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COMPARATIVE STUDY OF MICROEMULSION BASED GEL: HYDROGEL AND ORGANOGEL

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ABSTRACT:
The objective of the present investigation was to develop and evaluate microemulsion based gel for the topical delivery. Clobetasol propionate (CP) was taken as model drug for the study. The optimized microemulsion was incorporated in gelling agent hydrogel (carbopol 934 P) and organogel (alkatrene granules). Both the gels were evaluated for their potential to gel the microemulsion by varying their concentration without affecting its structure. The gels were compared by performing evaluation parameters such as rheological parameters, spreadability, *in vitro* and *ex vivo* permeation study. Optimized microemulsion based gel of alkatrene granules was found to exhibit significant as compared to Carbopol 934 P gel. The *in vitro* and *ex vivo* permeation results showed higher permeation and retention of alkatrene gel. Thus the present study indicates that microemulsion based alkatrene gel can be a promising vehicle for the topical delivery of drugs based on the compatibility of microemulsion system with gel.

Keywords: Hydrogel, Organogel, Rheology, Sreadability, *In vitro* study, *Ex vivo* study.

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INTRODUCTION

The skin is an exceptionally effective barrier to most drugs for therapeutic treatment. Topical and transdermal products are important classes of drug delivery systems and their use in therapy is becoming more widespread. Although topical formulations to treat ailments have existed from ancient times, transdermal products, for which the skin is used as an alternative route for systemic and regional therapy, are relatively new entities. The purpose of topical dosage forms is to conveniently deliver drugs to a localized area of the skin[1]. Although microemulsions (ME) can be used to deliver drugs via several routes, these versatile systems have been extensively studied as vehicles for topical administration. However, due to low viscosity of microemulsion, their less retention capacity in the skin restrains its application in the pharmaceutical industry[2,3]. To overcome this disadvantage, gelling agents such as Carbopol 940, xanthan gum and carrageenan have been added into the microemulsion for forming microemulsion based gel in order to increase its viscosity which could be suitable for topical application[4]. Moreover, microemulsion based gel prevents the absorption of drug in the blood stream and provide higher drug accumulation in the skin for efficient action. Barot et al. reported a higher retention of terbinafine in the human cadaver skin after topical application of microemulsion based gel when compared to microemulsion containing the same drug[5]. Rao and Murthy reported that HPMC gels containing CP loaded liposomes when applied topically showed lower absorption of the drug in the bloodstream when compared to the same formulation containing free drug[6]. Zhu et al. showed that Panciclovir loaded microemulsion based gel has excellent sustained release capability and enhanced skin permeation and retention due to viscosity imparted by Carbomer 940[3]. Composition and structure of microemulsion enables them to incorporate greater amount of drug than other topical formulations such as ointments, creams, gels and lotions. These are characterized by high viscosity

and complete optical transparency. The gels are emerging as carriers for drug molecules with diverse physicochemical properties including macromolecules. Transdermal transport rates of scopolamine and broxaterol from organogels were faster than commercial patches[7]. Similarly, improved skin penetration of indomethacin and diclofenac has been observed with organogels in isopropyl palmitate[8]. Piroxicam has been successfully incorporated in lecithin organogels[9]. Recently results have shown that ketorolac tromethamine could be incorporated at high concentrations into lecithin organogels[10].

Clobetasol propionate possesses low water solubility and has log P value 3 which makes it suitable for encapsulating it in microemulsion globules. The topical delivery of CP encapsulated in microemulsion could enhance its percutaneous absorption and retention in the skin, which is necessary for the effective treatment of autoimmune disease. Enhanced retention in the skin and minimal absorption could minimize the side effects associated with the drug. Hence, the objective of the present investigation was to develop microemulsion based gel of CP.

The purpose of the present we were used our optimized microemulsion containing 3% isopropyle myristate, 15% cremophore EL and 30% isopropyl alcohol[11]. The optimized ME then incorporated into gel. It was investigated for the comparative study of microemulsion based hydrogel and organogel to improve bioavailability of water insoluble drugs and to reduce adverse effects.

MATERIAL AND METHODS

Materials

Clobetasol propionate was obtained as a gift sample from Sumit Laboratories (Vapi, India). Carbopol 934P was purchased from Corel Pharma (Ahmedabad, India) to prepare hydrogel. Alkatrene granules were obtained from Suvik Pharma. (Gandhinagar, India) for the preparation of organogel. An organic base, triethanolamine (TEA, Sigma, UK) was used for the neutralisation of the hydrogels. Light liquid parafin was received as gift sample from Suvik Pharma. (Gandhinagar, India),

Formulation of microemulsion based gel

Microemulsions tend to drain out when applied on the skin due to their low viscosity and thus the amount of drug reaching the target site would be quite less. Thus, the viscosity of ME was required to be increased with suitable gelling agent[12].

Microemulsion based hydrogel (MBC)

Gel was prepared using different polymers like Carbopol 934P in the 1% concentration. Carbopol 934P was allowed to hydrate in sufficient quantity of water for 24 h at room temperature. Further, microemulsion containing CP was gradually added to the Carbopol 934P dispersion under magnetic stirring. The dispersion was neutralized with triethanolamine to obtain microemulsion based hydrogel with adequate consistency suitable for topical application[13].

Microemulsion based organogel (MBA)[14]

A pharmaceutical preparation of gelatin in non-aqueous medium is the manufacturing of alkatrene gel (also called plastibase or jelen). Weighed quantity of alkatrene granules (10%) were dispersed in the Liquid paraffin (90%). The mixture than heated at the temperature greater than 100^0C with continuous stirring until the alkatrene granules gets dissolved. Suddenly lower the temperature ($<5^0$C) with continuous stirring. Precipitates of polymer were appeared which formed the opaque and smooth gel. Microemulsion containing CP was gradually added to the alkatrene dispersion under magnetic stirring to get desired consistency.

Characterization of microemulsion based gel

a) Viscosity and rheology studies

The viscosity of microemulsion was determined as such without dilution using Brookfield DV+II Pro Rheometer (Brookfield Engineering Labs, USA) with spindle DIN-87 in 5 g samples using small sample holder. The rheological properties of microemulsion based gel were studied by continuous shear investigations using the same equipment using the appropriate spindle. The shear rate was increased in ascending order from 0 to 200 D (1/s) (up curve) and then decreased from 200 to 0 D (1/s) (down curve) and the resulting shear stress (Pa) was measured[15]. The measurements were done at 25^0C.

b) Spreadability

Spreadability of ME loaded gel was determined using a wooden block and glass slide apparatus[16]. A weight of 100g was added to the pan and time was noted for the upper slide (movable) to separate completely from the fixed slide. Spreadability was expressed as the ratio of time required for the upper plate to slide down (t) by weight of the sample (w).

c) Assay

250 mg of gel was weighed accurately and dissolved in methanol and centrifuged at 10,000 rpm for 10 minutes. The aqueous layer was separated, transferred to a 5ml volumetric flask and diluted upto 5ml with acetate buffer. The resulting solution was analyzed by UV-Visible spectrophotometry analytical method. Gel without the drug was prepared and treated as above and used as blank.

In vitro release studies

In-vitro release studies were performed using Franz diffusion cell with an effective diffusion area was used for the experiment[16]. Dialysis membrane - 70 (LA 393),

having the MWCO of 12000, average flat width of 29.31 mm, average diameter of 17.5 mm and approximate capacity of 2.41 ml/cm, obtained from Himedia Laboratories Pvt. Ltd. was used for the study. The drug loaded gel was placed on the membrane which was placed between the donor and receptor compartment of the Franz diffusion cell.

Weighed quantity of hydrogel and organogel enriched with CP loaded ME were applied to the donor compartment. At predetermined time intervals the fluid in the receptor chamber was sampled over a period of 8 h and analyzed using spectroscopic method of analysis.

***Ex-vivo* permeation studies**

Ex-vivo permeation studies were carried out employing healthy male albino Wistar rats (200±15 g). Rat skin was selected for the *ex-vivo* studies owing to its structural similarities to human skin. The experiments were performed after getting approval from the Institutional Animal Ethics Committee of K. B. Institute of Pharmaceutical Education and Research (KBIPER), Gandhinagar, India. The rats were housed in cages with adequate facility of food and water prior to use. Hairs from the abdominal region of the rats were shaved with electronic hair remover without scratching or damaging the surface in order to maintain the integrity of the skin. The rats were sacrificed and full thickness abdominal skin was excised. Subcutaneous fat tissue from the visceral side of the skin was removed surgically and wiped three to four times with cotton swab soaked in IPA to remove any fat material adhered to skin. A specific portion of the skin was cut and used for the permeation study after washing it with distilled water[17]. A Franz diffusion cell with an effective diffusion area was used for the experiment. The animal skin was placed between the donor and receptor compartments of Franz diffusion cell with the *stratum corneum* facing donor compartment. Both gel formulations were taken on donor compartment and the release profiles were taken. The cumulative amount of drug permeated through the skin (Q_n) was determined as per the following equation (1)

$$Q_n = \frac{C_n * V_0 + \sum_{i=1}^{n-1} C_i * V_i}{S} \quad (1)$$

RESULTS AND DISCUSSION

Rheological studies: Particle size is known to be an important rheological variable of dispersed systems. The greater mean size and the widest size distribution will preferentially show more viscous properties as compared to the formulations with lower particle size. The rheogram obtained by plotting shear rate D [1/s] versus shear stress τ [Pa] revealed no significant hysterises effects and up curve–down curve practically coincided under the considered experimental conditions (Figure 1A) which interprets the absence of real thixotropic system[18]. While figure 1B showed that the down curve is slightly downwards than the up curve which shows the evidence of slight thixotropic behaviour of the system. Both the gel began to flow only after a shearing stress, corresponding to the yield value was exceeded, after which the viscosity decreased with increasing rate of shear indicating non-Newtonian system with pseudoplastic flow behaviour especially in MBC. While in case of MBA, flow was thixotropic with non-Newtonian system with pseudoplastic flow[19]. Due to smaller particle size of ME its incorporation resulted in only marginal increase in the viscosity of plain gel base. For the drug content estimation both showed almost 99% of clobetasol propionate even after incorporation to gel (Table 1).

Table 1: Rheological parameters of MBC and MBA

Rheological parameters	MBC	MBA
Viscosity* (Pa-s)	25.473 ± 1.08	23.047 ± 1.12
Yield stress (Pa)	32.86 ± 1.10	29.73 ± 0.96
Spreadability (sec/gm)	4.73 ± 0.55	7.76 ± 0.51
Assay		
Drug content	99.2%	99.6%

Note: * First viscosity reading when torque exceeds 10

Spreadability:

The potential usefulness as a topical dosage form with desired semisolid consistency was demonstrated by spreadability values indicating the ease of application on the skin. Spreadability values suggesting easy spreading on the skin and good consistency. Both ME based gel showed easy application and time required was higher as that of reference but MBC had less time as compare to MBA. This is due to higher consistency of organogel (MBA). Figure 2 showed the significant time was required to apply organogel which suggested that microemulsion based alkaterene gel required to be rubbed for 5-10 minutes to achieve desired penetration.

***In-vitro* and *Ex-vivo* permeation studies**

In vitro and ex vivo drug release of hydrogel was compared to organogel. In both studies drug permeation of MBC showed higher release rate as compare to MBA which gave controlled drug release pattern (Figure 3 and Figure 4) up to 8 h. The drug release from MBC was much higher and faster as compared to the MBA. The release of clobetasol propionate from hydrogel gel was 5 times higher at the end of 8 h. Carbopol 934P based gel in a concentration of 1% showed release pattern having permeability coefficient (Kp=8.09) and alkaterene 10% demonstrated permeability coefficient (Kp=6.4) also having good spreadability. Cumulative clobetasol permeation was less for MBA, which implies greater retention of drug in to skin than MEC.

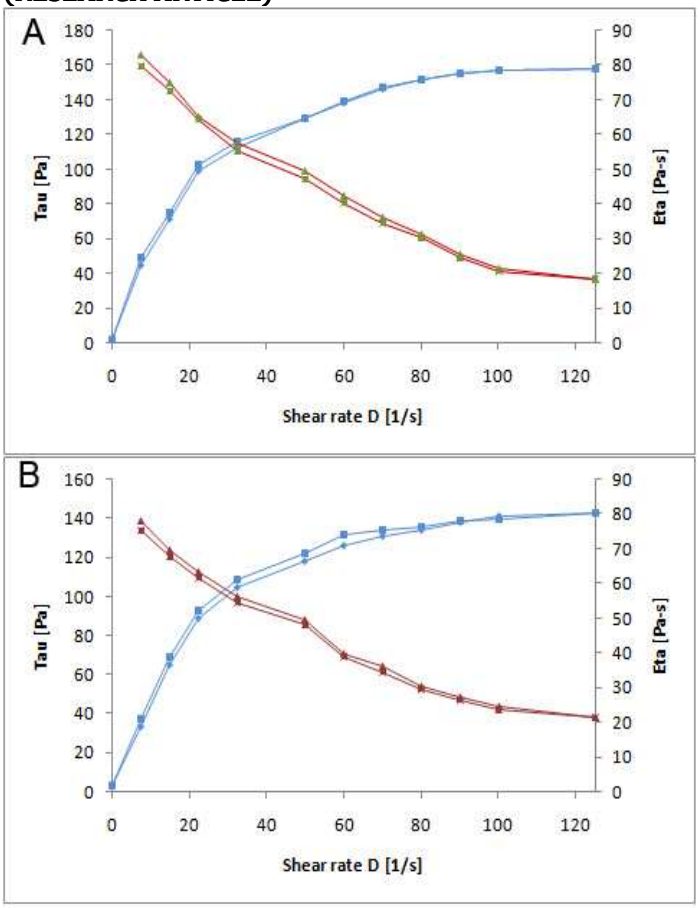
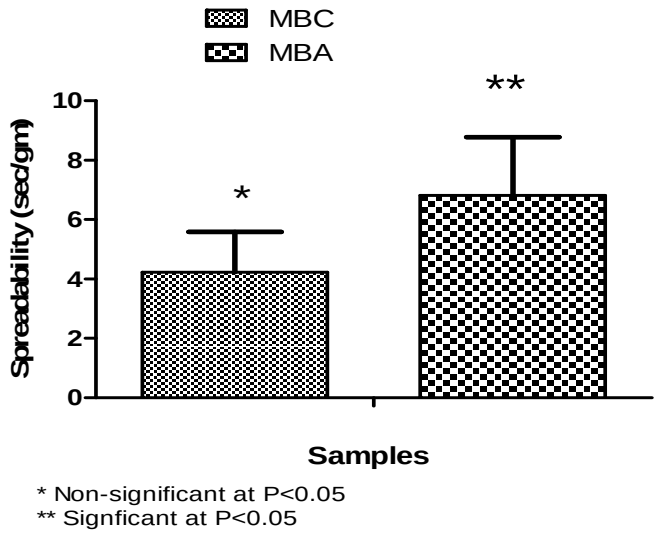


Fig. 1: Flow curve; A) Hydrogel (MBC) and B) Organogel (MBA)



* Non-significant at P<0.05
** Signficant at P<0.05

Fig. 2: Spreadability profile of gel formulations

The globules of microemulsion containing drug could increase the permeation through the skin by fluidization of lipid bilayers of the *stratum corneum* which is possible due to the presence of surfactants and co-surfactants[19].

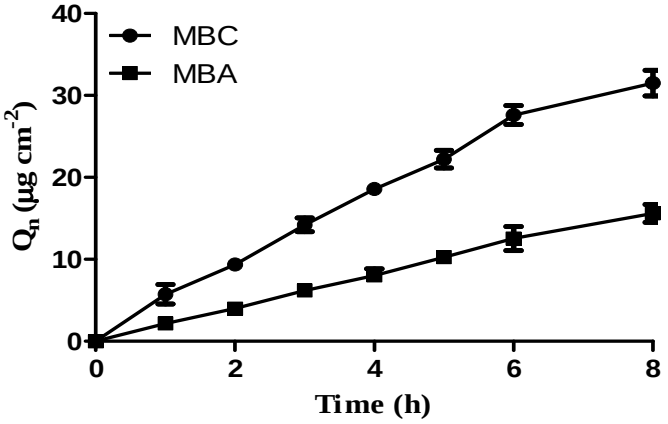


Fig. 3: *In vitro* release study of hydrogel (MBC) and organogel (MBA)

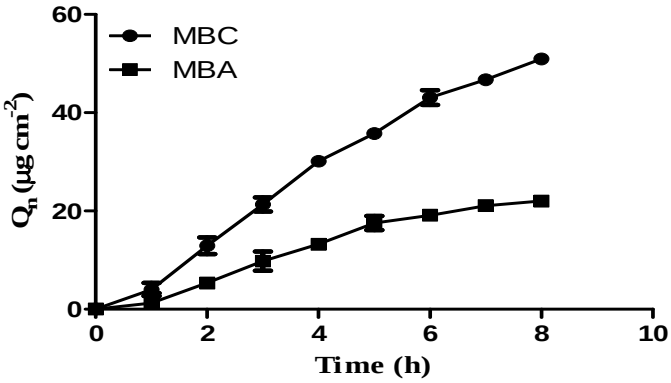


Figure 4: *Ex vivo* release study of hydrogel (MBC) and organogel (MBA)

CONCLUSION

This study has been concerned with the comparison of different in vitro and ex vivo methods for studying topical delivery. Dynamic oscillatory rheology and spreadbility were used to measure the bulk properties of the polymer/mucin mixtures relative to the polymer alone, while speadability study represented time required to spread the gel at application site for desired penetration. Thus MBA based microemulsion gel not only showed superior performance and better safety but would be more appealing with better patient compliance specially to treat the dermal diseases when applied to the skin as compared to the MBC.

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(RESEARCH ARTICLE)

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