RESEARCH ARTICLE

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Formulation and Development of Microemulsion Based Gel (Mbg) of Ibuprofen for Topical Drug Delivery

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Abstract: The aim of the present study was to formulate an Ibuprofen loaded microemulsion based gel (MBG) for the topical delivery. The oil phase selected for the preparation of stable microemulsion was IsoPropyl Myristate (IPM). Tween-80 and PEG 400 were selected as surfactant and co-surfactant respectively. For the ease of application microemulsion was gelled by using carbopol 940. The optimized MBG was evaluated for pH measurements, spreadability, swelling index study, drug content and *in-vitro* permeation study. The *in-vitro* skin permeation was carried out in pH 7.4 phosphate buffer on excised mice skin using franz-diffusion cell for 4 h and was compared with a conventional gel formulation. The results showed that release of drug from MBG was found to be 97.78% as compared to 79% from conventional gel formulation. The study also showed flux value 0.453µg/cm^2/min for MBG as compared to 0.353 µg/cm^2/min which was found in the case of conventional gel. Hence MBG is the promosing alternative for the topical delivery of the drug.

INTRODUCTION

Microemulsion (ME) are clear, transparent, thermodynamically stable dispersions of oil and water, stabilized by an interfacial film of surfactant frequently in combination with a co-surfactant and having diameter of the droplets in the range of 100-2000 A (10-200 nm). Recently, there has been a considerable interest for the microemulsion formulation, for the delivery of hydrophilic as well as lipophilic drug as drug carriers because of its improved drug solubilization capacity, long shelf life, ease of preparation and improvement of bioavailability. [1]

Advantages of ME over coarse emulsion include its ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, and enhanced penetration through the biological membranes, increased bioavailability and less inter and intra individual variability in drug pharmacokinetics. [2] Recently, ME were reviewed for several applications, such as topical use, oral use, parenteral use, and cosmetics but the topical application of microemulsion has gained increasing interest. The superior transdermal flux from microemulsion has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs. This generates an increased thermodynamic activity towards the skin. [3, 4, 5] It was demonstrated that permeation rates from microemulsion were significantly higher than those from conventional emulsions.

Recently, microemulsion-based hydrogel (MBH) formulations have generated considerable interest as a potential topical delivery system. [6] Based on its special network structure, the MBGs have received particular attention especially as drug delivery systems. One important consequence is that the stability of the MBGs is much better compared to that of conventional hydrogels. One reason for this is that the MBGs are prepared from w/o microemulsion which is thermodynamically stable systems, and the organic solvent as external phase which could offer superior resistance to microbial contamination compared to aqueous phase. Moreover, due to the increasing of viscosity of the system by incorporating gelatin into W/O microemulsion, the MBGs are suitable to be used as a kind of sustained release drug delivery systems. Other properties that make the MBGs attractive as drug delivery vehicles include their electrical conductivity to be applied in iontophoretic drug delivery systems. [7]

Ibuprofen is a second generation non-steroidal anti-inflammatory agent, which is widely used to reduce fever and treat pain or inflammation caused by many conditions such as headache, toothache, back pain, arthritis, menstrual cramps, or minor injury. Its biological half–life have been reported to be 2 to 4 hrs, necessitates multiple daily dosing for maintaining therapeutic effect throughout the day. The oral use of Ibuprofen is associated with side effects like gastrointestinal disturbances, nausea, vomiting, anorexia, diarrhoea, constipation, stomatitis, flatulence, bloating, epigastric pain, and abdominal pain. Topical application of the drug prevents these side effects and offers potential advantage of delivering the drug at the site of action. [8]

Therefore, the aim of this study was to develop suitable microemulsion based gel (MBG) system after screening of oils, surfactants, and cosurfactants for topical delivery of Ibuprofen to improve its skin permeability with enhanced safety. Microemulsion was prepared using pharmaceutically acceptable ingredients without using additional chemical enhancers.

MATERIALS AND METHODS

Materials

Ibuprofen and carbopol 940 was procured from Yarrow Chem, Mumbai, India. Isopropyl myristate (IPM) was purchased from Himedia Lab., Mumbai, India. Tween 80 and PEG 400 were procured from Burgoyne Burbidges & Co., Mumbai, India. All other chemicals used were of analytical reagent grade. Distilled water was used throughout the experiment.

Screening of Oils (Solubility Study)

In order to find out appropriate oil that had good solubilizing capacity of Ibuprofen and thus could be used as

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Table 1: Optimization of Oil Phase (IPM)

Formulation Code	Ingredients		
	IPM (%)	S_{mix} (1:1) (%)	Water (%)
ME-1	5	45	50
ME-2	10	40	50
ME-3	11	39	50
ME-4	12	38	50
ME-5	13	37	50
ME-6	14	36	50

Table 2: Optimization of Aqueous Phase

Formulation Code	Ingredients		
	IPM (%)	S_{mix} (1:1) (%)	Water (%)
ME-7	11	64	25
ME-8	11	59	30
ME-9	11	54	35
ME-10	11	49	40
ME-11	11	44	45
ME-12	11	39	50

Table 3: Optimization of S_{mix} Ratio

Formulation Code	Ingredients		
	IPM (%)	S_{mix} (54%)	Water (%)
ME-13	11	1:2	35
ME-14	11	1:3	35
ME-15	11	1:4	35
ME-16	11	2:1	35
ME-17	11	3:1	35
ME-18	11	4:1	35

Table 4: Optimized Formula for Microemulsion Formulation

Formulation Code	Ingredients		
	IPM (%)	S_{mix} (1:3) (%)	Water (%)
ME-19	11	54	35

the oil phase in microemulsion, the solubility of Ibuprofen in various oils were measured. Oils employed were Castor oil, Arachis oil, Isopropyl myristate (IPM), oleic acid, Olive oil and Coconut oil. The solubility of Ibuprofen in various oils was determined using the shake flask method. An excess amount of Ibuprofen was added in 2 mL of the oil in glass test tubes. After sealing, the mixture was vortexed for 10 min in order to facilitate proper mixing of Ibuprofen with the oils. Mixtures were then shaken on the rotary shaker for 24 h. Mixtures were then centrifuged for 15 min. From the supernatant liquid, 1 mL was taken and diluted suitably with methanol. The concentration of Ibuprofen in the supernatant was determined by using UV-Visible spectrophotometer (Shimadzu 1700, Japan) at 264 nm. Based on these results appropriate oil was selected and used in the preparation of microemulsion containing 1% w/w Ibuprofen.

Screening of Surfactants and Cosurfactants (Emulsification Study)

In order to find out appropriate surfactant and cosurfactant, a 10% w/w solution of surfactants and cosurfactants were preprared and in all the solutions drop by drop IPM was added. Surfactant and cosurfactant having the more capacity to solubilize the maximum amount of oil were selected to prepare the microemulsion. Tween 80 and pluronic F60 were employed as surfactants and PEG 200, PEG 400 and PEG 600 were employed as cosurfactants.

Formulation of Ibuprofen Microemulsion

Microemulsion was prepared by using water titration method. Ibuprofen was added to the oil and Surfactant: cosurfactant mixture (S_{mix}) and then the appropriate amount of water were added to the mixture drop by drop to form clear microemulsion system. Ibuprofen at 1% w/w was incorporated in optimized formulation. Different formulations of the microemulsion are shown in Table 1 to Table 4.

Preparation of Ibuprofen Microemulsion Based Gel (MBG)

Carbopol 940 was selected as gel matrix to prepare the MBG formulation. A weighed amount of carbopol 940 was soaked in the water for 2 h and then microemulsion was added to this solution. This was then neutralized by adding triethanolamine and finally MBG formed. The conventional gel formulation was prepared by adding

Table 5: Optimization of Amount of Microemulsion for MBG

Formulation Code	Amount of Water in which Carbopol 1 % w/w to be Soaked (%)	Amount of Ibuprofen ME (ME19) (%)
MBG-1	97.5	2.5
MBG-2	98	2
MBG-3	98.5	1.5
MBG-4	99	1
MBG-5	99.5	0.5

Table 6: Optimization of Carbopol 940 Concentration

Formulation Code	Amount of Carbopol 940 (% w/w)
MBG-6	0.5
MBG-7	1
MBG-8	1.5

Table 7: Solubility of Ibuprofen in Various Oils

Oils	Solubility (mg/ml)
Castor oil	68.22±5.32
Arachis oil	165.11±4.56
IPM	172.66±5.89
Olive oil	121.11±3.25
Oleic acid	160.22±2.59
Coconut oil	127.11±4.25

Table 8: *In-vitro* Permeation Parameters of Ibuprofen from the Formulations across the Hairless Mouse Skin

Formulation	Flux (µg/cm²/min)	Drug Release After 4 h (%)
Conventional gel	0.357	79
MBG	0.453	97.78

1% w/w Ibuprofen to PEG 400 and was gelled by the addition of Carbopol 940 (1% w/w) and triethanolamine.

EVALUATION PARAMETERS

Clarity

The clarity of various formulations was determined by visual inspection under black and white background

pH Measurement

A 10% w/w aqueous solution of gel was prepared and pH was measured using pH meter.

Spreadability Study

It was determined by wooden block and glass slide model developed in the laboratory. For the test, 1 gm of gel was uniformly spread between two glass slides and the entrapped air was removed by placing 500 gm weight for 5 min. The excess of gel was scrapped off. Weight of 80 gm was placed on one side of the model and the time required to separate the two slides was noted. Spreadability was calculated by using the following formula,

$$S=ML/T \quad (1)$$

Where; S=Spreadability, M=weight applied (80 gm), L=length of the glass slide (cm), T=time required for two slides to separate (sec).

Swelling Index [9]

Swelling of the polymer depends on the concentration of the polymer, ionic strength and the presence of water. To determine the swelling index of prepared topical gel, 1 gm of gel was taken on porous aluminum foil or a cellophane paper and then placed separately in a 50 mL beaker containing 10 mL phosphate buffer pH 7.4. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index was calculated as follows,

$$\text{Swelling Index (SI)}\ \% = [(Wt - Wo) / Wo] \times 100 \quad (3)$$

Where, SI (%) =Equilibrium percent swelling, Wt=weight of swollen gel after time t, Wo =original weight of gel at zero time.

Drug Content

A specific quantity of prepared and conventional gel containing drug equivalent to 10 mg was taken and dissolved in 10 mL methanol. The volumetric flask containing gel solution was shaken for 2 h on a mechanical shaker in order to get complete solubility of drug. The solution was then filtered and estimated spectrophotometrically at 264 nm using methanol as blank.

In-vitro Skin Permeation Study

In-vitro skin permeation study was performed by using Franz diffusion cell with an effective diffusion area of 4.9 cm^2. The excised skin sample (dorsal side of 5~6 weeks old hairless mice, 18~20 g) were clamped between the donor and the receptor chamber of Franz diffusion cell with the stratum corneum facing the donor chamber. Then, 1 g of MBG containing 0.05% w/w Ibuprofen was administrated onto the donor chamber. The receptor chamber was filled with 15 mL phosphate buffer pH 7.4. The receptor medium was maintained at 37±0.5°C and stirred at 500 rpm throughout the experiment. For each experiment, 1 mL sample was withdrawn from the donor compartment at predetermined time intervals and same volume was replaced with fresh phosphate buffer pH 7.4. The absorbance of withdrawn sample was measured after appropriate dilution at 264 nm to estimate concentration of Ibuprofen.

RESULTS AND DISCUSSION

Screening of Oils (Solubility Study)

Table 7 summarizes solubility of Ibuprofen in various oils at 30°C. Among all the oils Ibuprofen has shown the highest solubility in IPM followed by Arachis oil and oleic acid. Thus, IPM was selected as the oil phase for the development of the formulation.

Screening of Surfactants and Cosurfactants (Emulsification Study)

Among the different surfactants and cosurfactants employed in the emulsification study, Tween 80 and PEG 400 had the maximum capacity to solubilize the oil and hence Tween 80 and PEG 400 were selected as surfactant and cosurfactant respectively for the development of the microemulsion.

Formulation of Ibuprofen Microemulsion

Different components of the microemulsion were optimized for the formulation of the stable microemulsion. To optimize IPM proportion six different formulations (ME1–ME6) have been prepared. In all these six formulations proportion of water was kept constant (50%) allowing changing the IPM proportion from ME1-ME6. It was found that ME1-ME3 containing IPM 5, 10 and 11% respectively formed a clear and transparent microemulsion. Above 11% of IPM, appearance of microemulsion results in cloudy. Hence ME3 (IPM 11%) has selected for further studies. Similarly ME7-ME13 has been prepared for optimization of water and from the data ME9 (35% water) was selected for further studies. After optimizing IPM and water proportions, studies have been carried out (table 3) to select surfactant: co-surfactant ratio (S_{mix}). So from all the data finally the optimized proportion of different components that was used for preparation of stable microemulsion is shown in table 4.

Preparation of Ibuprofen Microemulsion Based Gel (MBG)

Microemulsions have lower viscosity and are difficult to apply on skin. So for the ease of application they are tried to be gelled with suitable gelling agent. Carbopol 940 was employed as gelling agent for Ibuprofen microemulsion. The amount of Ibuprofen microemulsion used for this purpose was optimized. Five different formulations were prepared as shown in Table 5. It was found that F5 batch containing 1% of microemulsion have shown clear and translucent gel as compared to all other formulations. Hence, Ibuprofen microemulsion used for this purpose contained 1% (w/w) Ibuprofen.

For the preparation of gel, amount of gelling agent was also optimized. Three different concentrations of Carbopol 940 were evaluated as shown in Table 6. It was observed that carbopol 940 at a concentration of 0.5% was unable to yield gel of acceptable consistency whereas at a concentration of 1.5% a very hard and rigid gel was formed. Only Carbopol 940 at a concentration of 1% w/w was able to thicken the microemulsion, could yield gel consistency without disturbing the microstructure of the Ibuprofen microemulsion.

Clarity

The gels prepared were translucent and homogenous with absence of lumps.

pH Measurement

It was previously reported that, for microemulsion to be non-irritant and safe for transdermal application, their pH has to fall in the physiologic accepted range for transdermal preparations, i.e., pH 4-7 units. pH measurements of 10% (w/w) aqueous solutions of the MBG system was 5.77 and that of conventional gel was 6.9. Therefore, the pH of both prepared gels was within the required range and was considered to be safe for topical application.

Spreadability Study

The rheological properties of topical preparations influence the performance of drug delivery systems. The spreadability is important for uniform and ease of application of topical preparation from patient compliance point of view. It was determined by wooden block and glass slide model developed in the laboratory. Spreadability of MBG was 33.8 gm.cm/sec and that of conventional gel was 14.76 gm.cm/sec. It indicates that MBG was easily spreadable with small amount of shear as compared to conventional gel.

Swelling Index

From the data it was found that MBG has greater percentage of swelling as compare to the conventional gel. Figure 2 shows graphical representation of swelling index study.

In-vitro Skin Permeation Study

Figure 3 shows the *in-vitro* permeation profiles of Ibuprofen (0.05%) through hairless mouse skins which was conducted using the Franz diffusion cell in occlusive conditions at 37°C. The permeation parameter of the formulations was presented in Table 8.

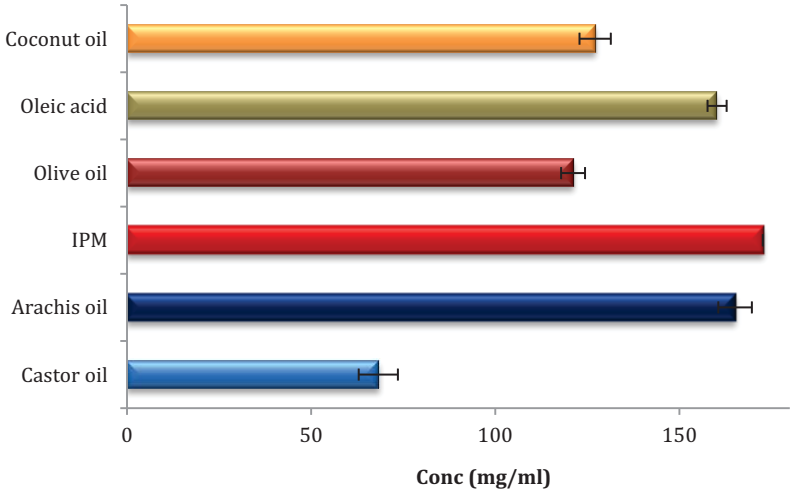

Figure 1: Solubility of ibuprofen in different oils

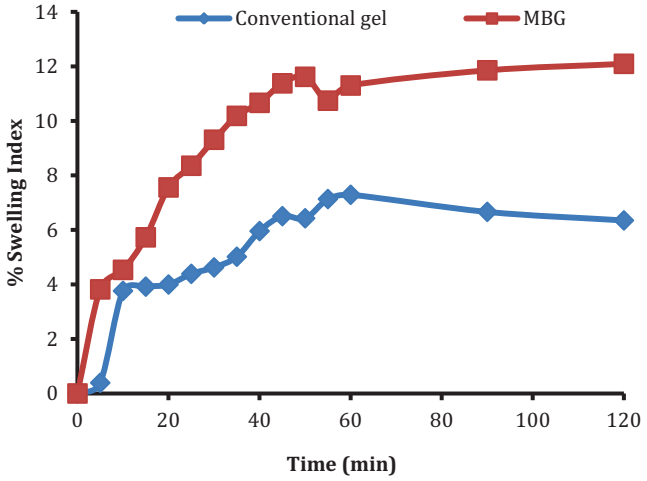

Figure 2: Swelling index study of ibuprofen gel

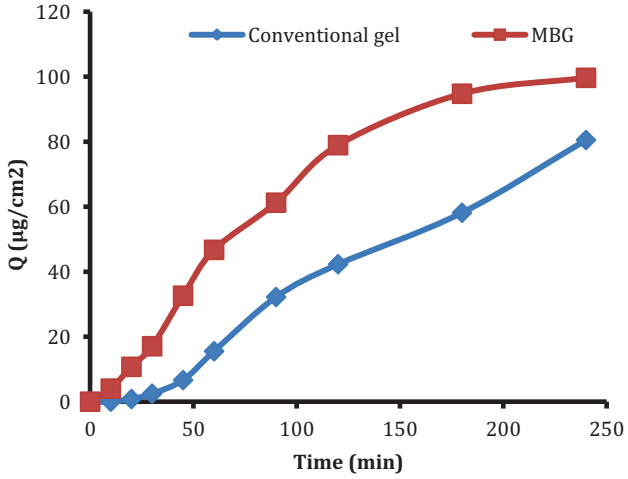

Figure 3: Permeation profiles of ibuprofen through hairless mouse skin from MBG and conventional gel formulations containing 0.05% of Ibuprofen

It was observed that the MBG showed higher drug permeation profile compared to its corresponding conventional gel, this could be due to the higher flux and high viscosity of MBG compared to that of conventional gel. The skin permeation of Ibuprofen determined for 4 h revealed that the prepared MBG was better in facilitating the drug penetration into the skin.

There are several mechanisms which could explain the ability of MBG to modulate drug transfer across the skin. One of the mechanism by which MBG may contribute to transdermal drug delivery may be ascribed to the good adhesiveness to skin due to the suitable viscosity of MBGs. Moreover, Carbopol 940 in MBG could enhance the skin permeation of Ibuprofen because of the tight contact of the preparation with skin and delayed release time. [10, 11] Moreover, it has been reported that the components of the microemulsion also would contribute to the enhanced drug transport across the skin. [12] Additionally, the characteristics of microemulsion such as high drug concentration, the small droplet diameter and the reaction between the surfactants and skin stratum corneum may also have contributed to the permeation enhancement.

CONCLUSION

In this study, Ibuprofen microemulsion was prepared and transferred into the gel using carbopol 940. Microemulsion consisting of 1% Ibuprofen, 11% IPM, 35% water and 54% S_{mix} were used for the formulation of the gel. The prepared MBG was superior to its conventional gel formulation in terms of clarity, spreadability and swelling index study. *In-vitro* skin permeation study showed that the permeation rate of Ibuprofen was much higher as compared to its conventional gel. Hence, MBG is a promising vehicle and viable alternative to conventional formulations by virtue of its ability to avoid the oral side effects and enhance permeation for the topical delivery.

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