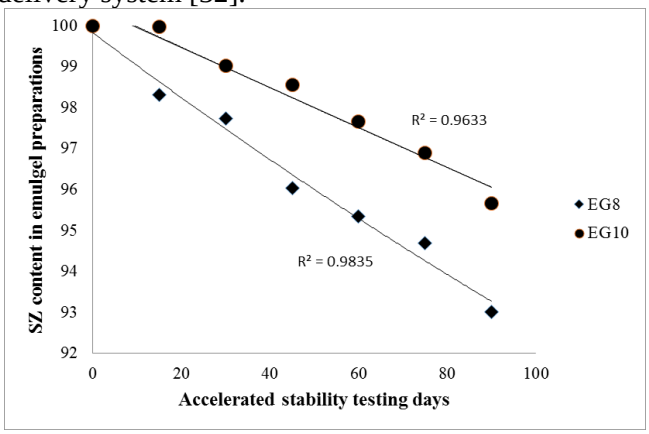

Fig. 6 SZ content in emulgel preparations against accelerated stability testing days

The photooxidation of SZ may lead to the formation of 2,4-(N-2-hydroxypropyl)diaza-3-methyl-1-nitro-1, 5-dione (photodegraded product, It has been supposed that endoperoxide may lead to the transformation to the dioxetane intermediate that then form the end product. The nitroimidazole drugs may undergo photooxidation and decreases the intensity of spectrometric absorption [43].

4.4. Thin Layer Chromatography (TLC) of SZ

Photolyzed emulgel preparations of SZ were studied by TLC. Pure SZ with photolyzed product of SZ (2,4-(N-2-hydroxypropyl)diaza-3-methyl-1-nitro-1, 5-dione) with alone SZ was determined in all formulations of SZ emulgel. The intensity of SZ was found greater in intensity of viscous emulgel. The spots were determined under UV light (209 nm) [44]. Similarly, the photodegradation of riboflavin was observed by [45]. Pure SZ spot intensity of emulgel was reduced due to difference in viscosity of different formulations of emulgel. [46] reported the formation of (2,4-(N-2-hydroxypropyl)diaza-3-methyl-1-nitro-1,5-dione) by photooxidation of SZ.

4.5. Absorption Characteristics of Photolysed SZ

SZ was instable at alkaline pH [37]. A UV-visible spectrophotometer was used to assay pure and photolyzed SZ emulgel preparations in alkaline pH (9.0, SZ emulgel (1%, w/w) was diluted to 10 mg of SZ concentration in a diluted solution. 2,4-(N-2-hydroxypropyl)diaza-3-methyl-1-nitro-1,5-dione photodegraded product of SZ) was observed at 209 nm in only alkaline medium (KOH, pH 9.0) no photodegradation product was observed in alkaline methanol, acidic and neutral medium (Fig. 3). The method has been found to be precise, accurate and selective for all w/o SZ emulgel formulations. It has also been observed that the prolonged exposure of light on SZ pure aqueous solution and emulgel formulations has eliminated the peak at 209 nm, as already reported by [46].

The spectrum of the photolyzed SZ emulgel formulation (EG 10) peak (λmax) has been revealed at 318 nm. As it has been observed, the peak (λmax) of photolyzed product of SZ was observed only in alkaline medium (KOH; pH 9.0) at 209 nm. A decrease was in the absorption of photolyzed SZ preparation with a span of 30 min interval. The peak of the end photodegraded product of SZ, 2,4-(N-2-hydroxypropyl)diaza-3-methyl-1-nitro-1,5-dione was not shown in neutral, acidic and methanolic alkaline media (Fig. 3). The change in the peak of SZ was observed at 277 and 311 in acidic (4.0) and neutral (7.0), respectively. The change in pH may cause a bethochromic shift of peak (λmax) of drugs [47]. A bathochromic shift of the norfloxacin peak was also observed by [48]. The photolyzed emulgel of SZ formulations shows the peak of the photodegraded product of SZ at 211 nm with the presence of an isosbestic point at 295 nm, indicating the formation of a single photodegraded product of SZ (2,4-(N-2-hydroxypropyl)diaza-3-methyl-1-nitro-1,5-dione) in alkaline medium (KOH; pH 9.0) [44]. It was noted that the photodegraded product peak was diminished after a longer exposure to light. [49] reported the photodegradation of SZ product after prolong exposure of light.

4.6. Application of the Assay Method

The two-component spectrometric method was used to analyze SZ and its photoproduct 2,4-(N-2-hydroxypropyl)diaza-3-methyl-1-nitro-1,5-dione at 318 and 209 nm, respectively. The analysis method has been validated for the application of assay of SZ and its photoproduct (Table 5). The two-component method has also been used in the analysis of riboflavin, thiamine and cyanocobalamin and their photoproducts [12, 45, 50, 51]. There was no significant interference in the absorption was observed in the spectra of control empty emulgel formulations between 600 and 200 nm due to the extraction of the oleaginous phase by chloroform in HCl-KCl buffer pH 2.0. Extraction at pH 2.0 increased the ionization constant of SZ [52]. The increase in the ionization constant of SZ in highly acidic pH has increased the polarity of SZ [53]. Thus, the chances of SZ solubility in chloroform have been minimized. Castor oil is easily miscible in chloroform, whereas, liquid paraffin is freely soluble in chloroform [54]. The separation of the oleaginous phase from emulgel by chloroform reduced the chances of interference in the analysis of SZ and its photoproduct.

4.7. Kinetics of Photodegradation of SZ

The photolysis of SZ in emulgel formulation followed clear first-order kinetics. A plot of the log concentration of SZ versus time determined the clear first-order rate constants (kobs) of SZ. The formulation characteristics of SZ emulgel preparations significantly affect the rate of reaction. The following factors were studied which may effect on the rate constant of SZ in the formulation of emulgel.

4.7.1. Effects on the Viscosity of SZ Emulgels

The viscosity affected the stability of SZ emulgel formulations. The viscosity of the formulations may significantly impact the stability [55]. The increase in the viscosity of SZ emulgel formulations with an increase in the concentration of humectants (propylene glycol and glycerol) and oil phase (castor and liquid paraffin, The increase in shearing force decreases the viscosity of emulgels, shown with non-Newtonian flow; mainly this has occurred due to its low flow resistance when applied at high shear conditions [56]. The reduction in viscosity of SZ emulgel formulations has possessed pseudoplastic behavior. The high characteristic of spreadability was observed with a decrease in viscosity of SZ emulgel formulations. Thus, by increasing the concentration of humectants, the spreadability of SZ emulgels was increased. The increase in the viscosity of the emulgel has decreased the photodegradation of SZ in the emulgel. The increase in viscosity hinders the motion of molecules and reduces the particular photochemical reactions

[57]. The effect of viscosity on the spreadability and kobs is shown in Fig. 7.

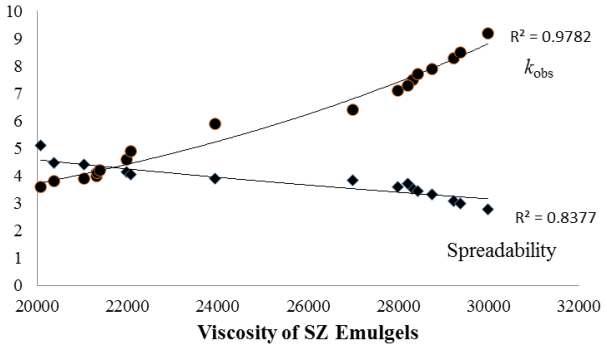

Fig. 7 Effect of viscosity against k_{obs} and spreadability of SZ emulgel formulations

4.7.2. Effects of Humectants on SZ Emulgels

Humectants moistened pharmaceutical preparations and were also used to improve the readability. The viscosity of glycerol and propylene glycol are ~935 and ~41 mPa/s, respectively. A linear relationship of photodegradation versus the reciprocal of viscosity indicates that the rate of photodegradation depends on the viscosity of the medium. [55] reported a linear relationship between kobs and viscosity in the photolysis of riboflavin. The viscosity of the pharmaceutical preparation significantly affects the stability of oxidizable drugs [58]. Oxidation metabolized SZ [6]. It has been observed that with an increase in the concentration of humectants (propylene glycol and glycerol) the viscosity of emulgel was increased and it may affects on the photostability of SZ. The lowest rate of photolysis of SZ in emulgel formulation (EG 10) was observed due to the highest concentration of glycerol. The addition of glycerol reduced the photodegradation of cyanocobalamin in aqueous solution. The viscosity may reduce the penetration of oxygen in the viscous pharmaceutical preparation. Thus, the chances of photooxidation of SZ were reduced [59]. [60] found the antioxidant property of glycerol, which may be enhanced oxidative stability of quercetin. [61] observed that the rate of photolysis of riboflavin was reduced by the addition of glycerol. Riboflavin reacted with glycerol, which acts as an electron donor. The decrease in quantum yield is mainly due to the viscosity of glycerol. Thus, an increase in viscosity achieved photostabilization [62].

4.7.3. Effects of the Oil Phase on SZ Emulgels

Castor oil and mineral oils were used in the formulation of SZ emulgel. These were also used in emulgel formulations to modify the characteristics of pharmaceutical vehicles on the skin for better penetration of the active drug. It was observed that the kobs of the SZ in the emulgel changed with the concentration of the oil phase. Liquid paraffin (mineral oil) containing emulgel formulations increased in rate of SZ degradation. [63] found that the photostability of the avobenzone was achieved by the mineral oil. However, emulgels containing castor oil showed better stability. Castor oil has shown oxidative stability [64]. In case of increasing the concentration of castor oil in nanoemulgels, the system stability also increases [65]. The dosage form and the excipients generally ascertain the photostability of the drugs [66]. [67] observed the stability of nevirapine by the use of liquid paraffin for emulsification in castor oil-based chitosan microemulsion. Oxygen plays an important role in the photolysis of drug. The photolysis of primaquine was investigated under the influence of oxygen. It was observed that the photostability of primaquine has decreased [68]. Similarly, [41] also found the stability of castor oil and mineral oil. The thermo-oxidative stability of bio-based products compared to petroleum-based lubricants and vegetable oils determined through the PetroOXY method. The photostability of tretinoin in castor oil was determined in [69]. Castor oil is more stable against oxidation than other vegetable oils [70].

5. Conclusion

This study involves the formulation of different emulgels with the variations in humectants and oil phases and its effect on stabilization of SZ. It has been observed that an increase in the concentration of castor oil and glycerol increased the viscosity of emulgel preparations. This may affect the rate of photolysis of SZ. The rate constant for the degradation of SZ has been observed to decrease with an increase in the concentration of castor oil and glycerol. Thus, the viscosity of emulgel is one of the prime considerations to decrease the photolysis of the drug. The chances of entrapment of oxygen and hindrance of molecules are also reduced. Therefore, it improves the stability of a drug and prolongs its shelf-life.

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