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Preparation and Physicochemical Evaluation of Topical Cream Ivermectin 1% for Treatment of Rosacea

Running title: Ivermectin Topical Cream Preparation

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Abstract

Background: Rosacea is a prevalent disease throughout the world. Various studies have shown that the hair follicle mites Demodex has a key role in the rosacea pathogenesis. The current study aims to formulate a formulation of ivermectin 1% for rosacea treatment.

Methods: The researchers sought an ivermectin topical cream in following a stable preparation for the treatment of rosacea. Investigation of the active ingredient in the formulation was conducted according to standards. The formulation was monitored as an ICH guideline within six months.

Results: The resulting formula did not show any physical instability during accelerated stability studies, and the appearance of the formula did not change. During the storage period, the preparation displayed no significant changes in density, viscosity, pH, and uniformity. Additionally, no microbial contamination was occurred in this formulation.

Conclusion: The study data indicated that the proper o/w cream produced from the active ingredient Ivermectin. Administration of ivermectin topical dosage form reduces the chronic use of antibiotic in the rosacea treatment. Our data can aid physicians to prescribe high potential formulation for rosacea treatment. This topical ivermectin with the standard formulation assessments showed the preparation was sufficiently stable and can use in the treatment of rosacea.

Keywords: ivermectin; rosacea; topical formulation; stability study

Introduction

Rosacea is a prevalent relapsing and chronic inflammatory disorder of the skin that can cause the chin, eyes, cheeks and nose being red. This condition causes frequent periods of redness, pimples, permanent expanded blood capillary and flushing [1]. According to the reports from Europe and the United States in 2017, the prevalence of rosacea is approximately in a range from less than 1% to 22%; this wide range is only due to delay of patient findings [2]. In the psychosocial perspective, facial appearance of rosacea plays a vital role in psychosocial disorders in the patients so that reduction of self-confidence increases their fear of being in society and their anxiety [3, 4]. The accurate mechanism of pathophysiology of rosacea is unknown, but several etiologies with a potential genetic history are involved in this disease. Increase in blood flow due to dilation of veins and high volume of blood in veining causes facial and flushing redness [5]. In this regard, the effects of immune system components such as 3 human leukocyte antigen (HLA) alleles and 2 single-nucleotide polymorphisms (SNPs) should be considered [6, 7].

In most patients, especially those having papulopustular rosacea, high density of Demodex mites was seen [8]. Demodex folliculorum usually lives in the follicular infundibulum and Demodex brevis in Meibomian and sebaceous glands. They are most abundant in the skin of the scalp, upper chest and face [9]. Demodex is recognized to colonize normal human skin ubiquitously; the Demodex population is around 5/cm^2 of the skin in the adult population [10]. They typically do not result in any dermatological diseases, but when the parasites enter the dermis, they can

cause rosacea, acne, and folliculitis. The signs aggravate with an increase in their population [11]. There is a significant relationship between Demodex density and rosacea. The presence of Demodex was similarly established with facial pruritus with or without erythema [12].

In the past, there were traditional methods for the treatment of rosacea, but now it has become a treatable disease. The US Food and Drug Administration approved some topical treatments such as azelaic acid cream, metronidazole gel, sodium sulfacetamide and brimonidine [9]. However, in practice, metronidazole 1% in forms of topical gel, cream and lotion as well as Azelaic acid gel 15% has an effective influence on the treatment of inflammatory rosacea lesions [11]. Another effective treatment in this condition is a topical form of an antiprotozoal drug named ivermectin that has anti-inflammatory effect on rosacea inflammatory lesion [13, 14].

Ivermectin has been used as a broad-spectrum anti-parasitic factor for over 20 years in both human and veterinary medicine [15]. A review study revealed that both oral and topical ivermectin investigated for the treatment of papulopustular rosacea exhibited benefits [16]. Topical application of ivermectin, by the anti-inflammatory property and straight killing act on mites, has been suggested for the curing of rosacea from 2014 [17]. Ivermectin originates from natural macrocyclic lactones, called avermectins isolated from the soil actinomycete, *Streptomyces avermectinius*. The anti-parasitic impact of ivermectin is arbitrated through suppression of the muscular and neuronal activity of parasites, causing paralysis. The great affinity binds and drug selectively to chloride glutamate-gated ion channels expressed on the nerves and muscles of invertebrates. The affinity of ivermectin for these receptors is low, supporting the suitable tolerability of ivermectin with minimal side effects [18-20]. Ivermectin inhibits overgrowth of Demodex mites, which may colonize the pilosebaceous units of patients with the disease and can decrease inflammatory patches of rosacea. Commercial forms of ivermectin cream are produced and used in clinics [14]. However, formulation and stability data are not available for many specialists, the purpose of our study was to preparation and evaluate ivermectin topical cream.

Materials and Methods

Ivermectin was obtained from Zhejiang (China). Span 60, citric acid, sodium phosphate dibasic, methanol and, acetonitrile was purchased from Merck (Germany). Carbomer was purchased from Corel Pharma Chem Company (India). Methyl and propylparaben were gained from Alborz Bulk company in Iran. Cetyl palmitate and tween 80 were obtained from Oleon (Belgium). Cetostearyl alcohol were procured from Mosselman Company (Belgium). Isopropyl myristate and stearyl alcohol were got from BASF Chemical Company (Germany) and Oleon Company (Malaysia), respectively. All materials were obtained in analytical grade.

Preparation of cream

All the lipid components (cetyl alcohol 5% w/w, stearyl alcohol 3%, isopropyl myristate 7%, cetyl palmitate 3%, 3% span 60 and ivermectin 1%) were mixed together and melt completely on a heater-stirrer. Furthermore, all the aqueous phase components (3% tween 60, methyl and propyl paraben, 0.18% and 0.02% respectively, and distilled water up to 100%) were mixed separately and heated up to 70±1 °C. The buffering agents (citric acid 0.48% and bi-phasic phosphate sodium 1.8%) were added to the aqueous phase to adjust pH and finally added to the lipid phase at 70±1 °C and then mixed under a mixer (IKA RW 20 Labortechnik, Staufen, Germany) with a 1500-rpm circuit. The prepared topical cream was checked to control its organoleptic parameters, pH, density, viscosity, emulsion type, assay, release and uniformity.

Organoleptic parameters

The organoleptic parameters (color, odor and texture) of topical cream were evaluated by the sight, smell, and touch. In continue, a fresh prepared formulation was considered as a standard during the stability period.

Determination of pH

The formulation was tested for its pH as it is responsible for the stability and irritability at the application place. The digital form of pH meter (model Metrohm 827 from Switzerland) was used to determine the pH of formulation [21]. Measurements were performed in three times.

Density measurement

The precise volume of pycnometer device was determined by filling entirely with water and for reducing the air bubbles, the sides were calmly tapped.

The vessel was weighted when it full of cream, and modestly the density was measured.

Viscosity

The quality of formulation was revealed by its viscosity. The topical cream viscosity was evaluated by a Viscometer of Polyvisc (Brookfield-USA) by means of a spindle R7 at 100RPM. Determinations of viscosity were carried out at 25°C. Each measurement was done in triplicate [22].

Uniformity

The uniformity of cream is revealed by similarity of assay analysis of top, middle, and bottom of all tubes. Therefore typically 0.25–1.0 g taken from a tube to assay an active ingredient.

Emulsion Type

In this assessment, deionized water was used to dilute the cream. If the cream is entirely soluble in water and produces a diluted consistent dispersion, the mentioned emulsion is oil in water and vonversely [23].

Stability studies

The selected and appropriate sample creams were passed six month accelerated assessments at 40 ± 2 °C/75 ± 5% of RH according to the ICH guidelines, and the physicochemical parameters were assessed in this period.

Assay

Ivermectin cream is now patent and there are no identification assessments in pharmacopeia. Therefore, the prepared cream was used to conduct in-house assay tests. Additionally, 0.5 gram of ivermectin cream was added in 100 ml diluted methanol and was passed through a polypropylene 0.45 nm syringe. A mixture of methanol/ water/ acetonitrile (25/20/55) was prepared for the mobile phase. After making a clear solution, it was injected into a HPLC system (Knouer-Netherlands) with a C18 column (flow: 1.5), and the calibration curved was drawn at a 254 nm wavelength UV detector.

In vitro release study

In vitro release of ivermectin from preparation was calculated via cellulose nitrate membrane with 0.45-micron mesh size. The synthetic membrane was fixed on the Franz cells by a surface of 12.56 cm^2 and 34 ml of receptor capacity. The receptor vessel containing methanol was continuous stirred at 100 rpm by a stirrer. Afterward, 0.4 g of the preparation was applied on the donor partition. The heat was retained at 32.0 ±1°C by water. Sampling was performed every 60 minutes during 11 hours, and at every point, 2 mL aliquots were drained from the receptor segment. Afterward, an equal volume of appropriate receptor fluid was returned to the receptor vessel to keep sinking circumstances. The samples were evaluated using an ultra violet spectrophotometer (Cecil BioQuest CE 2501, UK) (Wavelength of 254 nm). The release data were examined using three kinetics models comprising first order, zero order, and Higuchi kinetic models. The kinetic models for the preparation were assessed, and the coefficient of determination (R^2) of all models was calculated based on the information achieved during *in vitro* drug release analysis.

Microbial assessments

10-gram cream included ivermectin/ or 10-ml clear solution of ivermectin cream in 90 ml phosphate buffer (pH=7.2) (mixture A) was added less than 1 hour in Soybean Casein Digest/ or Casein Digest-Soy Lecithin Polysorbate 20 medium. Additionally, for fungal counting 1 ml from 0.1 dilution was added to 2 plates of 15-20 ml SDA medium that was solidified to 45 °C, and then incubated for 5-7 days. For bacterial counting, 20 ml of TSA medium was solidified to 45 centigrade and incubated for 3-5 days at 35°C. Colonies were counted after the incubation, whole microbial counts were performed through pour plate, next counting was done. Counting was passed in plates comprising fewer than 10 colonies for fungal count and 100 colonies for microbial count.

- Bile tolerant gram-negative bacteria (Enterobacteriaceae) count
- Escherichia coli count
- Salmonella count
- Pseudomonas aeruginosa count
- Staphylococcus aurous count
- Candida albicans count

Preservative effectiveness analysis

An inoculum comprising 3 bacteria (*S. aureus*, *E. coli*, *P. aeruginosa*), a mold (*Aspergillus niger*) and a yeast (*C. albicans*) was mixed with the product in fluid form. The blend containing tween 80 was poured to suitable phosphate buffer with pH: 7.2 to achievement a count of approximately 1×10^8 CFU/mL. The absorption of the inoculum was seen at 580 nm. 10 grams of preparation was added to 90 ml buffer phosphate and 10^1 and 10^2 dilutions was prepared. However, the fungal process was alike to the over excluding the SDA culture with 10^1 dilution was incubated for 5-7 days. Negative and positive controls were used

throughout the examination. Microbiological tests were repeated for formulations after 14 and 28 days at 25°C.

Results and Discussion

Rosacea poses a therapeutic challenge due to its probable multifactorial pathogenesis. Contributing reasons may include vascular abnormality, immune abnormality, neurogenic dysregulation, ultraviolet damage presence of cutaneous microorganisms, and skin barrier dysfunction. The presence of skin microorganisms has been proposed as a factor aggravating skin inflammation. There is a developing interest in using ingredients having anti-parasitic characteristics, as there is impending for Demodex mite growth which has a key role in rosacea pathophysiology [24]. The role of this parasite in the pathophysiology of this illness as well as in its diverse subtypes has not been demarcated. Some pathogenic mechanisms have been assumed: (1) obstruction of follicles and sebaceous channels by the mites and epithelial hyperplasia and reactive hyper keratinization, (2) a vector role for microorganisms, (3) an external body granulomatous response to the mite chitinous skeleton, and (4) stimulation of the host's humoral and cell-mediated immune responses by the mites and their remaining products [25].

Ivermectin is a derivative of the ivermectin drug class used for the therapy of inflammatory pustules and papules as first-line medication [26]. Ivermectin has both antiparasitic and anti-inflammatory characteristics [27,28]. The new mechanism of ivermectin through affecting in Demodex mites seems to create it a principally efficient treatment choice. At the level of anti-parasitic property, its performance is an agonist on ion channels. Afterwards, ivermectin stops synaptic conduction of glutamate. These neuro channels are situated mainly in muscle and nerve cells. Demodex mite's occurrence paralysis over the resultant chloride channels inhibition, and gastrointestinal dysfunction triggers the parasite to be expired from [5]. Ivermectin could be ordered in oral form or topical dosage form, but the healing of papulopustular rosacea has been evaluated mostly by topical dosage form [29].

Considering that incomplete accepted treatment choices exist for patients with papulopustular rosacea, good efficacy (both decrease in inflammatory lesions and long time in remission), fast onset of action, considerable tolerability profile, and appropriateness for long-term treatments make ivermectin a practical alternative to the presently accessible treatments. Ivermectin cream has a moderately low side effect profile. This treatment modality boasted more developed quality of life, reduced lesion amounts, and more satisfactory participant and physician valuation of illness severity [30]. The outcomes of a relapse study performed by Taieb et al. indicated that a primary successful cure with ivermectin 1% cream QD notably extended reduction of rosacea [31].

In phase III trials in patients with moderate to severe rosacea, ivermectin 1% cream once a day reduced the signs of rosacea and improved quality of life compared to control group [28]. In this study, a stable drug product was formulated using a suitable evaluation method (Table I). The fresh topical cream had homogenous mass, white color, and good spread ability. To evaluate the emulsion type, microscopic images confirmed the dispersion of oil droplets in water media (Figure 1). In this regard, patient preference and ***compliance*** are better with ***less greasy*** and light topical bases.

Table 1: Results of stability assessment and antimicrobial analysis of ivermectin at 40 ± 2°C and the 75 ± 5% RH.

Test	Period of Storing			Limit
	Initial	3rd month	6th month	
Description	Approved	Approved	Approved	White cream, homogenous cream mass
Odor	Approved	Approved	Approved	Chemical odour
pH	6.51	6.60	6.54	NLT 5.00 NMT 6.6
Viscosity (cp)	8617.5	14720	14040	NLT 8000 NMT 18000
Density (g/cm^3)	0.914	0.970	0.970	NLT 0.980 NMT 0.999
Uniformity	Accepted	Accepted	Accepted	
Assay (%)	99.25	114.08	107.95	85-115
Identification	Approved	Approved	Approved	-
Remark / Conclusion	Approved	Approved	Approved	
Microbial listing & tester for certain microorganism	<10	<10	<10	NMT 100 NMT 10
Total Aerobic Microbial Count (CFU/g)	<9	<9	<8	Must be negative
Total Yeast Count (CFU/g)	<8	<8	<9	Must be negative
Staphylococcus aureus	-	-	-	Negative
Pseudomonas aeruginosa	-	-	-	Negative
Escherichia Coli	-	-	-	Negative
Candida abicans	-	-	-	Negative
Antimicrobial effectiveness test	Pass	pass	pass	

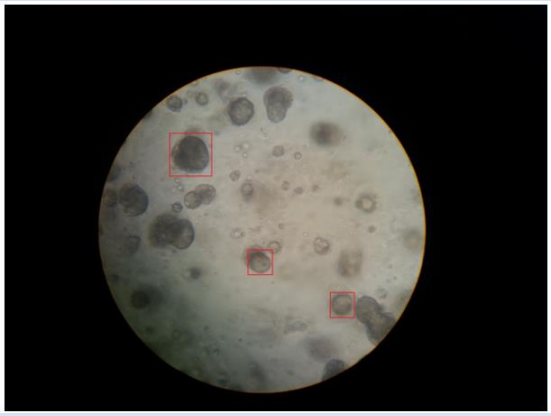

Figure 1: The microscopic picture of the product displays the spreading of lipid drops (in the squares) in water.

To be considered ideal in this study, a cream base (I) had to be consistent without display marks of physicochemical instability; (II) had to be able to maintain the active components in a stable form without any aggregating and precipitating; and (III) had to have considerable thickness not to run off the skin after application. The topical cream was assessed to the accelerated stability study according to ICH rules for a six-month period. Tests were examined at 40±2°C/75±5% RH. During the storage period, the preparation displayed any change in odor, dye, pH, and phase separation (Table I). According the table I, the pH at the zero, third, and sixth months was 6.51, 6.60, and 6.54, respectively. pH values were alike to the skin's standard pH and this value did not change drastically over the 6-month period. pH is a potential serious quality aspect of topical cream preparations. pH may affect stability and physicochemical characteristics of semisolid products. Also, pH can affect the permeability characteristics of active ingredient through the skin membrane. Therefore, this parameter needs to be controlled within stability studies. In our study, the range of pH of the formulations was around 6.5, indicated that no changing in product stability [32].

The viscosity at the initial, third, and sixth months was 8617.5, 14720, and 14040 cp, respectively. Understanding the rheological factors of topical

cream formulations is serious to drug delivery and drug stability during the shelf life. Also, depending on its viscosity, the rheological performance of a semisolid product may affect its application to healing site(s) and consistency of therapy and therefore the delivered dose [33, 34]. The density of initial topical cream was 0.914, and at the third, and sixth months, it was 0.970, and 0.970, respectively. Density of cream preparations is sensitive to manufacturing procedure due to possibility for air trap in the product. Air entrapment in the product may lead to change in assay results of the cream and most importantly the preferred dose may not be delivered throughout 'in-use' conditions. Furthermore, any changing in density indicates the emulsion instability. In this study density result was below 1 g/cm^3 and remained stable during whole stability period.

Finally, the uniformity test results revealed that the prepared topical cream remained uniform and homogenous during formulation process. A microbial assessment during whole stability period showed the colonies and fungal counts was less than 10, representing that antimicrobial activity has been acceptable and effective. Furthermore, preservative agents were in the desired range of antimicrobial activity. The assay analysis of active ingredient in the preparation was necessary. In Figure 2, HPLC graphs are seen. Therefore, as Table I shows, the percent of assay of ivermectin at the initial, third, and sixth months were in the proper range. The assay percentage of ivermectin was 99.25, 114.08, and 107.95 at the initial, third, and sixth months, respectively. They were in the acceptable range (85-115 %). Owing to the presence of adequate and suitable buffering agents and preservatives in the formulation, preparation was stable in the whole period.

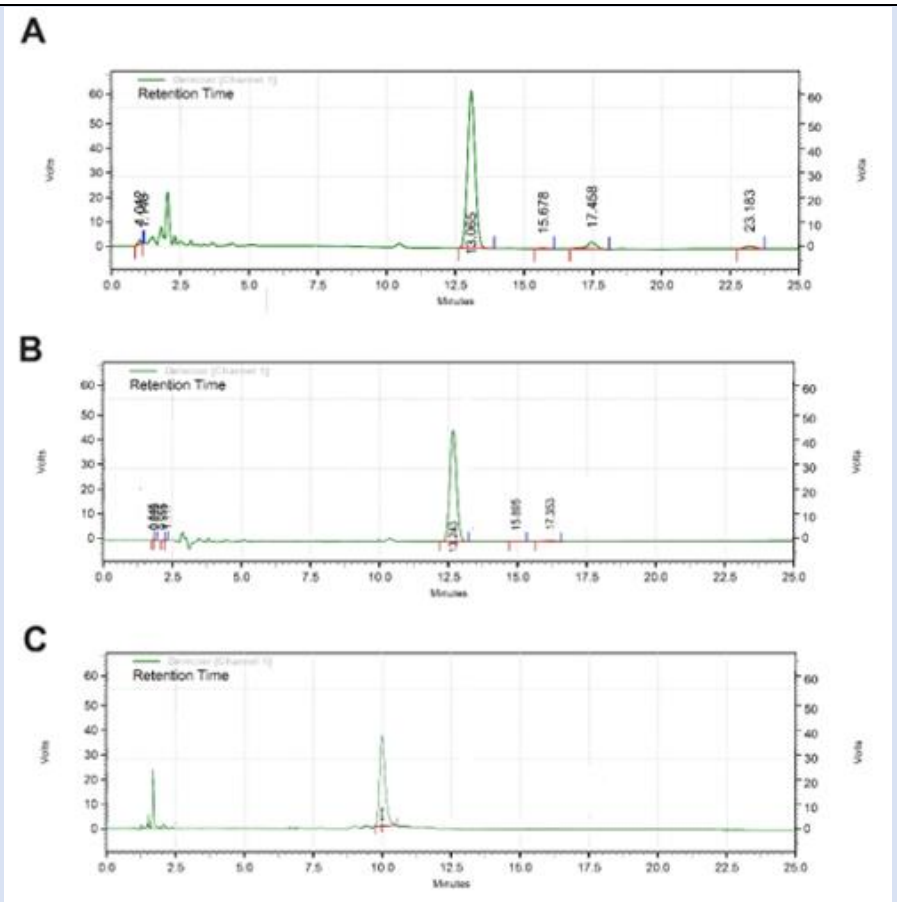

Figure 2: Assay of ivermectin by HPLC method at A) Zero, B) 3rd and C) 6th month.

In vitro release studies revealed that the preparation displayed suitable drug penetration into the synthetic membrane and proper drug release of ivermectin in 11 hours, that could reflect a reliable curative outcome of the formulation. Az figure 3 depicts, in 1 hour, 35% of ivermectin was released from the cream base. Then, the release pattern was in plateau until 8 hours. From point 8 to 9, there was a jump in the release curve to 60%. It reached the maximum release of 90% at 11 hours. During accelerated stability study, all samples had the similar release pattern, showing that the structure of creams remained stable;

therefore, the rate of release did not change. Constant release of ivermectin reduces the usage frequency and limits the side effects of the active ingredient. Based on our outcomes, as Table II shows, the release data kinetically fitted with the Higuchi order model to the greatest extent. The R^2 of the found equations in the Higuchi model was close to 1 (0. 9591). Higuchi model describes the drug release from matrix system.

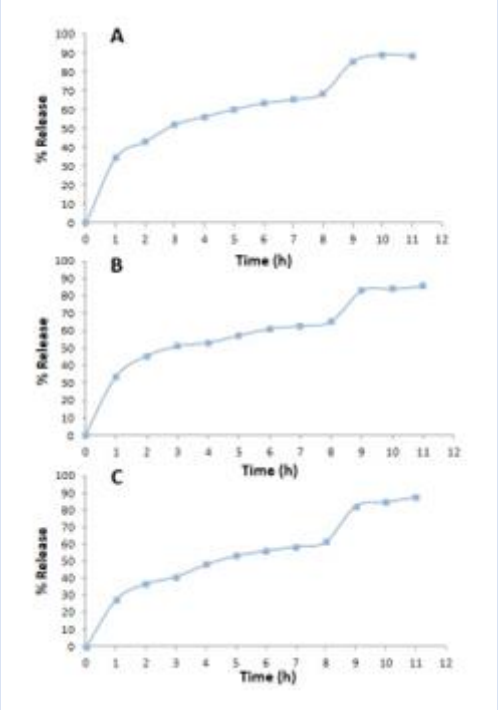

Figure 3: *In vitro* and percentage of release of ivermectin permeated through cellulose nitrate membrane at A) ziro, B) 3rd and C) 6th month.

Table 2: The kinetic mathematical models used for the release data

Kinetic models	Zero order (R^2)	First order (R^2)	Higuchi (R^2)
Equation	$F = k_0 t$	$Ln (1 - F) = -k_f t$	$F = k_H t^{½}$
Ivermectin	0.8859	0.4574	0.9591

All analysis of ivermectin cream was performed on fabricated formulation and not the commercial brand formulation. This would be our limitation in our study.

Conclusion

Topical cream of ivermectin 1% has developed as a new drug to treat papulopustular rosacea. Although, ivermectin 1% is an effective medicine, low adherence due to topical application remains challenging. Due to reduce the chronic use of antibiotic, topical drugs including ivermectin will remain to thrive as a particular function in the rosacea treatment. The prepared topical cream of ivermectin 1% was an O/W emulsion. This formula was assessed according to the ICH standards and was stable during long-term and accelerated conditions. Our data can help scientists to develop high potential preparation to treat rosacea.

Declarations

Acknowledgment

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Declaration of interest statement

All authors declare no conflict of interest.

Authors' roles

Atefeh Naeimifar and Niloofar Delbari gathered the data; Mahnaz Qomi guided the experiments. Saman Ahmad Nasrollahi proposed and managed the research. Ramin Asgharian investigated the tests. Atefeh Naeimifar prepared the primary text of article. Each author reviewed the primary draft and accepted the last version of the article.

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