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FORMULATION AND EVALUATION OF IVERMECTIN EMULGEL FORMULATIONS

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Abstract

Ivermectin, a broad-spectrum antiparasitic agent, has demonstrated significant therapeutic efficacy against various skin conditions. However, it's poor skin permeability and limited stability often hinder its clinical application. Emulgel, a hybrid dosage form combining the advantages of both emulsions and gels, has emerged as a promising topical delivery system to enhance the skin permeation and stability of poorly permeable drugs. In this study, we aimed to formulate and characterize an Ivermectin emulgel to address the challenges associated with its topical delivery. The emulgel was prepared using a two-step method, involving the preparation of an oil-in-water (o/w) emulsion, which was then gelled with suitable gelling agents. Different concentrations of Ivermectin, oil phase, surfactants, and gelling agents were screened to optimize the formulation for maximum drug loading and stability. The optimized Ivermectin emulgel was characterized for its physicochemical properties, including pH, viscosity, spreadability, drug content, and rheological behavior. The study's findings support the potential application of the emulgel in treating various skin conditions caused by parasites and infectious agents. Further, in vivo studies and clinical trials are required to validate its safety and effectiveness in a clinical setting.

***Keywords*:** Ivermectin, Emulgel, evaluation.

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Introduction

Topical Dosage Forms Topical drug delivery systems allow localized administration of the drug anywhere in the body through ophthalmic, vaginal, skin, and rectal routes. Topical formulations encompass a wide variety of formulations intended for cosmetic or dermatological application, to healthy as well as diseased skin [1]. These formulations range in physicochemical nature from solid through semisolid to liquid [2]. Drug substances are infrequently administered alone, but rather as part of a formulation, in combination with one or more non-medicated agents that serve varied and specialized pharmaceutical functions [3]. Drug absorption through the skin is enhanced if the drug substance is in solution, if it has a favorable lipid/water partition coefficient, and if it is a nonelectrolyte. For the most part, pharmaceutical preparations applied to the skin are intended to serve some local action and as such are formulated to provide prolonged local contact with minimal systemic drug absorption. Drugs that are applied to the skin for their local action include antiseptics, antifungal agents, skin emollients, anti-inflammatories, analgesics, and protectants [4].

Emulgels are emulsions, either of the oil-in-water or water-in-oil type which are gelled by mixing with gelling agent. The emulsified gel is a stable one and a superior vehicle for hydrophobic or poorly water-soluble drugs. In short, emulates are a combination of emulsion and gel. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, and transparent with long shelf life and pleasing appearance [5].

Ivermectin is a broad-spectrum anti-parasite medication. Ivermectin is mainly used in humans in the treatment of onchocerciasis, but is also effective against other worm infestations (such as strongyloidiasis, ascariasis, trichuriasis and enterobiasis). Topical ivermectin appeared to be more effective for papulopustular rosacea [6].

The aim of this work was to develop and optimize emulgel formulation of Ivermectin for effective topical treatment.

Material and method

Ivermectin is purchased from Dr. Reddy's Lab, Hyderabad, India. Carbapol 940, Carboxy methy Cellulose Low density, Chitosan, Chloroform, Citric acid, Coconut oil, Diethyl amine, Dioxane, Ethanol, Glycine, Lactic acid, Liquid paraffin, Methanol, Potassium di hydrogen orhto Phosphate, Propyl paraben, Propylene glycol, Sodium carboxy methyl, cellulose

Span 20 and Tween20 are purchased from Merck, India , Ltd, Mumbai, India.

Determination of Ciprofloxacin HCl Solubility

The solubility of (CF-HCl) was estimated in phosphate citrate buffer (pH 5.5). An excess amount of the drug was putted in 50 ml volumetricflask. The flask shaken by sonicator for 30 min then kept for 24 hrs. atroom temperature then filtered and diluted, the concentration of the filtrate was determined by analyzing the sample spectrophotometrically at the 290 λmax of the drug [7].

Preparation of Ciprofloxacin HCl Emulgel formulations

Thirty-six emulgel formulas were prepared and each emulgel formula was prepared by mixing equal quantities of a gel and emulsion portions. Preparation of the gel portion was done by dispersing and dissolving different amounts of polymers (PVP K30, CMC, or Carbopol 940) within 50 ml of deionized water with constant stirring at a moderate speed and the system was heated until we have a homogenous gel base, then thegel was leaved to cool down and homogenization for 48 hrs. Triethanolamine was added as neutralizing agent to formulas containing CP 940 as gelling agent. The oil phase of the emulsion was prepared by mixing certain quantity of Span 20 with certain amounts of light liquid paraffin or coconut oil. While the aqueous phase of the emulsion was prepared by dissolving estimated quantity of Tween 20, Propylene glycol in appropriate volume of deionized water. Methyl paraben and propyl paraben as preservatives were added at 0.3% w/w and 0.1% w/w concentration in the final formulas respectively.(CF-HCl) was dissolved in ethanol. Then incorporated in this aqueous portion of the emulsion. Both the oily and aqueous portions of the emulsion were separately heated to 70º- 80º C; then the oily phase was added to the aqueous phase gradually with continuous stirring until getting homogenous emulsion and then cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio to obtain the final emulgel product [8].

Evaluation of the Formulations

Physical examination

Each formulation was visually examined for homogeneity, clarity, grittiness, colour and potential phase separation.

pH measurement

A one-gram aliquot of the emulgel in one formulation was dissolved in distilled water and left to settle for about 2 h before measuring the pH using a digital pH meter (Panday et al., 2015). This was repeated for all the formulations. The acceptable pH range was 5-7 and this was necessary to avoid any skin irritation since pH of the human skin is usually within this range9.

Viscosity measurement

A viscometer was used to determine the viscosity of all the formulations at room temperature.

The torque readings were obtained between 15%–95% of the base scale. The L4 spindle type set at 10 rotations/min was used [10].

Spreadability studies

Spreadability was determined by placing 1 g of each emulgel within an already pre-marked circle of 1 cm diameter on a glass slab. Another pre-weighed glass slab was positioned on top and aweight that totalled to about 1 kg was put on the upper glass slab for 5 min. The resulting spread

of the emulgel caused an increase in diameter which was measured using an electronic digital

calliper [11].

Content uniformity determination

The meloxicam content in each formulation was evaluated in order to determine uniformity of meloxicam content in the formulations. A 1 g aliquot of each emulgel formulation (has approximately 5 mg of meloxicam) was dissolved in 100 mL freshly prepared phosphate buffer (pH 7.4) by means of sonication for about 2 h. The solution was then filtered with a Whatman filter paper and 10 mL of the filtrate was diluted to 50 mL with the buffer solution. UV-Vis spectrophotometer was used to measure the absorbance at 362 nm and quantify the meloxicam content. To rule out that other excipients did not absorb at the 362 nm analytical wavelength, a placebo product was formulated containing all ingredients used in the formulation except the API. A sample of the placebo was then prepared just like it was done for the other formulations and it was scanned in the UV spectrophotometer at a wavelength of between 240 – 450nm to determine its wavelength of maximum absorption. Absorbance value at 362 nm wavelength was alsoobtained [12].

In vitro drug permeation studies

These studies were conducted using a modified Franz diffusion (FD) cell. Cellulose nitrate membrane was soaked in freshly prepared phosphate buffer (pH of 7.4) for at least 24 h before use. One gram of each emulgel formulation was placed and smeared on the surface of the cellulose nitrate membrane which was fixed between donor and receptor compartments of the modified FD cell that had a diffusion area of 6.2 cm2. The cell was then placed inside the dissolution vessel of the dissolution tester machine. The vessel functioned as the receptor compartment and it was filled with phosphate buffer (pH7.4) which was the dissolution medium [13].

The temperature of the water bath was maintained at 37°C by the circulating water jacket and the assembly was rotated using USP dissolution apparatus 2 at 50 rotations/ min. A 10 mL sample was drawn at suitable time interludes and replaced with equal amount of fresh dissolution medium to maintain a constant volume. The aliquots were collected and analyzed by UV-Vis spectroscopy at 362 nm wave length and cumulative drug that permeated was calculated as a function of time for 8 h [14].

Drug release kinetics study

The *in vitro* drug permeation data obtained following the analysis of optimized formulations was used to analyze their drug release kinetics and mechanism. The data was converted to drug release data and with the use of DD Solver dissolution kinetic modeling software, it was fitted into the subsequent kinetic equations.

A) Zero – order equation

$Qt = Q0 + K0t$

Where Qt and Q0 is the amount of drug released at time t and time zero, respectively, and K0 is the zero-order release constant15,16.

B) First – order equation

$\ln Qt = \ln Q0 + k1t$

Where Qt and Q0 is the amount of drug released at time t and time zero, respectively, and K1 is the first-order release constant [17].

C) Higuchi's equation

$Q = KH\sqrt{t}$

Where Q is the amount of drug released at time t and KH is the higuchi diffusion rate constant [18].

D) Korsmeyer-Peppas equation

$Mt/ M\infty = KKP \times tn$

Where Mt/ M∞ is the fraction of drug released at time t, KKP is the Korsmeyer-Peppas release constant and n is the drug release exponent which describes drug release mechanism.

The model that fit best was selected by comparing R2 values obtained from all the models [19].

Stability study

The developed formulation was stored for stability testing as per ICH guidelines for1 month.Then the optimized formulation F10 was kept for accelerated stability study at 40°C± 2°Ctemperature and 75%RH± 5% RH for 1 month. After an interval of 1 month chemical stability of the formulations was assessed by estimation of the percent drug remaining in theformulations (Drug content), and physical stability was evaluated by monitoring any change inpH, appearance, color [20].

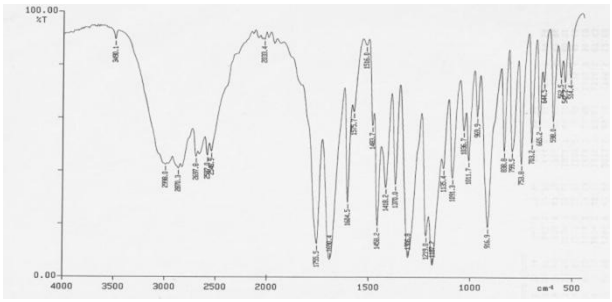

Figure 1: Ivermectin FTIR.

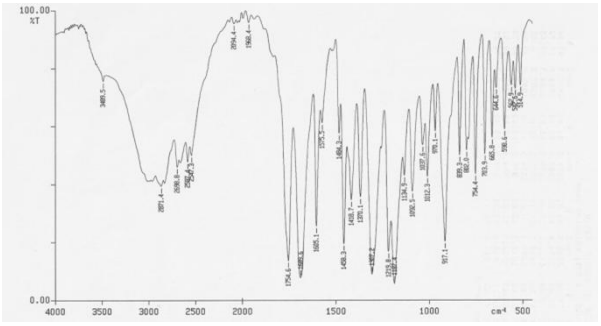

Figure 2: Ivermectin +PVP K30+CMC+ Carbopol 940.

Table 1: Emulgel formulations composition.

Code	PVP K30 (gm)	CMC (gm)	CP940 (gm)	Liquid paraffin (gm)	Coconut Oil (gm)	Span 20 (gm)	Tween 20 (gm)
EG1	0.5			6		2.0	1.5
EG2	0.80			6		2.0	1.5
EG3	1.00			6		2.0	1.5
EG4	1.25			9		2.0	1.5
EG5		0.5		9		2.0	1.5
EG6		0.80		9		2.0	1.5
EG7		1.00			6	2.0	1.5
EG8		1.25			6	2.0	1.5
EG9			0.5		6	2.0	1.5
EG10			0.80		9	2.0	1.5
EG11			1.00		9	2.0	1.5
EG12			1.25		9	2.0	1.5

Drug = 0.5 gm, distilled water= 100 ml in each formulation

Table 2: Physical characterization of emulgel formulations.

Batch Code	Color	Appearance	pH
EG1	White	Gel	5.52
EG2	White	Gel	5.43
EG3	White	Gel	5.62
EG4	White	Gel	5.57
EG5	White	Flowable	5.32
EG6	White	Flowable	5.48
EG7	White	Flowable	5.39
EG8	White	Flowable	5.43
EG9	Faint pink	Gel	6.2
EG10	Faint pink	Gel	6.4
EG11	Faint pink	Gel	6.6
EG12	Faint pink	Gel	6.8

Table 3: Physical characterization of emulgelformulations.

Code	% Content	Spreadability (g.cm.min-1)	Residence time (min)	Viscosity (mPa.s)
EG1	98.31±0.08	212.35±0.08	2.32±0.09	20426
EG2	98.53±0.05	223.24±0.13	2.05±0.07	20532
EG3	98.62±0.11	226.52±0.24	2.45±0.13	20612
EG4	99.38±0.24	230.62±0.32	2.62±0.21	20598
EG5	97.47±0.08	260.43±0.43	5.38±0.08	24538
EG6	98.56±0.21	272.15±0.68	5.62±0.32	25612
EG7	98.72±0.08	283.58±0.37	5.79±0.46	23824
EG8	98.32±0.26	275.45±0.62	5.84±0.06	26135
EG9	98.61±0.02	302.75±0.62	8.52±0.32	31248
EG10	98.51±0.03	312.57±0.44	8.28±0.45	32512
EG11	98.62±0.07	332.25±0.62	8.03±0.62	33427
EG12	99.74±0.06	326.35±0.74	8.73±0.74	33587

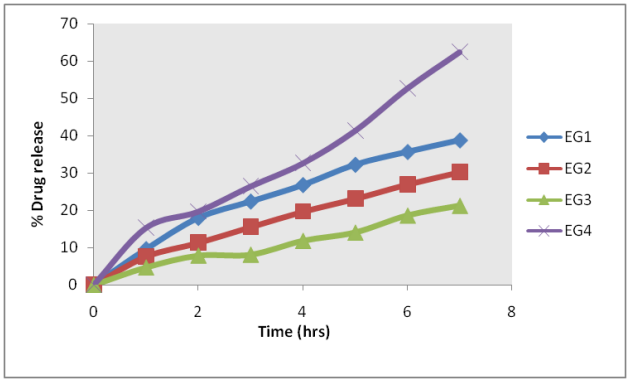

Figure 3: *In vitro* release profile of different of emulgel formulations(EG5-EG8).

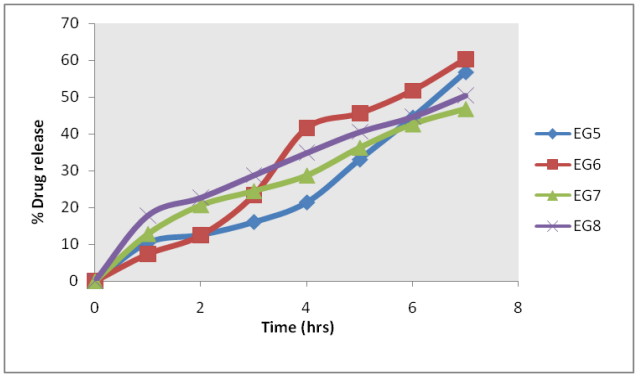

Figure 4: *In vitro* release profile of different of emulgel formulations (EG5-EG8).

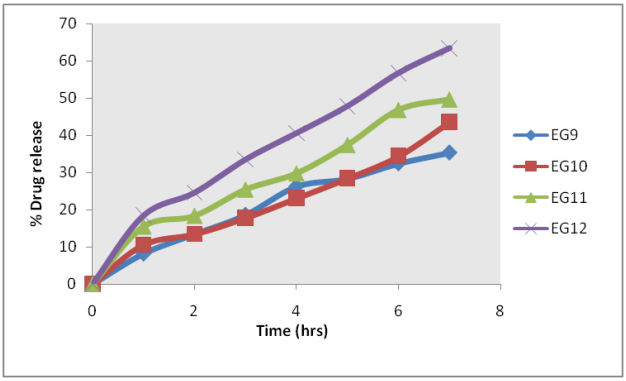

Figure 5: *In vitro* release profile of different of emulgel formulations(EG9-EG12).

Table 4: Drug release kinetic parameters for different emulgel formulations.

Batch Code	Zero order model		First order model		Higuchi model		Korsmeyer-Peppas model		
	R	K	R	K	R	K	Slope(n)	R	K
EG1	0.9632	1.6734	0.9564	-0.0189	0.9527	10.5321	0.8415	0.9930	2.5079
EG2	0.8847	3.3740	0.9350	-0.0515	0.9830	9.8362	0.5407	0.9976	10.740
EG3	0.9141	2.3780	0.9443	-0.0307	0.9426	10.2571	0.6153	0.9943	11.194
EG4	0.9596	1.9233	0.9237	-0.0225	0.9563	10.3641	0.7688	0.9966	5.198
EG5	0.9624	1.5861	0.9168	-0.0181	0.9642	9.8363	0.9635	0.9921	2.281
EG6	0.8787	2.8712	0.9310	-0.0430	0.9711	9.4781	0.5417	0.9890	15.812
EG7	0.8982	3.6384	0.9564	-0.0575	0.9837	10.3572	0.6236	0.9981	7.847
EG8	0.9646	2.6360	0.9545	-0.0348	0.9735	8.8942	0.7077	0.9977	4.737

EG9	0.9643	2.0220	0.9574	-0.0243	0.9266	10.3901	0.8265	0.9947	2.8 01
EG10	0.8549	4.2181	0.9310	-0.0768	0.9744	8.9465	0.5721	0.9954	11.596
EG11	0.9231	2.6472	0.9530	-0.0348	0.9354	10.4172	0.6184	0.9967	7.1554
EG12	0.9590	2.0263	0.9543	-0.0232	0.9644	8.6148	0.7018	0.9978	4.5353

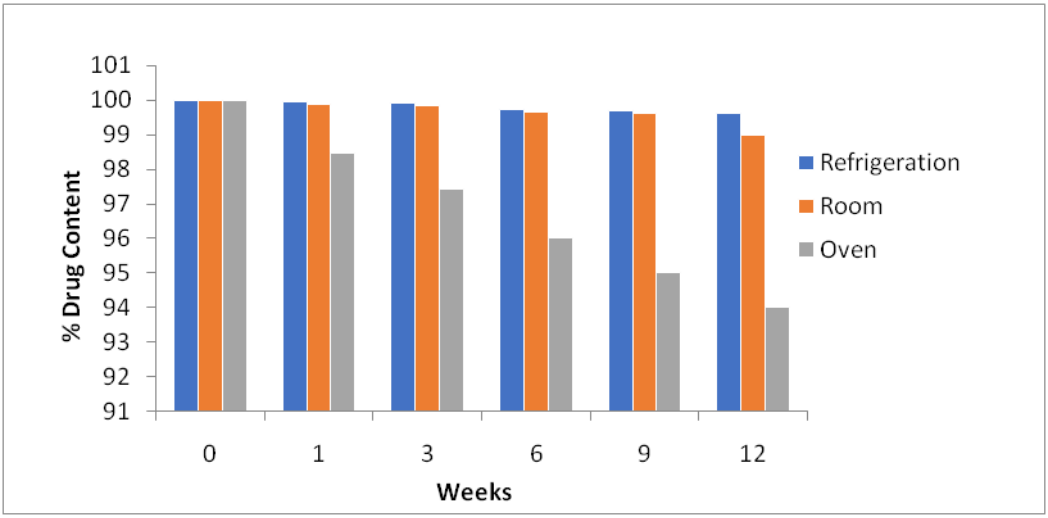

Figure 6: Stability studies of emulgel formulations of batch EG12 at different temperature.

Ivermectin was received from Dr. Reddy's Laboratories, Hyderabad, India as a gift sample. The received sample was authenticated by different test i.e. melting point, test according to Indian Pharmacopoeia and analytical methodology was performed on sample to justify the authenticity of sample. The m.p of the received sample was in the range of 154-1560C, that was matching with the data as mentioned in Indian pharmacopoeia. This justifies the authenticity of given sample of Ivermectin.

Twelve Ivermectin emulgel formulations were developed by incorporating different ingredients i.e. PVP K30, CMC, and Carbopol 940 in different ratio. Prepared formulations were evaluated on different parameters. Emulgel formulations of batches EG1 to EG8 were of white color and EG9 to EG12 were of faint pink, this may be due to use of different polymers. Some formulations were in gel form and some were with flowable properties. The pH values of emulgel formulations were found to be in between 5.32to 6.8. The pH values of emulgel formulations were found to be in between 97.47±0.08 to 99.74±0.06. This may be attributed to the use of different polymers in different ratio.All emulgel formulations have shown good spreadabiliy in between 212.35±0.08 to 332.25±0.62 g.cm.min-1. This indicate all formulations can be used efficiently topically. The residence time of emulgel formulations were found to be in between 2.05±0.07 to 8.73±0.74 (min). Viscosity of emulgel formulations were found to be in between 20426 to 33587 (mPa.s). In 7hrs study, the batch EG12 has shown maximum drug release 63.38±0.19, while the minimum drug release 21.244±0.82% was shown by formulations of batch EG3.Formulations were translucent, homogenous, cream-like emulgels with acceptablepH and drug content. Their viscosity and spreadability was optimal to allow ease in applicationand increase the surface area for drug permeation.

Different kinetic model for *in vitro* release study of emulgel formulations of Ivermectin are shown in Table 11. With the help of PCP disso software, obtained results were checked for different kinetic models.The highest regression coefficient (r2) value was obtained for Korsmeyer– Peppas (0.9983) followed by Higuchi (0.9844), by, zero (0.9748), and first (0.9464) model using PCP disso version 2 software. Study reveals that release was governed by the diffusion.

Accelerated stability studies for 12 weeks shows that the selected emulgel formulations of IvermectinEG12 are capable to be stable at 450C as well as at refrigeration temperature. Therefore, the EG12 formulations of Ivermectin may be kept at room temperature without affecting the properties.

Conclusion

The present was an effort to develop and evaluate Ivermectin emulgel formulations with a view to use topically. On basis different evaluation parameters, current study concludes, formulation of batch EG12 was the optimum formulation.

Conflict of Interest

No Conflict of Interest

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Author Contribution

All authors are contributed equally

Inform Consent and Ethical Approval

Not Required

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