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Research Article

Borneol For Topical Drug Penetration

Effect of Borneol to Enhance Topical Drug Penetration for Lipophilic Drug

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Abstract: Progesterone is a C21-steroid hormone, lipophilic, having log P of 3.56 and therefore, poor permeation of active moiety in the skin is a major challenge of transdermal delivery. There are many strategies to overcome the permeation of drugs through the skin, such as using nanocarriers, applying physical and chemical permeation enhancers and others. Penetration enhancers act by modifying the hydration properties of stratum corneum and altering the structure of lipids and proteins in the intercellular channels carrier mechanism. The present work estimates the *in-vitro* permeation of progesterone from microemulsion-based transdermal formulations containing Borneol as penetration enhancers. Progesterone was taken as a model drug. The microemulsion was formulated by a simple stirring method, followed by adding Myritol as oil, Tween 80 as a surfactant, and + PEG 400 as a co-surfactant. The globule size of the final microemulsion formulation was found to be in the range of 200- 394 nm with PDI 0.123, and Zeta potential study indicated -23.1 mV showing good stability. TEM images showed that the F14 batch is spherical, and its size was identical to that obtained from laser diffraction. For ease of application, microemulsion was converted to gel using Carbopol 980. Borneol with a concentration of 4% showed a drug release of 83% after 9hrs. The formulation's viscosity, pH and texture profile was found to be optimum. The final formulation follows Korsmeyer-Peppas release kinetics. A stability study of microemulsion gel was performed for 180 days at refrigerated temperature and room temperature. The formulation showed better storage via stability study with good spreadability. Thus, developed Borneol containing microemulsion-based transdermal formulation can be a promising alternative to deliver progesterone for hormone replacement therapy in any indication such as breast tenderness, infertility, lumpy (fibrocystic) breasts, low blood sugar, increased blood clotting etc.

Keywords: Micro-Emulation, Gel formulation; Borneol, Penetration Enhancer, Transdermal Drug Delivery System

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1. INTRODUCTION

As a potential noninvasive route of administration, transdermal drug delivery is one of the reliable methods, as it offers numerous benefits over traditional routes of administration, including the avoidance of first-pass metabolism, a decreased incidence of side effects, and higher patient compliance. However, the main problem with transdermal delivery is the poor permeation of drug molecules. As a result, various studies are being conducted to improve its percutaneous permeability. [1-3] The method includes formulation optimization using Nanocarriers such as Polymer Nano Particles, Lipid Nanoparticles, Nano-emulation, dendrimers, Liposomes etc. Authors have used these strategies and found proven results in the permeation of drugs using the above methods. [4-6.] Using a physical and chemical permeation enhancer that modifies the physical and chemical properties of the stratum corneum's hydrating property is one method for enhancing drug penetration through the skin. Another method involves altering the structure of lipids and proteins in the intercellular channel's carrier mechanism.[7] Penetration enhancers play a significant role in developing effective transdermal products. One of the first and most extensively studied penetration enhancers was dimethyl sulphoxide (DMSO). There has recently been a search for natural compounds as permeation enhancers that also exhibit low toxicity while maintaining their enhancing activity because many chemical enhancers, such as DMSO, DMF, a zone, and ionic surfactants, are linked to unpleasant effects. Many powerful enhancers have been discovered, but in most cases, their effects are associated with toxicity.[8] Examples of natural permeation enhancers include essential oils, terpenes, fatty acid esters, terpenoids, herbal extracts, and fatty acid glycols. According to the results of several studies, iontophoresis combined with enhancers like linolenic acid causes the stratum corneum's highly compact cells to transform into a loose network of filaments, breaks the keratin pattern, and causes the stratum corneum cell layers of the human epidermis to swell. These effects enhance the stratum corneum's ability to protect the skin. [9,10] Studies have shown that iontophoresis, combined with enhancers like linolenic acid, transforms the stratum corneum's tightly packed cells into a loose network of filaments, disrupting the keratin pattern, and causes the stratum corneum's cell layers to swell, which improves the medication's flow through the skin.[11] Numerous potent enhancers have been found; however, they typically have harmful side effects.[12] In recent years, the nature of the stratum corneum barrier and the interaction of enhancers with the stratum corneum have become better understood, and the development of structure-activity relationships for enhancers will aid in the development of optimal properties with minimal toxicity. [13,14] Borneol (B.O.), also known as bingpian in China, is a cyclic terpene alcohol (shown in Figure 1) obtained from the traditional Chinese plant *Cinnamomum camphora (L.)*. Various studies have been performed to check the effect of Borneol to enhance the diffusion of drugs through the skin and other membranes and have shown proven results.[15] However, the studies lack investigating the permeation of highly lipophilic drugs. Therefore, in this work, we have attempted to check the role of Borneol as a penetration enhancer for TDDS through *in vitro* drug release study of the highly lipophilic drug Progesterone.

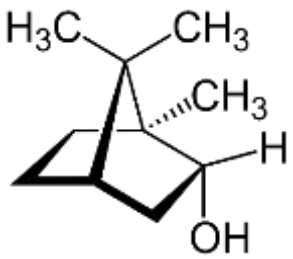

Fig 1. Chemical structure of Borneol

2. MATERIALS AND METHODS

1.1 Material

Progesterone was provided as a gift sample from Walter and Bushnell Pvt. Ltd. Borneol and PEF 400 were procured from Sigma-Aldrich. Dimethyl sulfoxide (DMSO) and Carbopol 980 were purchased from Rankem. Tween 80 was supplied from Loba Chemie Pvt Ltd. Ethanol was taken from supplier Chanshu Hongsheng Fine Chemical Co. Ltd.

1.2 Formulation development

Progesterone was adjusted under a ternary phase transition and solubilized in a wide range of solvents using surfactants and co-surfactants. Microemulsion gel was prepared to contain novel penetration enhancers and DMSO as a reference standard. The gel was developed using Carbopol 980. [16]

1.3 Drug release

The per cent drug release tests were carried out using a Franz diffusion cell. Donor and receptor compartments comprise the two parts of the cell. The receptor compartment was filled with 30% ethanolic PBS (pH 6.8) and stirred continuously to maintain ideal conditions. After uniformly applying gel formulation, the dialysis membrane was climbed between the donor and receptor compartments and clamped. At periodic intervals, 1 mL of the receptor compartment's sample was obtained.[17,18]

1.4 Particle size determination, Transmission electron microscopy & Zeta potential

The microemulsion formulation was evaluated for particle size using a Beckman coulter nano-sizer (Desla nano) and TEM 73-74). In addition, to assess the globules on the electrophoresis and electrical conductivity of the microemulsion (Malvern Instruments, U.K.) Malvern Zeta Sizer was used.[19] The final formulation was also checked for Spreadability and Homogeneity.

1.5 Effect of permeation enhancer

The microemulsion gel containing Borneol in different concentrations as a penetration enhancer was evaluated (Table 1).

Table 1. Formulation of gel containing Borneol as permeation enhancer

S. No.	Formulation code	Borneol %w/w	Carbopol (g)	F14 (g)	Borneol (g)	Water(g)
1	BO1	1%	0.1	1	0.05	Q.S. to 5g
2	BO2	2%	0.1	1	0.10	Q.S. to 5g
3	BO3	3%	0.1	1	0.15	Q.S. to 5g
4	BO4	4%	0.1	1	0.20	Q.S. to 5g

The formulated gels were further evaluated for viscosity, consistency, extrudability, and Texture profile analysis regarding cohesiveness, adhesiveness, compressibility, hardness, in vitro, and stability studies.

1.6 In-vitro skin permeation study

In vitro research on rats was evaluated for skin permeation using the franz diffusion cell assembly. To reach equilibrium, the rat skin was then maintained in a pH 6.8 phosphate buffer solution for 1 hour before the experiment. The 10 per cent lactic acid PBS (pH 6.8) used in the receptor compartment was added, and the ideal conditions were kept by constant stirring. After uniformly applying gel formulation, the donor and receptor compartments were clamped together, and the rat skin was attached between them. At the same time, the donor compartment was maintained empty. At regular intervals, 1 mL of the sample was taken from the receptor compartment. The collected samples were accordingly diluted and were spectrophotometrically analyzed at 241 nm (λmax of progesterone). The process was repeated for blank gel and marketed gel formulation. Experiments were performed six times. [20-22]

1.7 In vitro drug release kinetics

The release kinetics were tested using information from in-vitro permeation experiments of an improved gel formulation. Based on mathematical models of drug release, such as zero order, first order, Higuchi, and Korsmeyer-Peppas, the *in-vitro* release kinetic of the BO4 prepared formulations gel was evaluated. [23]

1.8 Stability studies

According to the International Conference on Harmonization (ICH) requirements, stability investigations were carried out. BO4 formulation gel was kept in 10 mL glass vials at 5±3°C, and 25±2°C and samples were withdrawn at 30, 60, 90, 120, 150 and 190 days for stability studies—% Drug release over time. Stability studies for the formulation were carried out in triplicate. [24]

3. STATISTICAL ANALYSIS

All experiments were conducted three times, and the average values were used for modelling. The statistical analysis was done by plotting linear graphs and analyzing R^2 using Microsoft Excel (2019).

4. RESULTS AND DISCUSSION

4.1 Formulation development

A mixture of Myritol, Tween 80, and PEG 400 were utilized for the microemulsion formation. This mixture had 10.89 per cent by weight of Myritol as oil, 57.18 per cent of Tween 80 as a surfactant, and 31.94 per cent of water. After preparing the microemulsion preconcentrate, a clear microemulsion was formed when the water was added to it. But after a few minutes, the drug started to precipitate out and the drug bed formed at the base in all cases. A similar study by Yue Wu et al. in 2018 demonstrated nanoemulsion formulation of the Borneol for targeting brains and has facilitated the delivery of doxorubicin hydrochloride in its presence [25]. Likewise, the permeation effect of Borneol and menthol was studied by Xingxing Dai *et al*. and Ran Wang on ligustrazine (logP 1.3) and 5-Fluorouracil respectively, which proved its efficiency as penetration enhancer [26,27].

4.2 *The pH of the optimized formulation:*

The improved microemulsion formulations were found to have a pH of 6.2 ± 0.67.

4.3 Particle size determination

The drug's stability and bioavailability evaluation is based on the droplet size measurement. The globule size and PDI of the F14 microemulsion gel were 394 nm and 0.123, respectively. The obtained result is shown in Figure 2.

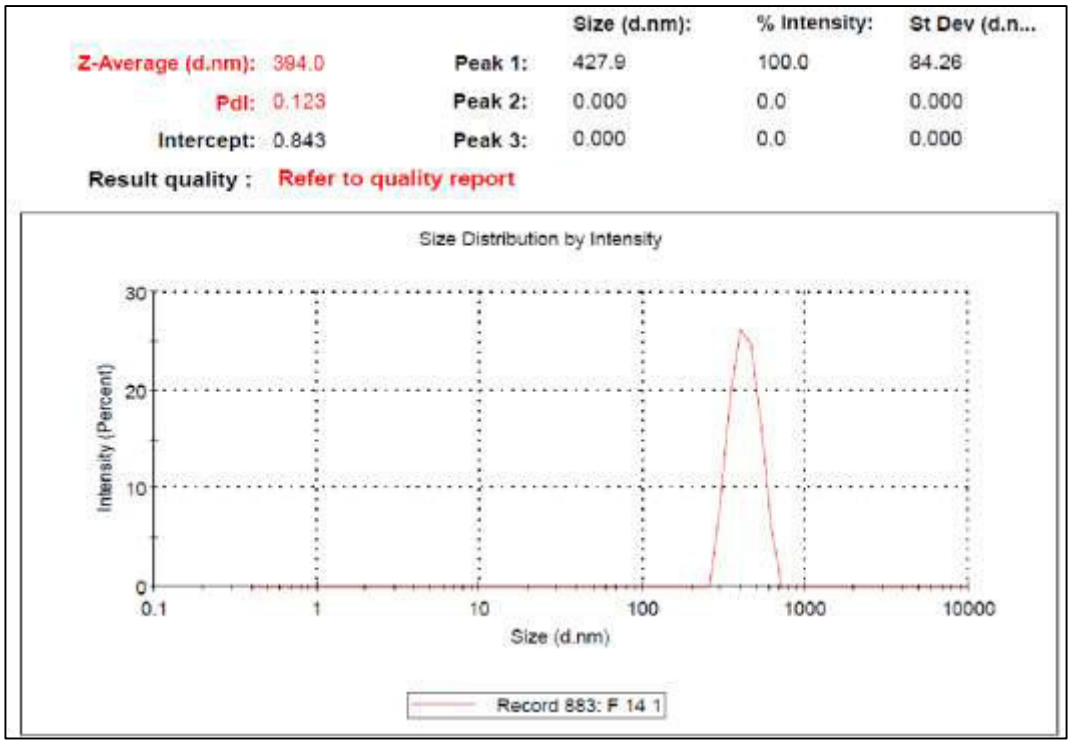

Fig 2: Particle size determination of microemulsion

4.4 Zeta potential

The formulation's zeta potential was reported to be -23.1, which denotes good stability, as shown in Figure 3.

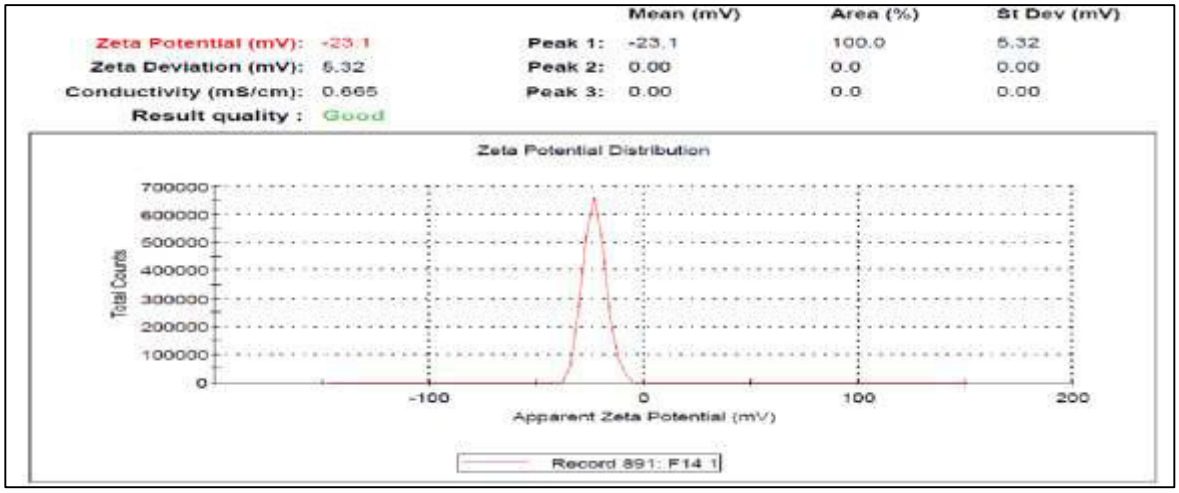

Fig 3: Zeta potential of formulation of microemulsion

4.5 Transmission electron microscopy

The obtained TEM results of the final formulation of the microemulsion are shown in Figure 4. The observations direct the presence of spherical drug-loaded globules in microemulsion, which was in good agreement with globule size analysis results obtained from zeta potential. A similar type of study using a TEM experiment was done by Xingxing Dai *et al.*, where they mentioned that Borneol tends to disorder the stratum corneum layer and form water pores.[29]

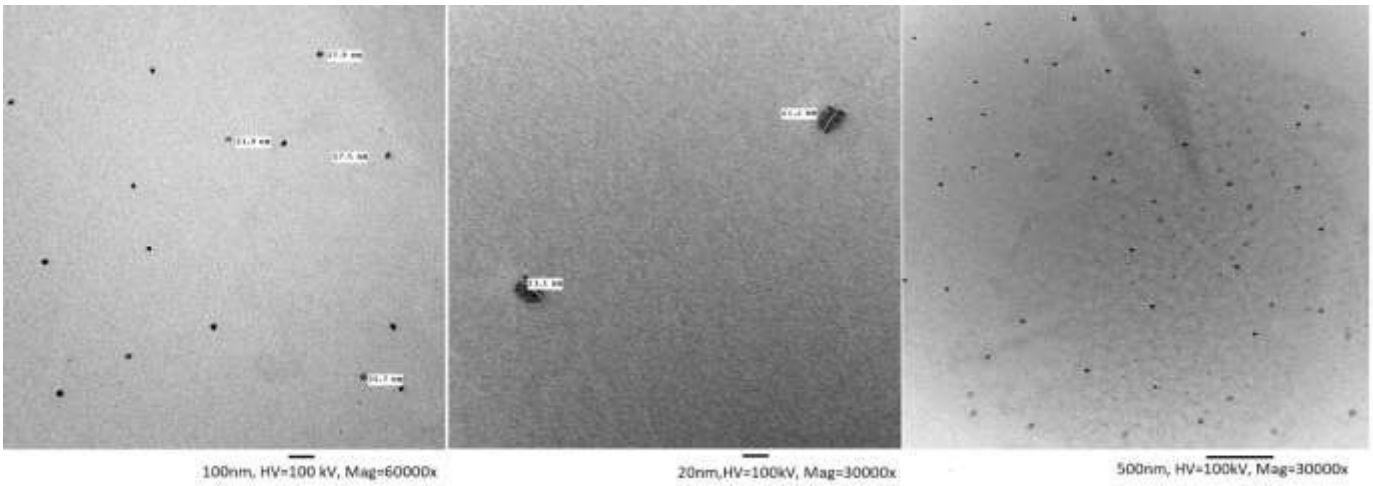

Fig 4. TEM of formulation of microemulsion

4.6 Drug content

Results showed that all gel formulations contained drug content in the range of 86.842 ± 0.09 % to 96.491 ± 0.77 %. These results indicate the uniform distribution of progesterone in the carbopol gels and an insignificant amount of drug loss during the formulation process.

4.7 Spreadability and Homogeneity

Results of spreadability and homogeneity of microemulsion gel formulations showed that the Greater spreadability of C1.5, having 24.45 g.cm/s, suggests enhanced therapeutic efficacy of the drug.

4.8 Percentage drug release

The drug release after nine hr in all the formulations was found to be from 27.443 ± 0.82 % to 58.179 ± 0.04 %. The probable reason for the drug's slow release is the gel network's higher complexation due to the presence of polymer content. This also suggests the comparatively longer diffusion pathway of the topically administered drug. Figure 5 shows significant drug release in gel formulation having 2% of Carbopol. Hence, for further studies, gel with this specific formulation was utilized for the study of the effect of different permeation enhancers.

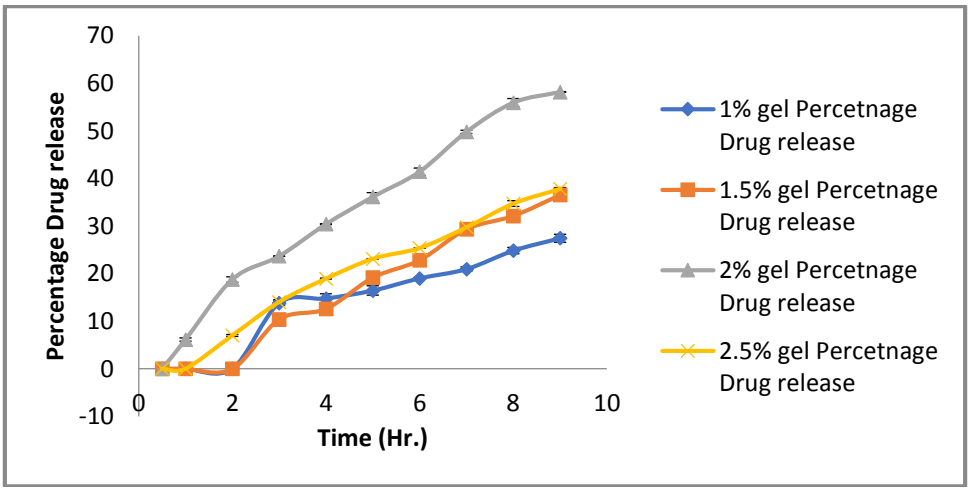

Fig 5: Percentage of drug release of different concentrations of microemulsion containing Carbopol gel

4.9 Effect of Borneol as permeation enhancer

The drug content, spreadability, homogeneity and % drug release of dent formulations of microemulsion gel formulations containing borneolBorneol as a permeation enhancer waswere evaluated. Table 2. shows that all gel formulations contained drug content in the range of 95.89 ± 0.11 % to 98.24 ± 0.01 % and the results of spreadability and homogeneity of microemulsion gel formulations. The drug release after 9 hnine hr in all the formulations was found to be from 46.190 ± 0.48 % to 83.097 ± 0.23 %. Figure 6 shows significant drug release in a formulation having 4 % borneol.

Table 2: % drug content, spreadability and homogeneity of microemulsion gel with Borneol as a permeation enhancer

S. No.	Formulation code	% Drug content	Spreadability (g.cm/s)	Homogeneity
1	BO1	97.89 ± 0.76	20.09 ± 0.11	Good Homogenous
2	BO2	98.12 ± 0.10	22.10 ± 0.32	Good Homogenous
3	BO3	95.89 ± 0.11	25.08 ± 0.89	Good homogenous
4	BO4	98.24 ± 0.01	29.19 ± 0.01	Good homogenous

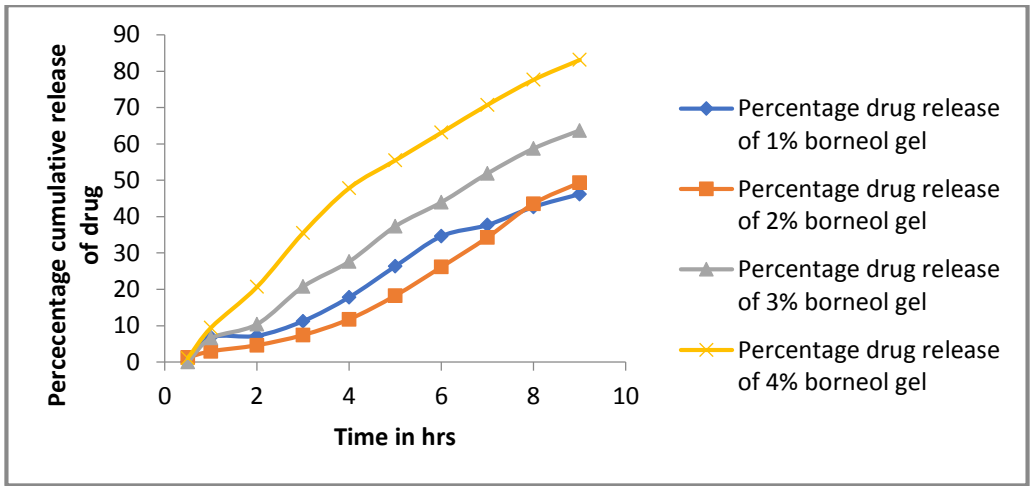

Fig 6: Percentage of drug release of microemulsion gel varying borneol concentration

4.10 Viscosity

It was found that the viscosity of formulation was found to be within a limit. In comparison, the control gel's viscosity was higher than the optimized formulation gel, as shown in Figure 7. The formulation gel did not break at different speeds, representing its mechanical strength.

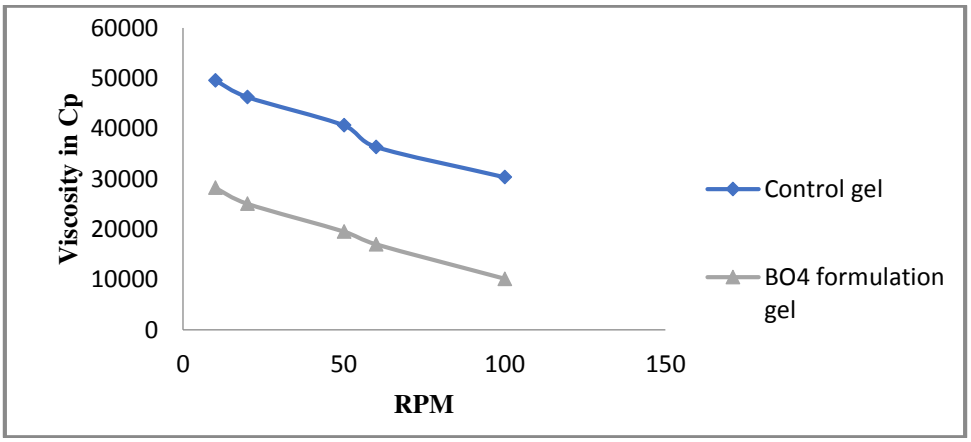

Fig 7: Viscosity of control gel and BO4 formulation gel

4.11 pH, Consistency and Extrudability

The pH of the final formulation containing Borneol was found to be 6.7 ± 0.048. The consistency and extrudability values were 6.1 ± 0.12mm and 16.56 ± 0.23g/cm^2, respectively.

4.12 Texture Profile Analysis

The optimized BO4 formulation has maximum firmness (16.12 ± 1.23gm), work of shear (076 ± 0.87gm.sec), stickiness (12.04 ± 1.12 gm. sec), and work of adhesion (-12.18 ± 0.12gm.sec). It can also be interpreted that the optimized formulation BO4 has greater firmness than the control gel. The gel strength was optimum at 4.23 ± 1.89 gm mm-1sec^{-1} with a cohesiveness of 0.68 ± 0.22.

4.13 In-vitro skin permeation study

The percentage cumulative drug release of carbopol gel, microemulsion, microemulsion gel, basil oil M.E. gel and Borneol ME gel is illustrated in Figure 8. Results suggest that the prepared BO4 formulation gel displayed higher drug release than the marketed formulation. Hence, making prepared gel a fit candidate for transdermal delivery. So, BO4

was selected for further study. Furthermore, the transdermal penetration enhancement effect of Borneol in hyperlipidemia rabbits was studied by Zong-li Liao *et al.* for the herbal cake-partitioned moxibustion on liver lipids, HSL and HMG-CoA reductase[28].

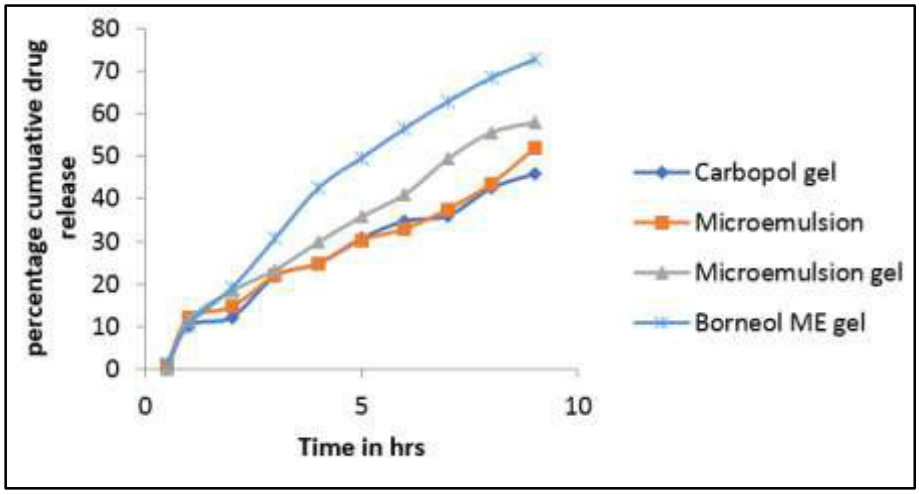

Fig 8: Cumulative drug release of blank gel and optimized formulation gel

4.14 In-vitro drug release kinetics

The drug release profile predicts the transport systems involved in the drug release—data from the BO4 formulation gel's in-vitro drug release kinetics. Model fitting on experimental release data is an adequate first step for estimating release parameters. The R^2 value is typically used to evaluate different models because it tends to change depending on how many parameters are present in the system. Table 3 lists the value of R^2 corresponding to each model. The formulation did not follow zero-order, first-order, or Korsmeyer-Peppas kinetics. The release profile of the BO4 formulation gel, as depicted in Figure 7, could be best explained by the Higuchi model, which has an R^2 of 0.993. The mechanism of drug release is not fully understood. However, the molecular dynamics study by Xingxing Dai *et al.* has shown that borneol act in conc dependent manner by providing a pull effect by forming water pores into the hydrophobic bilayer. [29] Qi-Feng Yi *et al.* noticed the effects of several medications with variable log P values for medications such as 5-fluorouracil, antipyrine, aspirin, salicylic acid, and ibuprofen. The results supported our outcome that Borneol can significantly increase the transdermal penetration of the drug.[30]

Table 3: Kinetic parameters of BO4 formulation gel

Formulation Name	Zero-order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K_o	R^2	K_o	R^2	K_o	R^2	K_o
BO4 Formulation	0.963	8.012	0.963	0.990	0.993	30.83	0.929	1.345

4.15 Stability studies

Further optimization of BO4 formulation gel was carried out by stability studies comprising a change in pH, spreadability, homogeneity, and percentage of drug content. The pH value of the prepared BO4 formulation gel was kept at room temperature, and the refrigerated conditions were found to vary from 7.4 to 5.8 in 180. However, this pH range is considered safe for topical application. Moreover, spreadability after stability studies were conducted in a room, and the refrigerated temperature increased with time. This might be the viscosity's effect, which slightly increased with time, causing enhanced spreadability. Also, the gel formulation under both conditions was found to be homogeneous. Only a slight change in the homogeneity of the formulation kept at room temperature after a 150-day stability test cycle was observed. As shown in Table 4, however, results indicate a modest drop in drug content in the formulation held at ambient temperature. At the same time, there was no appreciable change in drug content over time when stored in a refrigerator. The created BO4 formulation gel was found to be stable under the stability testing conditions, according to the results mentioned above.

Table 4. Percentage drug content of BO4 formulation gel at different temperatures

S. No.	Conditions	Initial drug content	After 30 days	After 60 days	After 90 days	After 120 days	After 150 days	After 180 days
1	At refrigerator temperature (5 ± 3°C)	100%	99.56 ± 0.96	99.90 ± 0.69	99.88 ± 0.54	98.49 ± 0.01	98.01 ± 0.04	98.21 ± 0.04
2	At room temperature (25 ± 2°C)	100%	98.44 ± 0.44	98.09 ± 0.66	97.77 ± 0.43	97.82 ± 0.04	96.82 ± 0.09	96.66 0.08

5. CONCLUSION

As a model drug, progesterone was to be delivered transdermally using a micro emulsion-based gel which was the goal of this investigation. Progesterone into microemulsion with herbal permeation enhancers offers enhanced drug delivery, prolonged drug release, and intensified penetration into the skin. Progesterone was first formed as a microemulsion using a straightforward stirring approach. Myritol, oil, Tween 80, and + PEF 400 were added later. Zeta potential study indicated -23.1 mV showing good stability. TEM images showed that it is spherical, and its size was identical to that obtained from Laser diffraction. For ease of application, microemulsion was converted to gel using Carbopol 980. A 2% concentration of Carbopol 980 was optimized based on the consistency of the gel and drug release study. Borneol with a concentration of 4 % (BO4) showed a drug release of 83% after 9hrs. Further viscosity, pH, consistency, extrudability, and texture profile analysis were performed for BO4. A drug release kinetics study was performed by varying kinetic models. R^2 value in the Korsmeyer-Peppas plot was nearest to one. This indicates release kinetics for final formulation follow Korsmeyer-Peppas. A 180-day stability study of microemulsion gel was conducted at ambient temperature and refrigerated temperature. Various parameters were evaluated, including spreadability, homogeneity, and percentage drug content. It was concluded that for better storage with good spreadability. So main aim to prepare micro emulsion-based gel for the transdermal delivery system has been achieved. The final formulation may be used for hormone replacement therapy after *in-vivo* validation.

6. ACKNOWLEDGEMENT

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7. AUTHOR CONTRIBUTION STATEMENT

Shekhar Sharma and Rupali Sharma experimented and analyzed the results. Rani Mansuri wrote the manuscript with guidance from Anupama Diwan. Anupama Diwan supervised the project.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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