Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Microemulsion Based Hydrogel Formulation for Topical Drug Delivery - A Concise Review

JAMEEL AHMED S MULLA* AND BIRADEV S KARANDE

Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Karad, Maharashtra, India - 415111

ARTICLE DETAILS

Article history:
Received on 15 April 2021
Modified on 22 May 2021
Accepted on 25 May 2021

Keywords:
Microemulasion,
Microemulsion-based Hydrogel,
Ternary Phase Diagram,
Preparation,
Characterization.

ABSTRACT

A hydrogel is a network of water-insoluble polymer chains that can also be found as a colloidal gel with water as the dispersion medium. Hydrogels are natural or manufactured polymers that are superabsorbent (they can hold over 99 percent water). Topical medicines are utilized for localized effects at the application site due to medication penetration into the deeper layers of the skin or mucous membranes. Microemulsions are thermodynamically stable, fluid, transparent (or translucent) colloidal dispersions made up of an oil phase, aqueous phase, surfactant, and co-surfactant in appropriate ratios that form a single optically isotropic solution with droplet diameters typically ranging from 10 to 100 nanometers. Transparency, low viscosity, and, most importantly, thermodynamic stability and capacity to form spontaneously separate micro-emulsions from conventional emulsions. As a topical medication delivery system, micro-emulsions provide a number of advantages over standard creams, gels, and solutions. The Hydrogel technology based on microemulsion will be able to sustain therapeutic concentration at the site of action while also increasing bioavailability. This review focuses on the method of preparation, characterization, evaluation, and stability investigations of microemulsion-based hydrogel.

INTRODUCTION

Pharmaceutical research nowadays is focused on finding appropriate drug delivery systems to meet the therapeutic demands of patients. The discovery of new chemical entities should coincide with the development of novel drug delivery systems, as the majority of compounds identified were hydrophobic in nature. Microemulsion has gained significance in the effective delivery of hydrophobic medications as part of the push to create innovative delivery strategies [1]. In recent years, the creation of so-called "intelligent" or "smart" hydrogels has gotten a lot of attention in soft matter research. Hydrogels having a high water content that can undergo reversible phase transitions in response to changes in temperature, pH, magnetic field, light, solvent, and ionic strength are known as "intelligent" hydrogels.

Author for Correspondence:
Email: jameelahmed5@rediffmail.com

Hydrogels made of N-isopropyl acrylamide (NiPAAm) are known to change volume and transparency when heated above 32°C, the gel's lower critical solution temperature (LCST) [2]. Microemulsion is a transparent emulsion that is frequently referred to as O/W or W/O emulsion.

Product with droplet sizes ranging from 10 to 100 nm and little tendency to agglomerate. It is made up of a proper ratio of oil phase, surfactant, co-surfactant, and aqueous phase. Transparency, optical isotropy, low viscosity, and thermodynamic stability are among microemulsion's physicochemical features. Topical drug administration appears to be a viable route of drug administration. Several mechanisms have been postulated to explain the benefits of microemulsions for drug administration in the topical and dermal areas. First, due to the huge amount of a drug integrated in the formulation, the thermodynamics towards the skin are boosted. Second, the drug's higher thermodynamic activity could help it partition into the skin. Third, by serving as permeation enhancers, the microemulsion components may diminish the

stratum corneum's diffusional barrier and improve the rate of drug permeation into the skin. The penetration ability of formulations may also be affected by the hydration effect of microemulsion on the stratum corneum [3].

Several drug penetration augmentation strategies have been investigated via the transdermal route in recent years. Microemulsion formulations are one of the most promising among them. Microemulsions, as colloidal carriers, are one of the promising technologies that has sparked a lot of interest in penetration augmentation these days. It is made up of an oil phase, a surfactant, a co-surfactant, and an aqueous phase in the proper proportions [4].

Several alternative processes have been postulated to explain the increased drug penetration through the skin by microemulsions, including:

1) Due to their high solubility potential, promote thermodynamic activity towards the skin;
2) Microemulsion components can operate as permeation enhancers by lowering the stratum corneum's diffusional barrier and enhancing drug penetration into the skin;
3) Increase the drug's penetration rate from microemulsions by lowering the drug's affinity for the microemulsion's internal phase and so favoring its partitioning into the stratum corneum [5].

Selection of Oil, Surfactant, and Co-Surfactant for Microemulsion:

Selection of oil, surfactant, and co-surfactant are based on the solubility data. Pillai *et. al.* reports the solubility of butenafine in various oils and surfactants, such as isopropyl palmitate, aerosol OT, and sorbitan monooleate, was examined in order to select distinct components for producing butenafine microemulsions. An excess of butenafine was added to 10 mL of each of the selected oils and surfactants, and the mixture was agitated for 24 hours at 20°C. The supernatant was carefully drained off, filtered, and spectrophotometrically examined at 223 nm [6]. Sah *et. al.* studied the solubility of methoxsalen in various oils such as isopropyl myristate, isopropyl palmitate, oleic acid, and ethyl oleate to find the best oil to utilize as the oil phase in microemulsions and give optimum methoxsalen skin permeation [7]. Chen *et. al.* reports the oils were utilized in the creation of various microemulsions containing 3% ibuprofen, 3% oil, 30% Tween 80, 15% PG, and 49% water, and their influence on the skin penetration of ibuprofen from the generated microemulsions was assessed *in vitro* using pig-skin [8].

Pseudo-Ternary Phase Diagram Construction

The CHEMIX school 3.51 software can be used to create pseudo-ternary phase diagrams (Arne Standnes) [9]. Based on the solubility investigation, the oil phase was chosen as benzyl alcohol, and the surfactant was chosen as N-methyl-2-pyrrolidone. The co-surfactant was made up of a 3:2 weight ratio of ethanol and phosphatidylcholine. The pseudo-ternary phase diagrams were then made by mixing homogeneous liquid mixes of oil, surfactant, and co-surfactant with water at room temperature. The surfactant and co-surfactant mixture (Smix) was first made with a weight ratio of 1:2 or 1:3[10]. Oil, surfactant, and co-surfactant solutions were created for each phase diagram and then diluted with water by adding water drop by drop using a micropipette. The samples were divided into two categories: optically clear and turbid. Translucent and isotropic mixes were identified as microemulsion areas. The percentages of the three phases, i.e. oil, water, and a surfactant/co-surfactant mixture, were calculated [6].

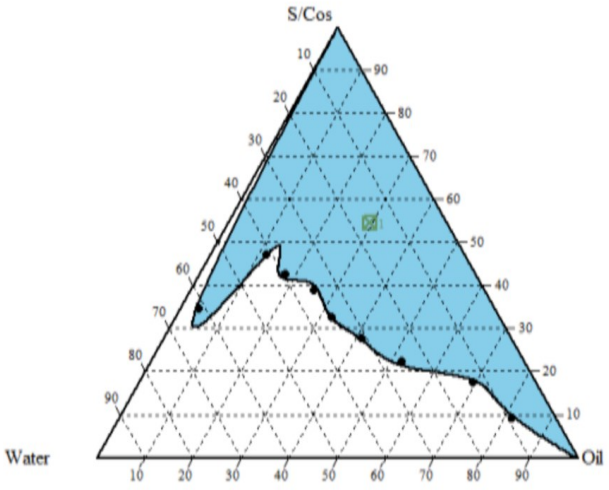

Figure 1: Microemulsion pseudoternary phase diagram. The shaded portion indicates microemulsion region in phase diagram

Microemulsion Preparation:

Almost all administration routes have been used to leverage the unique carriers. Drug-carrier interactions are typically noncovalent, owing to the combined strength of weak binding forces. With the advancement of technology and the desire for specialized distribution, such as

microemulsions, many newer carriers are emerging. Microemulsions are isotropic combinations of oil, water, and surfactant, often in combination with a cosurfactant that are transparent and stable. Pharmaceutical scientists are currently interested in these systems because they have the potential to operate as drug delivery vehicles by including a wide range of pharmacological compounds. Spontaneous creation, ease of manufacture and scale-up, thermodynamic stability, and increased drug solubilization and bioavailability are all advantages [11].

Lornoxicam (1 %w/w) was dissolved in an oily phase containing camphor and menthol in equal amounts. After that, the lornoxicam solution was combined with a surfactant and co-surfactant mixture. Finally, a suitable amount of water was added drop by drop to the lornoxicam solution mixture to create a microemulsion [12].

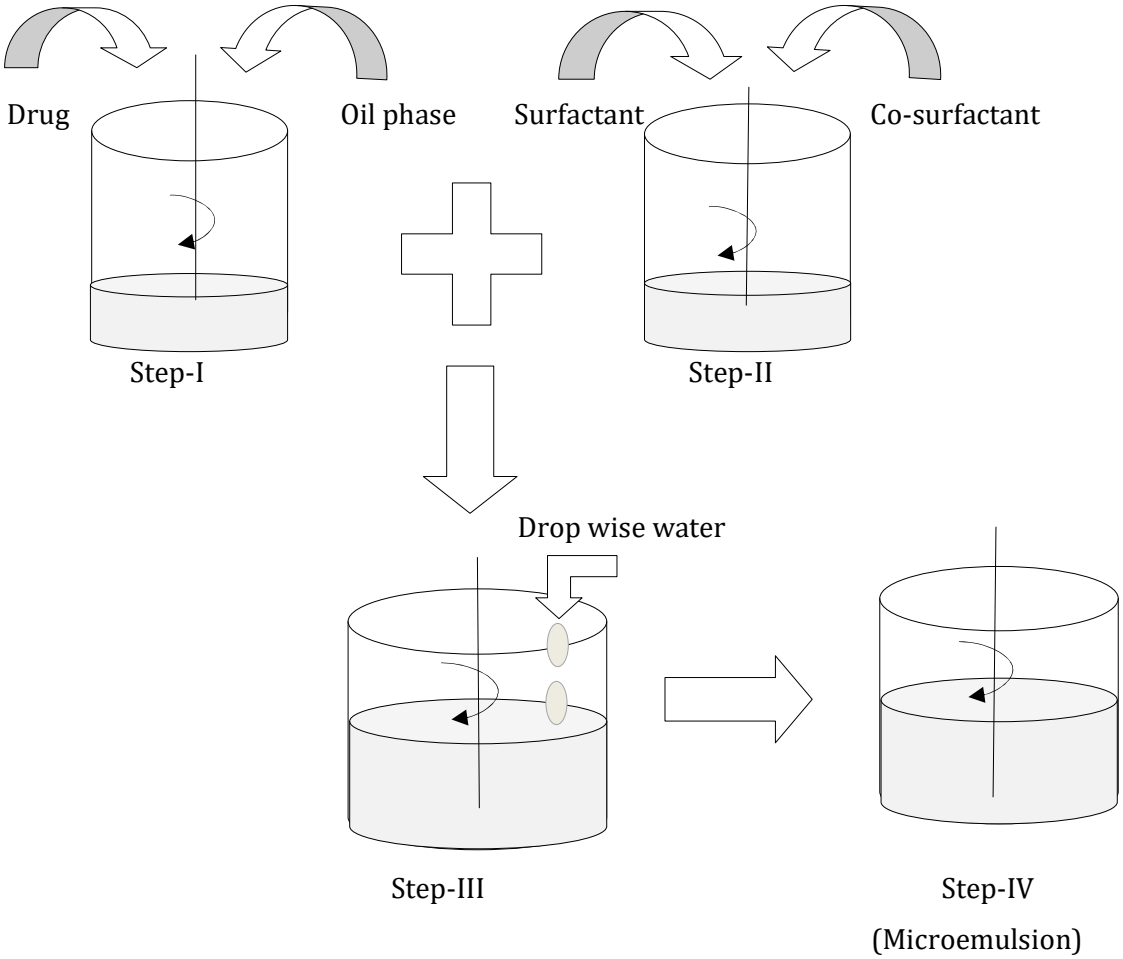

Figure 2: Preparation of microemulsion

Microemulsion-Loaded Hydrogel Preparation

As a potential topical delivery system, microemulsion-based hydrogel (MBH) formulations have sparked a lot of interest. The presence of distinct polarity microdomains within a single-phase solution allows for the solubilization of both hydrophilic and lipophilic molecules. When compared to a solvent without a surfactant system, micro emulsions have advantages such as thermodynamic stability, optical clarity, ease of manufacture, and high diffusion and absorption rates. Furthermore, the components in micro emulsion have been shown to lower the stratum corneum diffusion barrier and increase medication penetration. As a result, it appears to be a viable method of drug administration for both transdermal and dermal drug delivery. Microemulsion's low viscosity, on the other hand, limits its use in the pharmaceutical business. Various gelling agents, such as gelatin, carbomer 940, xanthan gum, and carrageenan, are added to the microemulsion to generate microemulsion-based hydrogels (MBHs) to overcome this drawback [11].

Table 1: Reported microemulsion based hydrogel formulations

Sl.No	Drug	Microemulsion based system			Hydrogel/ Gelling agent	Reference
		Oil phase	Surfactant	Co-surfactant		
1	Dexamethasone	Almond oil, linseed oil, nutmeg oil, olive oil	Egg Lecithin	Isopropyl alcohol (IPA).	Carbopol 934	[17]
2	Aceclofenac	Castor oil	Tween 80	ethanol	Xanthan gum, methylparaben	[9]
3	Propranolol hydrochloride	isopropyl myristate, Capryol 90, Castor oil, oleic acid.	Lansurf SMO 81, Lansurf SMO 80, Lansurf SMO 20, Cremophor RH 40, Tween 65.	ethanol, IPA and propylene glycol.	Carbopol ETD 2020, HPMC K4M.	[5]
4	Methoxsalen	Isopropyl myristate, Isopropyl palmitate, Oleic acid, Ethyl oleate.	Tween 80	propylene glycol	Carbopol 934	[7]
5	Lornoxicam	Camphor , Menthol.	Tween 80	Ethanol	HPMC K15M, Carbopol 934p and Xanthan Gum.	[12]
6	Econazole nitrate	oleic acid,	Tween 80	Polyethylene glycol400	carbopol 934P	[11]
7	Metoprolol tartrate	Captex 355, Captex 500, Capmul MCM, Captex GTO, Labrafil M2125CS, isopropyl myristate, oleic acid and castor oil.	(Solutol HS 15, Cremophor RH40, Cremophor EL, Lansurf SML20, Lansurf SMO 80, Lansurf OA 10, Lansurf OA14, Caprol MPGO and Labrasol.	ethanol, propyleneglycol, tetraglycol and Lauro-glycol 90	Carbopol EDT 2020	[23]
8	Ibuprofen	Isopropyl myristate, Isopropyl palmitate, Oleic acid, Ethyl oleate	Tween 80	Propylene glycol (PG)	Xanthan gum	[8]
9	Fluconazole	(Lauroglycol 90, Transcutol P, castor oil, Captex 355 and Captex 500),	Solutol HS 15, Monomuls 90-O 18,Eumulgin B1PHA, Lansurf SML 20, Lansurf SMO 81, Lansurf OA 10, Lansurf OA 14 and Lansurf CO 12.	ethanol, isopropyl alcohol and propyleneglycol	Carbopol EDT 2020	[22]
10	Valacyclovir Hydrochloride	Iso propyl myristate, Oleic acid, Olive oil , Castor oil, Peeperment oil	Tween 80, Tween 20, Span 20)	Ethanol, Di Methyl Sulfoxide	Carbopol 934	[16]
11	Ibuprofen	castor oil, isopropyl myristate	octoxynol-12, polysorbate-20,	polyethylene glycol-40	xanthan gum	[24]
12	Butenafine hydrochloride	isopropyl palmitate	aerosol OT	Sorbitan monooleate	Carbopol 940, HPMC K4 M	[6]
13	Ibuprofen	camphor and menthol	Tween 80	ethanol (90% v/v)	carbopol 940	[20]
14	Minoxidil	oleic acid	Tween 80, Tween 20,	Polyethyleneglycol 200,Propyleneglycol.	hydroxypropyl cellulose	[4]
15	Voriconazole	Benzyl alcohol, Tetraglycol, Cotton oil, Soybean oil, Ethyl oleate.	NMP, Transcutol, Tween 20, Tween 80, Span 80.	Ethanol	Carbopol 940 xanthan gum	[10]
16	Itraconazole	benzyl alcohol	Transcutol	Ethanol , phasphatidylcholine	Carbopol, xanthan gum	[22]
17	Metronidazole	captex 500	tween 80	acconon CC6	Carbopol 940	[15]
18	Butenafine hydrochloride	isopropyl palmitate	aerosol OT	Sorbitan monooleate	Carbopol 940, HPMC K4 M	[6]
19	Bifonazole	Oleic acid,	Tween 80	Isopropyl alcohol	HPMC K100M	[9]
20	Sertaconazole	oleic acid	Tween 80,	propylene glycol	Carbopol 940	[3]
21	Mepivacaine	oleic acid	Labrasol	Transcutol P	Carbopol 980	[25]
22	Fluconazole	isopropyl myristate , olive oil, oleic acid, triacetin, cotton seed oil.	Tween 80, tween 20, cremophor EL	ethanol, butanol, PEG600, PEG200.	carbopol 934	[19]

Based on earlier research, carbomer 940 was chosen as the hydrogel matrix. The MBH containing penciclovir was made according to the standard procedure. Carbomer 940 was swollen in a small amount of water for 24 hours to generate a high viscous solution, and then the penciclovir-loaded microemulsion was slowly added to the viscous Carbomer 940 solution while magnetic stirring was performed. The pH levels were then adjusted to 6-9, and MBH was produced. Carbomer 940 was found in MBH at a quantity of 0.6 percent (w/w) [13].

A spray-by-spray (SbS) crosslinking approach was used to create hydrogels. At each actuation, the pharmaceutical-grade spray pump sprays exactly 140 µL of an alginate (Alg) solution at 1% w/v. The following is how the SbS method got standardized: On a mildly damp glass petri dish (36 mm diameter), a 1 percent (w/v) Alg aqueous solution was sprayed twice, followed by a single spray of a 2 percent (w/v) $CaCl_2$ aqueous gelling solution. Instantly, a thin layer of hydrogel formed. For each preparation, three layers were deposited, one on top of the other. Only the Tea Tree Oil microemulsion at 20% (Me_{TTO20}) formulation was chosen for the manufacture of ME-containing hydrogels, and it was incorporated into an Alg hydrogel by dispersing 20 percent (v/v) of MeTTO20 in Alg solution (1 percent w/v) under magnetic stirring [14].

Microemulsion and MBH Characterization

pH* Level*:

A digital pH meter was used to determine the pH of hydrogel compositions. Using a calibrated digital pH meter at 25°C, the pH of each formulation was measured in triplicate and average results were calculated [12]. A digital pH meter (Infra Instruments Pvt. Ltd., Chennai, India) was used to measure the pH of the dispersion at 20°C. 1 g of gel was carefully weighed and dispersed in 10 ml of clean water. Before each usage, the pH meter was calibrated with buffered solutions of various pH.

Measuring the Viscosity:

To determine the flow behavior of the produced hydrogels, rheological tests can be carried out. Pandey S *et. al.* utilized Brookfield synchrolectric viscometer to determine the viscosity [15]. Microemulsion was measured using Spindle number 62 after it was poured into a 250 mL beaker [11]. For each sample, experiments can be carried out in triplicate, and the results were provided as an average standard deviation [16].

Microemulsion Droplet Size and Conductivity Measurements:

The negative zeta potential suggests that the microemulsion globules were free of charge, indicating that the system was stable. Because there was no charge on the globules, there was no flocculation, and the microemulsion was found to be stable [17].

Ahmed A *et. al.* used photon correlation spectroscopy to determine the average droplet size and polydispersity index of the microemulsion at 25±0.5°C using a He-Ne laser at 632 nm. A CM 180 conductometer (Elico, India) was used to measure the microemulsion's conductivity [18]. Transmission electron microscopy (TEM) is a type of electron microscopy that examines the structure of a sample. TEM was used to determine the form and morphology of the microemulsion droplet. The photomicrograph depicts the droplet's spherical shape and nano size range. It also demonstrates that decreasing the nano size range increases the microemulsion's transparency [7].

Scanning Electron Microscopy (SEM)

Zhu W *et. al.* reported that photomicrographs of the formulation taken with a scanning electron microscope reveal Smooth, oval, and discrete particles arose from the optimized formulation. The skin was a multilayered organ with several histological layers on anatomical level. The stratified, avascular, cellular epidermis, the underlying dermis of connective tissue, and the subcutaneous fat layer were the three tissue layers that were commonly described. Furthermore, many skin appendages were supported by the highly vascularized dermis and epidermis. By examining section photomicrographs and SEM photographs of skins before and after treatment, the effect of microemulsion and MBH on skin was examined [13].

Kamaria P *et. al.* also reported that photomicrographs of the formulation taken with a scanning electron microscope reveal smooth, oval, and discrete particles arose from the optimized formulation [16].

Microemulasion and Microemulsion-Based Hydrogel Stability:

The thermodynamic stability of the produced microemulasion was examined using a freeze-thaw cycle (21 to 25°C) followed by centrifugation at 13000 rpm for 30 minutes and 4000 rpm for 4 hours. Three freeze-thaw cycles

were also performed on the microemulasion to observe any phase separation and assess physical stability [19]. The optimized microemulsion-based hydrogel formulation was put in PVC collapsible tubes and stored for a period of six months at three different temperatures (4, 25 and 40°C). Total drug concentration, pH, transparency, clarity, non-grittiness, and color change were all measured in samples taken at regular intervals [15]. The hydrogel thickened microemulsion demonstrated good physical stability in the centrifuge test [20].

Permeation Studies In Vitro:

Zhang YT *et. al.* carried out experiments on *in vitro* transdermal permeation as previously described. Briefly, mouse abdomen skin was meticulously excised with the fur shaved off and the subcutaneous fat was removed, while skin integrity was preserved throughout the treatment. Excised skin was attached to a Franz diffusion cell. Diffusion areas ranged from 1.0 to 2cm in each donor compartment [21]. Chen H *et. al.* reported that the amount of ibuprofen that permeated through pig ear skins as a function of time was plotted. The slope and intercept of the straight line generated by graphing the amount of ibuprofen permeated versus time in steady state circumstances were used to compute the ibuprofen permeation rate (J, μg cm^{-2} h^{-1}) and lag time. By dividing the skin flow by the ibuprofen donor concentration, the skin permeation coefficient (P) was obtained [8].

Studies on Skin Irritation:

Sahoo S *et. al.* tested the irritating potential of the proposed formulation after topical administration on rabbits (weighing 2.0–2.5 kg) in skin irritation study [3]. Singh M *et. al.* have documented the findings of a single application and multiple application skin irritation test. On the dorsal side, the scores were calculated after a single application of optimized Microemulsion-based hydrogel, Fluconazole marketed gel, normal saline, and formaldehyde (standard irritant). The experiment lasted 48 hours. The formulation was administered twice in a 24-hour period. Microemulsion-based hydrogel had a score of less than 0.5, indicating that it was nonirritant after 48 hours [19]. The following equation was used to obtain the overall scores for the irritation test [9]:

Irritation levels on average = (Reaction scores for erythema + reaction ratings for edema)/ intervals of time (h)

CONCLUSION

This concise review highlighted the method of preparation, characterization, evaluation, and stability investigations of microemulsion-based hydrogel.

REFERENCES

[1] Shah NV, Ghelani TK, Saini V, Joshi UT, Seth AK, Chauhan SP, Aundhia C, Maheshwari R. Development and characterization of microemulsion based system of aceclofenac. Indo Am J Pharm Res. 2011 Jun 10;2(1):110-24.

[2] Friedrich T, Tieke B, Meyer M, Pyckhout-Hintzen W, Pipich V. Thermoresponsive copolymer hydrogels based on N-isopropylacrylamide and cationic surfactant monomers prepared from micellar solution and microemulsion in a one-step reaction. The Journal of Physical Chemistry B. 2010 May 6;114(17):5666-77.

[3] Sahoo S, Pani NR, Sahoo SK. Microemulsion based topical hydrogel of sertaconazole: Formulation, characterization and evaluation. Colloids and Surfaces B: Biointerfaces. 2014 Aug 1;120:193-9.

[4] Sunitha S, Jitendra W, Sujatha D, Santhosh Kumar M. Design and evaluation of hydrogel-thickened microemulsion for topical delivery of minoxidil. Iranian Journal of Pharmaceutical Sciences. 2013 Oct 1;9(4):1-4.

[5] Olariu I, Coneac G, Vlaia L, Vlaia V, Anghel DF, Ilie C, Popoiu C, Lupuleasa D. Development and evaluation of microemulsion-based hydrogel formulations for topical delivery of propranolol hydrochloride. Digest Journal of Nanomaterials and Biostructures. 2014 Jan 1; 9(1):395-412.

[6] Pillai AB, Nair JV, Gupta NK, Gupta S. Microemulsion-loaded hydrogel formulation of butenafine hydrochloride for improved topical delivery. Archives of dermatological research. 2015 Sep; 307(7):625-33.

[7] Sah AK, Jain SK, Pandey RS. Microemulsion based hydrogel formulation of methoxsalen for the effective treatment of psoriasis. Asian J Pharm Clin Res. 2011;4(4):140-5.

[8] Chen H, Chang X, Du D, Li J, Xu H, Yang X. Microemulsion-based hydrogel formulation of ibuprofen for topical delivery. International Journal of Pharmaceutics. 2006 Jun 6; 315(1-2):52-8.

[9] Sabale V, Vora S. Formulation and evaluation of microemulsion-based hydrogel for topical delivery. International journal of pharmaceutical investigation. 2012 Jul; 2(3):140.

[10] Kim YH, Song CK, Jung E, Kim DH, Kim DD. A microemulsion-based hydrogel formulation containing voriconazole for topical skin delivery. Journal of Pharmaceutical Investigation. 2014 Dec; 44(7):517-24.

[11] Panseria B, Desai K, Swamy SM. Formulation, development and evaluation of microemulsion based hydrogel of econazole nitrate. Pharma Science Monitor. 2014 Apr 2;5.

[12] Biswal B, Karna N, Nayak J, Joshi V. Formulation and evaluation of microemulsion based topical hydrogel containing lornoxicam. Journal of Applied Pharmaceutical Science. 2014 Dec; 4(12):077-84.

[13] Zhu W, Guo C, Yu A, Gao Y, Cao F, Zhai G. Microemulsion-based hydrogel formulation of penciclovir for topical delivery. International journal of pharmaceutics. 2009 Aug 13;378(1-2):152-8.

[14] Catanzano O, Straccia MC, Miro A, Ungaro F, Romano I, Mazzarella G, Santagata G, Quaglia F, Laurienzo P, Malinconico M. Spray-by-spray in situ cross-linking alginate hydrogels delivering a tea tree oil microemulsion. European Journal of Pharmaceutical Sciences. 2015 Jan 23; 66: 20-8.

[15] Pandey S, Das U, Patil A. Formulation and ex-vivo evaluation of metronidazole microemulsion loaded hydrogel for prevention of periodontitis. Journal of Pharmaceutical Investigation. 2014 Aug; 44(4):225-36.

[16] Kamaria P, Patwa A, Saxena A, Gaur K, Garg R, Agrawal P, Dashora A. Design and development of hydrogel based microemulsion of valacyclovir hydrochloride. J. Chem. Pharm. Res., 2015; 7(12):928.

[17] Chandra A, Sharma PK, Irchhiaya R. Microemulsion-based hydrogel formulation for transdermal delivery of dexamethasone. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm. 2014 Aug 28; 3(1).

[18] Ahmed A, Rowshan A, Sengupta RU. Formulation and in vitro/ex vivo characterization of microemulsion based hydrogel formulation of aceclofenac for topical application. Asian J Pharm Clin Res. 2016; 9(1):87-91.

[19] Singh M, Gangwar N, Parashar P, B Tripathi C, Arya M, A Saraf S, Saha S. Topical delivery of fluconazole via microemulsion incorporated hydrogel for the management of fungal dermatophytosis. Current drug therapy. 2016 Aug 1; 11(2):129-41.

[20] Gohel MC, Nagori SA. Fabrication and evaluation of hydrogel thickened microemulsion of ibuprofen for topical delivery. Indian J Pharm Educ Res. 2010 Apr 1; 44: 189-96.

[21] Zhang YT, Li Z, Zhang K, Zhang HY, He ZH, Xia Q, Zhao JH, Feng NP. Co-delivery of evodiamine and rutaecarpine in a microemulsion-based hyaluronic acid hydrogel for enhanced analgesic effects on mouse pain models. International journal of pharmaceutics. 2017 Aug 7; 528 (1-2): 100-6.

[22] Coneac G, Vlaia V, Olariu I, Muţ AM, Anghel DF, Ilie C, Popoiu C, Lupuleasa D, Vlaia L. Development and evaluation of new microemulsion-based hydrogel formulations for topical delivery of fluconazole. Aaps Pharmscitech. 2015 Aug; 16(4):889-904.

[23] Vlaia L, Olariu I, Coneac G, MUŢ AM, POPOIU C, CORINA S, Anghel DF, ELISABETA M, MAXIM SK, VLAIA V. Development of microemulsion-loaded hydrogel formulations for topical delivery of metoprolol tartrate: Physicochemical characterization and ex vivo evaluation. FARMACIA. 2016 Nov 1; 64 (6):901-13.

[24] Djekic L, Martinovic M, Stepanović-Petrović R, Micov A, Tomić M, Primorac M. Formulation of hydrogel-thickened nonionic microemulsions with enhanced percutaneous delivery of ibuprofen assessed in vivo in rats. European Journal of Pharmaceutical Sciences. 2016 Sep 20; 92:255-65.

[25] Singh A, Bajaj A, Babul N, Kao H. Formulation and evaluation of novel topical mepivacaine microemulsion hydrogels for neuropathic pain relief. The Journal of Pain. 2013 Apr 1; 14 (4):S87.