MICROEMULSION BASED GEL DRUG DELIVERY SYSTEM

Yuga Satish Sonegaonkar*, Sushma Singh, Dr. Nilesh Khutle
Department of Pharmaceutics, Dr. L.H. Hiranandani College of Pharmacy, Ulhasnagar.

ARTICLE INFO
Article history
Received 13/01/2016
Available online
10/02/2016

Keywords
Triamcinolone Acetonide,
Psoriasis,
Microemulsion,
Microemulsion Based Gel.

ABSTRACT
The present study was conducted to investigate the microemulsion based topical drug delivery system of anti-inflammatory drug triamcinolone acetonide for psoriasis in order to bypass its gastrointestinal adverse effects and to improve patient compliance. The pseudo ternary phase diagrams were developed for combinations of Capmul MCM EP oil phase, Cremophor EL as surfactant and Transcutol P as cosurfactant using water titration method. The developed microemulsion was characterized for globule size and polydispersibility index. The average globule size of the microemulsion was found be less than 100nm. Centrifugation studies were carried out to confirm the stability of the developed formulation. The formulation was thickened with a gelling agent carbopol 940, to yield a gel with desirable properties facilitating the topical application. The developed microemulsion based gel was characterized for pH, spreadability, refractive index and viscosity. Optimized formulation was then subjected to In vitro drug release. Optimized microemulsion based gel formulation was found to exhibit significant prolonged release as compared to drug suspension. Optimized gel obtained was analysed for transdermal permeability by using franz diffusion cell diffusion cell through an excised rat skin. Thus the present study indicates that microemulsion can be a promising vehicle for the topical delivery of triamcinolone acetonide as it increases the solubility of the drug thus in turn loading capacity of the drug as well.

Please cite this article in press as Yuga Satish Sonegaonkar et al. Microemulsion Based Gel Drug Delivery System. Indo American Journal of Pharmaceutical Research.2016:6(01).

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INTRODUCTION
Psoriasis is a common, chronic inflammatory, relapsing/remitting, immune-mediated systemic disease characterized by skin lesions including red, scaly patches, papules, and plaques, which usually itch. The skin lesions seen in psoriasis may vary in severity from minor localized patches to complete body coverage.

Several topical therapeutic agents are available for the treatment of psoriasis. Nevertheless, none of them can be regarded as an ideal drug molecule. This may either be due to their inherent side effects or their improper incorporation in the conventional vehicles. It is a well-known fact that due to variation in the physicochemical characteristics of the carrier and of the active compounds used; the degree of drug absorption through skin may vary, and therefore, may be the drug efficacy. Hence, the carriers based on scientific approach can modify the physicochemical properties of the drugs and can help to decrease the intensity and frequency of side effects associated with these active moieties. Formulations like gels, creams, ointments, and lotions are frequently used for the topical delivery of the antipsoriatic agents. However, these formulations are often not able to mask the drug-related issues causing obvious problems with patient acceptance and compliance. The topical delivery vehicle must be suitably designed and developed to attain the desirable attributes for use in extremely dehydrated and thickened psoriatic skin having lipid imbalance and sensitive to irritants.

Triamcinolone acetonide is anti-inflammatory synthetic corticosteroid which is used to treat psoriasis. It is a class IV drug which has low solubility and low permeability. Triamcinolone acetonide when administered orally undergoes extensive first pass metabolism. Triamcinolone acetonide also possesses short half-life of 88 min. Thus from above listed properties of drug and taking into account that psoriasis disease first line of treatment is done by topical route. Topical route is selected for administration of triamcinolone acetonide. Microemulsion is suited formulation for topical delivery of triamcinolone acetonide because the rate of the drug permeation from microemulsion may be increased, since the affinity of a drug to the internal phase in microemulsion can be easily modified to favour partitioning into stratum corneum, using different internal phase, changing its portion in microemulsion.

The surfactant and cosurfactant in microemulsion may reduce the diffusional barrier of stratum corneum by acting as penetration enhancer. The percutaneous absorption of triamcinolone acetonide also increases due to hydration effect of stratum corneum the water content in microemulsion is high enough to provide hydration to dehydrated psoriatic skin.

A large amount of triamcinolone acetonide can be incorporated in the formulation due to the high solubilizing capacity that might increase thermodynamic activity towards the skin. Surface area is assumed to be high due to small droplet size. Therefore, droplets settle down to close contact with the skin providing high concentration gradient and improved drug permeation. Moreover, low surface tension ensures good contact to the skin. Also, the dispersed phase can act as a reservoir making it possible to maintain an almost constant concentration gradient over the skin for a long time.

For conventional formulations it can be stated that the effectiveness of the active agent is directly related to the composition of the formulation. In general, the potency of the corticosteroids in the formulations could be listed in order such as; ointments > gels > creams > lotions. Ointment possesses limitation that is greasy nature and hardness of the removal from the skin due to their lack of water-washability. Whereas gel provide advantage that is easy application, easy to attach to the skin, good patient compliance and lack of irritating components.

Hence objective of current research work is,
1. To select suitable excipient for formulating microemulsion based system for topical administration of Triamcinolone acetonide.
2. To formulate and characterize the microemulsion based system developed.
3. To perform the stability of the formulation.

MATERIAL AND METHOD:
Triamcinolone acetonide was generous gift sample from Avik Pharmaceutical (Gujarat). Campul MCM EP, Capmul MCM NF, Capmul MCM C8EP, Capmul MCM C8 NF were obtained from Abitech corp. (IMCD group Mumbai, India). Cremophor RH40, Cremophop EL, Solutol HS15 were obtained from (BASF, Mumbai, India). Labrafil M2125CS, Labrafil M1944CS, Transcutol P were obtained from Gattefosse (Mumbai, India). Tween 80, Tween 20, Span 80, Span 20, Propylene glycol, was purchased from (Molychem, Mumbai, India).

SOLUBILITY STUDIES:
The solubility of drug in various oils was screened.

Method
An excess amount of Triamcinolone acetonide was added to 1g of selected vehicle in a vial. The mixture is then cyclomixed for 10 minutes in order to facilitate the proper mixing of triamcinolone acetonide in selected vehicle. The mixtures were then shaken for 72 hours in orbital shaker. Mixtures were then centrifuged at 3000 rpm for 30mins. The supernatant was collected and diluted with methanol. Further the amount of triamcinolone acetonide dissolved in various vehicles was quantified using UV spectrophotometry.
Screening of surfactants for emulsifying ability

Different surfactants were screened for its emulsification ability selected in oil phase. Emulsification ability of various surfactants was screened on the basis of % transparency and emulsification ability. 300 mg of surfactant was mixed with 300 mg of the selected oil phase. The mixture was gently heated at 45–60°C for homogenizing the components. The isotropic mixture, 50 mg, was accurately weighed and diluted with double distilled water to 50 ml to yield fine emulsion. The ease of formation of emulsions was monitored by noting the number of volumetric flask inversions required to give uniform emulsion. The resulting emulsions were observed visually for the relative turbidity. The emulsions were allowed to stand for 2hr and percent transmittance was assessed at 638.2 nm by UV-spectrophotometer using double distilled water as blank.

Screening of co-Surfactants

The turbidimetric method was used to assess relative efficacy of the co-surfactant to improve the emulsification ability of the surfactants and also to select best co-surfactant from the large pool of co-surfactants. 150 mg accurately weighed selected surfactant and 150 mg of cosurfactant was heated and vortex for few minute then mixed with 300 mg of oil heat together to form mixture. The isotropic mixture, 50 mg, was accurately weighed and diluted with double distilled water to 50 ml to yield fine emulsion. The ease of formation of emulsions was monitored by noting the number of volumetric flask inversions required to give uniform emulsion. The resulting emulsions were observed visually for the relative turbidity. The emulsions were allowed to stand for 2 hr and their percent transmittance was assessed at 638.2 nm by UV-spectrophotometer using double distilled water as blank.

Formulating microemulsion based on Pseudo ternary phase diagram

The ratios of surfactant to co-surfactants were chosen to be 1:2, 1:1, 2:1, and 3:1, and such mixtures were prepared. These mixtures of surfactant/co-surfactants were mixed with the oil phase to give the weight ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1. Water was added drop by drop and stirred until homogeneous dispersion or solution was obtained. After each addition, the system was examined for the appearance. The end point of the titration was the point where the solution turn to gel or turbid. After preparing the pseudo ternary phase diagram the medicated microemulsions were formulated. Total 13 batches of microemulsion was prepared using phase titration method and based on pseudoternary diagram results.

Optimization of formulae

The selected ratios from the systems analyzed were then subjected to alternate freeze thaw cycles. Each ratio was subjected to refrigeration temperature i.e 0ºC for 24 hrs and for the next 24 hrs they were subjected to room temperature. Likewise 3 freeze thaw cycles were carried out and the mixture was observed for any phase separation, drug precipitation or any instability.

Centrifugation

Batches that pass the freeze thaw cycle test are further subjected to centrifugation. The mixture is centrifuged at 4000 rpm for 15 minutes and again observed for any signs of phase separations or drug precipitation.

Robustness to dilution

Robustness of triamcinolone acetonide to dilution was studied by diluting it 50, 100 and 1000 times with external phase water. The diluted nano-emulsions were stored for 12 h and observed for any signs of phase separation or drug precipitation.

EVALUATION OF MICROEMULSION

The optimized batch was further evaluated for properties like globule size, zeta potential, polydispersibility index, drug content, % transparency, viscosity and in-vitro drug release studies.

Globule size, zeta potential, polydispersibility index and refractive index

The formulation, 50mg was taken and diluted to 50ml with double distilled water and visual observations were done for its emulsification efficiency. Glouble size, zeta potential and polydispersibility index refractive index were determined using Horiba zeta-sizer.

Drug content

The stock solutions of formulation were prepared in 10 ml volumetric flasks with exactly weighed 10 mg of (Filtered through 0.45 micron) formulation and dissolved with help of methanol. The solutions were sonicated for 10 min and adjusted to the volume with phosphate saline buffer pH 7.4. UV absorbance at 242nm was observed by keeping Phosphate saline buffer pH 7.4 as a blank solution.

Percent transparency

The Percent transmittances of each batch were checked by UV at 638.5 nm, taking Doubled distilled water as blank.

Viscosity

Oswald viscometer was used for viscosity measurement. 10 gm of sample was filled in it and time required for sample to drop between the markings was noted.
TEM
Transmission electron microscopy analysis is done to study morphology of microemulsion.

In vitro release:
The in vitro drug release studies were performed using vertical franz diffusion cell with an diffusion area of 3.56 cm$^2$ and 20ml cell volume. The Dialysis membrane was hydrated in phosphate buffer pH 7.4 at room temperature for 24 hrs and then placed between donor and receptor compartment in such a way that it just touches the diffusion medium in receptor compartment. The receptor compartment was filled with freshly prepared phosphate saline buffer pH 7.4 that was maintained at 37°C and the solution was continuously stirred at 300rpm by magnetic stirrer. The microemulsion formulation was gently placed in donor compartment. Samples were periodically withdrawn from receptor compartment, replacing with same amount of fresh phosphate buffer pH 7.4 solution and samples were analyzed by using UV spectrophotometer at 242 nm after suitable dilution. Cumulative release was obtained.

FORMULATION DEVELOPMENT OF MICROEMULSION BASED GEL
Gels were prepared by using Carbopol in varying concentration was slowly mixed with one of optimized batch of microemulsion. This was allowed to stand for 2-3 hrs to hydrate carbopol. The microemulsion is neutralized by using triethanolamine to obtain gel.

EVALUATION OF MICROEMULSION BASED GEL

Visual appearance and clarity\[^{[22-23]}\]
Visual appearance and clarity was checked against a white and black background for presence of any particulate matter.

Drug content\[^{[22-23]}\]
The stock solution of formulation was prepared in 10 ml volumetric flasks with exactly weighing 10mg of formulation and dissolved in methanol (1-2ml). The solutions were sonicated for 10 min and adjusted to the volume with phosphate saline buffer pH 7.4. UV absorbance at 242 nm was observed.

In vitro release study
All the in-vitro permeation studies were carried out in franz diffusion cell. Dialysis Membrane was used as a membrane for the experiments. The receptor compartment was filled with 20 ml of Phosphate saline buffer pH 7.4. The solution in the receptor compartment was constantly stirred by means of Teflon Coated magnetic bead on a magnetic stirrer, so that the hydrodynamic conditions of the system were maintained. Triamcinolone acetonide gel equivalent to 1mg was applied uniformly on the membrane. The opening of the donor compartment was covered by foil, in order to prevent loss due to evaporation. An aliquot of 1ml was removed from the receptor medium at intervals of 0, 30 min, 1 hr, 2, 3 24 hrs and replaced immediately with the same volume of the plain diffusion medium.

Rheology studies
The Rheological studies of the samples were carried out using Brookfield viscometer. The viscosity of gel was determined using Spindle no .5. The shear rate was by changing the speed in RPM and corresponding shear stress was noted down from dial scale reading. The dial scale reading multiplied by factor (obtained from table) gave the viscosity in centipoises.

Spreadability
The apparatus consist of wooden block with a scale and two glass slides having a pan mounted on pulley. Excess of formulation was placed between two glass slides and 50g weight was put on upper glass slides for 5min to compress the formulation to uniform thickness. Weight was added in pan. Time in seconds required to separate two slides was taken as measure of spreadability.\[^{[24]}\]
The Spreadability was calculated by using formula

\[
S = \frac{mxL}{t}
\]
Where;  
S= Spreadability  
M= weight tied to upper slides  
L= length of glass slide  
T= time taken in seconds

Ex-vivo diffusion study:\[^{[25]}\]
Ex- Vivo skin permeation was performed by franz Diffusion cell with effective skin diffusion area of 3.56 cm$^2$. The excised sample of rat skin (Dorsal side) was clamped between donor and receptor compartment of franz diffusion cell with stratum corneum facing the donor compartment. Than fixed quantity of microemulsion gel containing 0.1% triamcinolone acetonide was applied on donor compartment. The receptor compartment was filled with phosphate buffer pH 7.4 was maintained at temperature 37°C with stirring at 100rpm. At predetermined intervals 1hr, 1ml was withdrawn and same volume of same medium was added immediately into receptor compartment. Procedure was repeated up to 24hr. The samples were analyzed by UV spectrophotometer at 242nm using blank as phosphate buffer pH 7.4.
Histopathology

The rat abdominal skin region measuring approximately 4 cm² was mounted on modified Franz diffusion cell. The microemulsion gel was applied identical to diffusion study and the effects were compared against water as control. The skin was fixed in 10% neutral formalin for 24 hours and then cut vertically against the surface at the central region (4mm width). Each section was dehydrated using graded solutions of ethanol and then embedded in paraffin wax. Tissues were divided into small pieces and stained with haematoxylin and eosin. The sections were observed under 100 x magnifications and photographed [24].

STABILITY STUDY OF MICROEMULSION BASED GEL

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of variety of environmental factors such as temperature, humidity and light. The stability of developed formulation was established over a period of 3 month.

The microemulsion based gel samples were stored at 40±20°C/75%RH for 3 months. The microemulsion based gel was evaluated at 0, 1, 2, 3 months. Organoleptic, Drug content, pH and in vitro drug release through diffusion study was evaluated.

RESULTS AND DISCUSSION

Solubility Study for Selection of Oil

Identifying the suitable oil having maximal solubilizing potential for drug under investigation is very important to achieve optimum drug loading. Thus, based on data of solubility of Triamcinolone acetonide in different oils Capmul MCM EP were selected for further study as it solubilized highest amount of Triamcinolone acetonide as compared to other oils.

Screening of Surfactants for emulsifying ability

Nonionic surfactants are generally considered less toxic than ionic surfactant. The % transmittance values of various dispersions are given in table. Emulsification studies clearly distinguished the ability of various surfactant to emulsify Capmul MCM
EP. Chremophor EL has highest emulsification efficiency with Capmul MCM EP for homogeneous emulsion formation. The aforementioned result suggested the use of Capmul MCM EP as an oily phase with Chremophor EL as a surfactant for further study.

Screening of co-surfactants

![Graph showing % Transmittance of co-surfactant for Capmul MCM EP.]

The investigation clearly distinguished the ability of various cosurfactants to improve the emulsification of selected surfactants. All the cosurfactant increased the spontaneity of the microemulsion formation. In case of Chremophor EL, Transcutol P shows maximum transmittance of 98.92% along with only 4 phase inversion and more spontaneous emulsification as compared to other cosurfactants. It is reported that lower the core polarity higher the effectiveness of the micelle solubilization is on a molar basis. For Chremophor EL, micelle core polarity is 1.05. It is suggested that Cremophor EL provide a relatively more favourable environment to poor water soluble compounds in aqueous solution. Chremophor EL is more effective in solubilizing water insoluble compounds. Hence Capmul MCM EP as an oily phase, Chremophor EL as a surfactant and Transcutol P as cosurfactant selected for further study.

Pseudo ternary phase diagram

![Phase diagrams for Surfactant:Cosurfactant (S:Cos) ratios 1:1, 1:2, 1:3.]

From the above phase diagrams it clear that surfactant/cosurfactant-1:1, 2:1 contains more microemulsion existence area. Hence selected for further study.
Trail batches for S: Cos 1:1 ratio.
Table 1 Trial batches of microemulsion for smix 1:1.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Oil:smix</th>
<th>Oil (mg)</th>
<th>Surfactant (mg)</th>
<th>Cosurfactant (mg)</th>
<th>Water (mg)</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>1:1</td>
<td>500</td>
<td>250</td>
<td>250</td>
<td>9000</td>
<td>Turbid</td>
</tr>
<tr>
<td>A2</td>
<td>1:2</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>8500</td>
<td>Turbid</td>
</tr>
<tr>
<td>A3</td>
<td>1:3</td>
<td>500</td>
<td>750</td>
<td>750</td>
<td>8000</td>
<td>Turbid</td>
</tr>
<tr>
<td>A4</td>
<td>1:3.2</td>
<td>500</td>
<td>800</td>
<td>800</td>
<td>7900</td>
<td>Turbid</td>
</tr>
<tr>
<td>A5</td>
<td>1:3.4</td>
<td>500</td>
<td>850</td>
<td>850</td>
<td>7800</td>
<td>Turbid</td>
</tr>
<tr>
<td>A6</td>
<td>1:4</td>
<td>500</td>
<td>1000</td>
<td>1000</td>
<td>7500</td>
<td>Clear</td>
</tr>
<tr>
<td>A7</td>
<td>1:5</td>
<td>500</td>
<td>1250</td>
<td>1250</td>
<td>7000</td>
<td>Clear</td>
</tr>
<tr>
<td>A8</td>
<td>1:6</td>
<td>500</td>
<td>1500</td>
<td>1500</td>
<td>6500</td>
<td>Clear</td>
</tr>
</tbody>
</table>

From table it is clear that batch A6(1:4),A7(1:5),A8(1:6) formed clear microemulsion.

**Trail Batches for S:Cos-2:1.**

Table 2 Trial batches of microemulsion for smix 2:1.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Oil:smix</th>
<th>Oil (mg)</th>
<th>Surfactant (mg)</th>
<th>Cosurfactant (mg)</th>
<th>Water (mg)</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>1:3</td>
<td>500</td>
<td>1000</td>
<td>500</td>
<td>8000</td>
<td>Turbid</td>
</tr>
<tr>
<td>B2</td>
<td>1:3.3</td>
<td>500</td>
<td>1100</td>
<td>550</td>
<td>7850</td>
<td>Turbid</td>
</tr>
<tr>
<td>B3</td>
<td>1:3.6</td>
<td>500</td>
<td>1200</td>
<td>600</td>
<td>7700</td>
<td>Clear</td>
</tr>
<tr>
<td>B4</td>
<td>1:3.9</td>
<td>500</td>
<td>1300</td>
<td>650</td>
<td>7802</td>
<td>Clear</td>
</tr>
<tr>
<td>B5</td>
<td>1:4.2</td>
<td>500</td>
<td>1400</td>
<td>700</td>
<td>7703</td>
<td>Clear</td>
</tr>
</tbody>
</table>

From table it is clear that batch B3(1:3.6),B4(1:3.9),B5(1:4.2) formed clear microemulsion. Batches which formed microemulsion from 1:1 and 2:1 smix ratios were further subjected to freeze thaw cycles.

**Table 3 Trail batches from smix 1:1 and smix 2:1 subjected to freeze thaw and centrifugation.**

<table>
<thead>
<tr>
<th>Batches</th>
<th>Freeze Thaw cycles</th>
<th>%Transmittance after freeze thaw cycles</th>
<th>Centrifugation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A6</td>
<td>Pass</td>
<td>95.1%</td>
<td>No phase separation and no drug precipitation</td>
</tr>
<tr>
<td>A7</td>
<td>Pass</td>
<td>96%</td>
<td>No phase separation and no drug precipitation</td>
</tr>
<tr>
<td>A8</td>
<td>Pass</td>
<td>96.17%</td>
<td>No phase separation and no drug precipitation</td>
</tr>
<tr>
<td>B3</td>
<td>Pass</td>
<td>97.12%</td>
<td>No phase separation and no drug precipitation</td>
</tr>
<tr>
<td>B4</td>
<td>Pass</td>
<td>97.09%</td>
<td>No phase separation and no drug precipitation</td>
</tr>
<tr>
<td>B5</td>
<td>Pass</td>
<td>96.98%</td>
<td>No phase separation and no drug precipitation</td>
</tr>
</tbody>
</table>

From the results of centrifugation and freeze thaw studies batch selected for study was one which had least concentration of surfactant which was A6 of S:Cos 2:1. To the optimized microemulsion formula drug was added and optimized drug loaded microemulsion formula was obtained.

**Table 4 optimized microemulsion batch.**

<table>
<thead>
<tr>
<th>Batch</th>
<th>drug (mg)</th>
<th>Oil (mg)</th>
<th>Surfactant (mg)</th>
<th>Cosurfactant (mg)</th>
<th>Water (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>10</td>
<td>500</td>
<td>1200</td>
<td>600</td>
<td>7690</td>
</tr>
</tbody>
</table>

**Drug content**

Drug content of batch C1 was found to be 99.7% which indicates that drug was completely entrapped into oil globule and uniformly distributed throughout microemulsion.

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**pH determination**

The pH value conventionally represents the acidity or alkalinity of an aqueous solution. pH of Batch C1 was observed 7.34. C1 formulation will not alter the physiological conditions of skin as it has pH 7.34 which is nearly equal to skin pH 7.4.

**Viscosity**

All liquids are viscous fluids due to presence of attractive forces which oppose the relative motion between neighbouring volume element in liquid. Viscosity is defined as shearing stress which is exerted across an area when there is unit velocity gradient normal to area. Viscosity of batch C1 was found to be 12.23 cps which is low for application of microemulsion on to skin thus microemulsion needs to be formulated into gel to increase the viscosity of formulation and for providing ease of application.

**Percent transmittance**

Percent transmittance of C1 was found to be 98.6% and microemulsion formed was transparent and appeared like homogenous single phase liquid observed for visual clarity against light. No traces of undissolved drug or other solid ingredient were found.

**Particle size distribution**

Droplet size of microemulsion is critical factor because it determines rate and extent of drug release and absorption. Small globule size of microemulsion droplets may lead to more rapid absorption.

<table>
<thead>
<tr>
<th>Peak indications</th>
<th>Z-Average (d.nm)</th>
<th>Size (d.nm)</th>
<th>%intensity</th>
<th>Std Dev(d.nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.34</td>
<td>33.22</td>
<td>80.7</td>
<td>15.10</td>
<td></td>
</tr>
</tbody>
</table>

**Polydispersity index and Refractive index**

The polydispersity index of C1 batch was found to be 0.296. The higher the polydispersity, the lower the uniformity of the droplet size in the formulation since the value of batch C1 is small it indicates that good uniformity of droplet size.

<table>
<thead>
<tr>
<th>Refractive index</th>
<th>Blank</th>
<th>C1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractive index</td>
<td>1.340</td>
<td>1.330</td>
</tr>
</tbody>
</table>

Refractive index value for formulation was compared with that of placebo, it was found that there was no significant difference between the values, therefore it can be concluded that the microemulsion was chemically stable; thus there were no interaction between excipients and drug.

**Zeta potential**

Emulsifiers not only act as a mechanical barrier but also through formation of surface charges zeta potential, which can produce repulsive electrical forces among approaching oil droplets and this hinders coalescence. The more negative is zeta potential; greater is the net charge of droplets and more stable the emulsion is.

<table>
<thead>
<tr>
<th>Z-Potential (mV)</th>
<th>Mean (mV)</th>
<th>Area (%)</th>
<th>Std Dev(d.nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10.7</td>
<td>-10.7</td>
<td>100</td>
<td>7.84</td>
</tr>
</tbody>
</table>
**In-vitro release**

![Graph showing cumulative drug release from microemulsion](image)

**Figure 5:** % Cumulative drug release from microemulsion.

In vitro release from microemulsion was found to be 98.43% at the end of 24 hr. Thus almost all the drug is released from microemulsion which can be concluded from the drug content which was found to be 99.7%.

**TEM analysis**

![TEM image of optimized batch of microemulsion](image)

**Figure 6:** TEM image of optimized batch of microemulsion.

Image indicates the ability of triamcinolone acetonide to produce spherical oil globule size, oil droplets are equally distributed throughout the film.

**FORMULATION DEVELOPMENT OF MICROEMULSION BASED GEL**

For converting microemulsion into gel, carbopol was selected as the gelling agent. Different concentration of carbopol 940 p varying from 0.5% to 2.5% was used for preparing gel of optimized C1 batch. All the batches were evaluated for drug content, pH and in vitro release and 0.5% of carbopol 940 p showed the highest drug release, pH and in vitro drug release and thus optimized microemulsion with carbopol 0.5% concentration was considered as the optimized microemulsion gel batch.

**Table 8 Optimized batch of microemulsion gel.**

<table>
<thead>
<tr>
<th>Batch</th>
<th>drug</th>
<th>Oil</th>
<th>surfactant</th>
<th>Cosurfactant</th>
<th>water</th>
<th>Carbopol 940 p</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>10mg</td>
<td>500mg</td>
<td>1200mg</td>
<td>600mg</td>
<td>7690mg</td>
<td>0.05g</td>
</tr>
</tbody>
</table>

**In vitro release**

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Comparison of *in vitro* release between drug suspension and microemulsion gel

**Figure 7:** % Cumulative drug release from microemulsion gel.

**Figure 8:** Comparative drug releases between drug suspension and microemulsion gel.

**Particle size**
Particle size of batch D1 was found to be 67.8nm.

**Rheological studies:**

**Table 9** Rheological behaviour of formulations.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Viscosity after gelation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5rpm</td>
</tr>
<tr>
<td>D1</td>
<td>41600</td>
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</tbody>
</table>
Rheological behavior of gel indicates the system was non-newtonian showing decrease in viscosity with increase in shear rate. The system was found to be pseudoplastic shear thining system.

Spreadability:

Spreadability of D1 batch was found to be 27.77 in 54 sec. Less the time required better is spreadability. The values of spreadability indicated that gel was easily spreadable with small amount of shear. Formulation developed showed good homogeneity with absence of lumps.

Ex vivo diffusion study

Ex-vivo diffusion study showed drug release 99.1.

SEM analysis:

Figure 10: SEM image of (a) microemulsion based gel and (b) triamcinolone acetonide.

SEM images of pure drug triamcinolone depict crystalline nature of drug whereas image of microemulsion gel depict gel structure and uniformity and homogeneity of microemulsion gel.

Histopathological evaluation:

Control: NAD (No Lesion of pathological significance was observed)
Test: There was no lesion of pathological significance was observed
The histology study of rat excised skin was treated with control and microemulsion gel showed no change in microscopic structure of skin. The surface epithelium lining and granular cellular structure were totally intact. No change in ultra-structure of skin morphology was seen and epithelial cell appeared to be unchanged. When the skin was treated with microemulsion formulation, definite changes were observed in the skin morphology. The disruption and extraction of lipid bilayers were clearly evident as distinct voids and empty spaces visible in the epidermal region. The disruption of epidermal layer indicated permeation of triamcinolone acetonide through stratum corneum.

STABILITY

It was concluded that no significant changes were observed in appearance, % drug content, pH and in vivo diffusion study of microemulsion gel. Stable and prolonged release formulation i.e. microemulsion gel can be produced as an alternative to conventional system which also provide reduction in frequency of dosing.

CONCLUSION

Microemulsion based gel formulation containing triamcinolone acetonide was prepared with the aim of increasing solubility and achieving maximum release through the skin thus by passing its gastrointestinal adverse effect. Thus a microemulsion based gel formulation was successfully prepared using Capmul MCMas oil, Cremophor RH40 as surfactant, Transcutol P as cosurfactant, water and carbopol 940 as a gelling agent. Solubility study showed triamcinolone acetonide has higher solubility in microemulsion formulation as compared to in their corresponding plain oils. This leads to increased drug loading. Therefore the microemulsion based gel of triamcinolone acetonide was prepared to obtain improved patient compliance.

REFERENCES


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