EFFECT OF OIL, SURFACTANT AND COSURFACTANT ON MICROEMULSION- A REVIEW

Dr. P. Veera Lakshmi[1*], Dr. J. Sai Chandra[2], Dr. K. A. Emmanuel[3], K.V.L.N. Murthy[4]

ABSTRACT

Lipid dosage forms are the most preferred delivery system for hydrophobic drug molecules. Lipid dosage forms has many advantages of higher degree of biocompatibility and versatility and also lipid dosage form gained more importance in recent years because of their ability to improve the solubility and bioavailability of drugs with poor water solubility. Lipid formulation can be altered in various ways to provide wide range of product requirements as per the disease condition, route of administration, toxicity and efficacy. Lipid formulations are most reliable strategy for formulating pharmaceuticals, for topical, oral, pulmonary, or parenteral delivery. Due to their capability as therapeutic agents, ideally, these lipid-soluble drugs are incorporated into inert lipid carriers such as oil, surfactant dispersion, liposomes, emulsion etc. Emulsion is one of the known systems since many years. Pharmaceutical application of the emulsion is widely speeded after the microemulsion and nano emulsions appearance. Microemulsions are clear, stable and isotropic mixture of oil, surfactant and cosurfactant. Emulsions and nano emulsions are not thermodynamically stable, compared with microemulsions. The main objective of this review paper is to discuss about the effect of oil, surfactant and cosurfactant on the microemulsions.

Keywords: Emulsion, Microemulsion, Surfactant, Cosurfactant, Oil

[1*]Asst. Professor, School of Pharmaceutical Sciences and technologies, JNTUK, Andhra Pradesh, INDIA-533003, Email: veeram.pharmacy@gmail.com
[2]Asst. Professor, JNTUH University College of Engineering Sultanpur, Telangana, INDIA- 502273.
Email: jsaichandra@gmail.com
[3]Professor, Dept of Chemistry, Y.V.N.R Govt. Degree College, Kaikaluru, Eluru Dist. Andhra Pradesh, INDIA -521333
[4]Lecturer, Department of Chemistry, SVR Degree College, Macherla, Andhra Pradesh, INDIA-522426

[*]**Corresponding Author:** Dr. P. Veera Lakshmi
[*]Asst. Professor, School of Pharmaceutical Sciences and technologies, JNTUK, Andhra Pradesh, INDIA-533003, Email: veeram.pharmacy@gmail.com

DOI: 10.53555/ecb/2022.11.8.31

INTRODUCTION

Emulsion is a liquid dosage form consisting of two immiscible liquids such as water and oil, which are mixed using mechanical shear and surfactant. Surfactant is responsible for reducing naturally occurring attractive forces in the form of surface tension. Surfactant with low HLB value shows water in oil emulsion and high HLB values shows oil in water emulsion [1, 2]. Emulsion prepared without adding surfactant would be not stable, and the phases of the emulsion will be separated in different layers. Therefore, the addition of surfactant is necessary to make emulsion stable for long period of time [3, 4].

Emulgel is the combination of gel and emulsion. Both oil in water and water in oil types of emulsion is used as carrier to deliverthe various drugs into the skin. Emulgel also have a great ability to penetrate through the skin. Gelling agent in the water phase converts the emulsion into an emulgel [5]. Emulgeldermatologically have many advantages such as greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, pleasing and transparent appearance [6].

Micro emulsion is clear, thermodynamically stable, isotropic liquid dosage form. It is formulated using oil, water, surfactant, and co-surfactant [7, 8]. Microemulsions are different from emulsion by their transparency, low viscosity, thermodynamic stability and spontaneity and at least 30% of water forms the spontaneous and thermodynamic stable dosage form [9]. Administration of the drugs using micro emulsions through the skin increase the local delivery of the drug by different mechanism [10].

Microemulgelis, a dual drug delivery system, done by converting a liquid microemulsion into a semi-solid gel. Because of its dual action of emulsion and gel, it is considered as one of the most promising new drug delivery systems. Microemulsion dosage form is selected because of its good solubility and ability to penetrate into the skin, whereas gel can sustain the drug release and provide a lengthy drug residence time. For skin-related disorders, microemulgel is the best delivery technology which shows better efficacy with minimum amount of medicine [11, 12].

Emulsion

Emulsion is a biphasic liquid dosage form possessing two immiscible liquids; emulsifying agent is added, which form film around the globules so that stable emulsion is formed. The globules size is 0.25 to 25 μm diameters [3, 4].

Ideal properties [3, 4]

• It must be stable at various temperature
• It must be not degraded by microbes on storage
• It must remain in its original type, without phase inversion.
• Must not rancid due to oxidation

Types of emulsion [3, 4]

Water in oil type (w/o)
Oil in water type (o/w)
Multiple emulsion

In water in oil type (w/o) emulsion, oil is in the dispersion phase and water is in dispersed phase. According to studies it is confirmed that stability plays major role in w/o emulsions and water in oil emulsions are stabilized using natural surfactants such as beeswax, resins and fat.

In oil in water emulsion, oil is in the dispersed phase and water is in the dispersion phase. Emulsifying agents used in the o/w emulsions is saponins, gum acacia and synthetic substance.

Multiple emulsions are the complexed mixtures where both oil in water and water in oil emulsion are existing simultaneously. They are stabilized using lipophilic and hydrophilic surfactants, respectively. Multiple emulsions are prepared by the re-emulsification of a primary emulsion or they can also prepare when an emulsion inverts from one type to another type. For example, w/o to o/w [3, 4].

Emulgel

Emulgel is the combination of gel and emulsion. Both oil in water and water in oil types of emulsion is used as carrier to deliver the various drugs into the skin. Emulgel also have a great ability to penetrate through the skin [5, 6].

Formulation consideration [13]

The challenges in the preparation of emulgel
• Finding systems which are non-irritating, non-toxic, non-comedogenic and non-sensitizing.
• Preparing accessorily effective emulgel
• The emulgelpreparation should have low allergic properties, good physiological compatibility and high biocompatibility.

Preparation of emulgel [14]

Step 1: Preparation of emulsion
Step 2: Preparation of gel base
Step 3: Incorporation of an emulsion into gel base

Microemulsion

According to the literature survey, 40 % of the new drugs are poorly soluble in water, which shows poor dissolution for the drug through oral administration that leads to poor bioavailability and such drugs always a challenge to deliver through oral route. However, some of the researchers

suggested that poorly water-soluble drugs can be enhanced by microemulsion formulation [7, 8].
Microemulsion is a clear, thermodynamically stable, isotropic liquid dosage form. It is formulated using oil, water, surfactant, and co-surfactant. Microemulsions are different from the emulsion by their transparency, low viscosity, thermodynamic stability and spontaneity. and at least 30% of water forms the spontaneous and thermodynamic stable dosage form. Administration of the drugs using microemulsions through the skin increase the local delivery of the drug by different mechanism [7-10].
When nanoemulsions are compared with microemulsions, nanoemulsions are not thermodynamically stable. Because nano emulsion undergoes degradation of the structure due to Ostwald ripening, flocculation, coalescence and gravitational separation, these results in particle size distribution change, physical properties change as well as chemical properties change. Whereas microemulsion will not undergo deformation on the long storage condition remains constant [15].

Microemulsion types (according to winsor classification) [7, 16]
Type (o/w): This type of microemulsion is formed when the surfactant is solubilized in water phase.
Type II (w/o): This type of microemulsion is formed when the surfactant is solubilized in oil phase.
Type III: This is one of the types of microemulsion where the surfactant is loaded in the interphase, which combines with both oil and water phase in this formulation, both oil and water phase are surfactant deficient which leads to the formation of three phase microemulsion.
Type IV: This is an extension of type III where a higher concentration of surfactant at interphase becomes single phase.

Methods of preparation of microemulsion
Phase titration method: Microemulsion was prepared by taking an appropriate amount of oil and surfactant: a cosurfactant mixture in a beaker, it was then mixed using sonication until the surfactant get solubilized and a clear solution is obtained. Then required amount of drug is dispersed (the amount of drug is determined by solubility studies) in oil and surfactant: cosurfactant mixture and dissolved with the help of a magnetic stirrer. Later on, the water phase is added dropwise until the system becomes transparent. Thus, the microemulsion is formed [7, 17, 18].

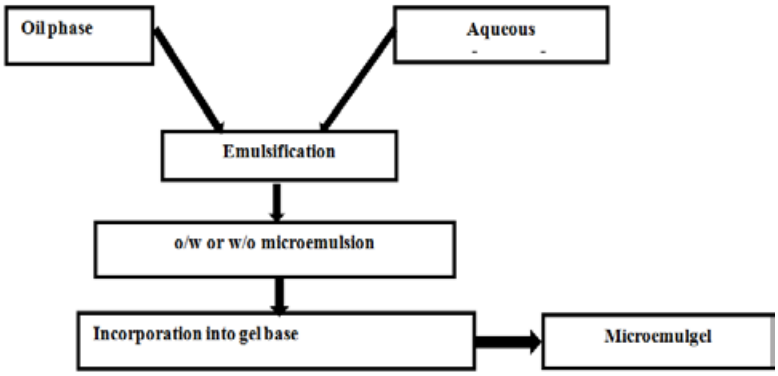
Phase inversion method: Phase inversion of the microemulsion is a conversion of o/w to w/o or vice versa. Phase inversion of the microemulsion is prepared by adding an excess amount of dispersed phase or by raising the temperature. This method results in extreme changes in particle size, which later shows change in *in vivo* and *in vitro* drug release profiles [19, 20].

Advantages [21, 22]
• Easy to solubilize hydrophobic or oil soluble drugs
• Most suitable system to increase the rate of absorption as well as bio availability by avoiding interfering variation.
• Microemulsions can be preferred to develop controlled and sustained release drug system.
• It is better choice system to minimize first pass metabolism.
• It can be used for different routes such as oral, parenteral and topical drug delivery.
• Suitable for long-term use since microemulsion is thermodynamically more stable compared to the conventional system.

Disadvantages [23, 24]
• Expensive, if additional use of excess amount of surfactant and cosurfactant.
• Excess concentration of surfactant can lead to mucosal toxicity.

Microemulgel
Microemulgel is a combination of emulsion and gels, exhibits characteristics of both. Microemulgel supports to deliver hydrophobic drugs by formulating oil in water microemulsion and this microemulsion can be incorporated into gel base [25, 26]. Microemulgel shows good patient acceptability. Due to its non-greasy in nature, it can be easily applied on to the skin as compared to the other topical dosage form such as ointments, creams which are very greasy, thick and excess amount required for rubbing [27].

Preparation process [28, 29]
Step 1: Preparation of o/w or w/o microemulsions by using values processed in oil and water step.
Step 2: Preparation of gel, using appropriate concentration of gelling agent and water.
Step 3: Incorporation of microemulsion in gel base with continuous stirring



Major components of microemulgel [30, 31]
• Oil
• Surfactant
• Cosurfactant

Effect of oil, surfactant and cosurfactant on microemulsion Oil : Oil shows the good solubility for the BCS class drugs. The oil also acts as a penetration enhancer in a microemulsion based drug delivery system. Short chain oil enter tail group region to a greater extent than along the chain, which leads in the swelling of the tail group and hence an increase in negative curvature that minimize the effect of HLB balance [30, 31]. Oils also influence the area of the microemulsion region for example, Muhammad Asri Abd Sisak *et al.* 2017, total 18 phase diagrams were constructed successfully for both oleic acid and IPM.
Each formulation showed a significant effect on the area of microemulsion region, oleic acid-based system could not give large microemulsions region. IPM showed best choice in order to get larger microemulsions region with higher concentration of water with transition phase from w/o to o/w [32]. The increase in the oil concentration, increases in the size of the droplet. The oils which show higher solubility for the drug also shows higher droplet size, this effects of oil on the droplet size are studied by Omar sarheed *et al.* 2020 [33]. Molecular volumes of the oil also show its effect on the microemulsion. For example, IPM (molecular volume 528.2 g/cm3) based microemulsion system showed a smaller area of microemulsion as compared to system based on oleic acid (molecular volume 523.9 g/cm3)[34-36].

Surfactant: Surfactant is the second criteria to consider for the preparation of microemulsion and surfactant should be chosen in such a way that gives very best solubility for drug [37]. During the emulsification method, surfactant should quickly absorb within the interface and stop the droplets aggregation, there are 4 types of surfactants non-ionic, zwitterionic, cationic or anionic surfactants, which stabilizes the systems. Ionic and nonionic surfactants have a potential to extend the microemulsion region. Examples of non-ionic surfactant are brij-35, and tween 20/80 or span 80 [38]. Surfactant shows its effect on drug solubility for example, Handy M. Dawaba *et al.*-2010, stated his research work about the effect of surfactant tween 80, which show the greater solubility for the piroxicam drug [39]. Omar sarheed *et al.* 2020, concluded that increase in the surfactant concentration a decrease in the droplet size [33]. The ratio or HLB values of the surfactant mixture also influence the penetration of the microemulsion for example, Liangmei Chen *et al.* 2011 constructed 5 pseudo ternary phase diagrams using various mixed surfactants
(Cremophor EL/span 80) HLB values (8.4, 8.0, 7.6, 7.2, 6.8) out of 5 mixed surfactants with different HLB values, the flux and the amount of drug penetration increased with increasing content of the lipophilic surfactant span 80 and the skin retention was highest for mixed surfactant with HLB value of 7.6. Hence, it was suggested that the presence of mixed surfactant was beneficial in the formulation of microemulsions [40].

Co-surfactant
The cosurfactant is generally used with the surfactant in the preparation of microemulsion, which decreases the interfacial tension between the two immiscible liquids to the transient negative value. At this negative value fine droplets are formed due to the interphase expansion and much surfactant/cosurfactant get absorbed on the surface until the bulk condition is source enough to make the interracial tension positive again. Cosurfactant of short medium chain length alcohols also ensures that interfacial film is flexible enough to misshape readily around droplets, as the interaction between primary surfactant molecules decrease both polar head group interaction and hydrocarbon chain interaction [41]. Research work of Muhammad asriabdsisak *et al.* 2017 the effect of co-surfactant depends on its chain length, where only an appropriate chain length is suitable for good microemulsion formation. PEG400 (long chain),

Transcutol (medium chain), propylene glycol (short chain), were used in his study to evaluate the effect of co-surfactant on the preparation of microemulsion. In his study, he concluded that medium chain length surfactant is most suitable co-surfactant in combination with single chain surfactant [32]. The surfactant having HLB value more than 20 often requires the presence of a cosurfactant to reduce surfactant effective HLB value within range of required microemulsion formulation [42-44].

Table 1: Examples for oil, surfactant and cosurfactant in research study [45-50]

Oils	Surfactant	Cosurfactant
Propylene glycol	Tween 80	Propylene glycol400
Karanj oil	Span 20	Capryol90
Oleic acid	Tween 20	Propylene glycol
Capryol90	Tween 80	PEG400
Palm oil	Tween 80	N-butanol
Orange oil	Tween 80	Propylene glycol
Oleic acid	Tween 80	Ethanol
CapryolTM90	Tween 80	Transcutol p

Table 2: Microemulgel marketed formulation:

Name the product	Active ingredients	Company
Voltrarenmicroemulgel	Diclofenac diethyl ammonium	Novartis pharma
Avindo gel	Azithromycin	Cosme pharma laboratories
Zorotene gel	Tezarotene	Elder pharmaceuticals
Clinagel	Clindamycin phosphate allantoin	Stiefel pharma
Acent gel	Aceclofenac, Methyl salicylate, capsaicin	Intra labs IndiaPvt Ltd
Topinate gel	Clobetasol propionate	Systopicpharma
Kojivitgel	Kojicacid, Dipalmitatearbutin, Octinnoxate	Micro gratia pharma
Excexgel	Clindamycin, Adapalene	Zee laboratories
Lupigylgel	Metronidazole	Lupin pharma
Pernox gel	Benzoyl peroxide	Cosme remedies Ltd
Clobengel	Clotrimazole, Beclomethasonedipropionate, Neomycin	Elder pharmaceuticals
Miconaz-H-microemulgel	Miconazole-nitrate, Hydrocortisone	Medical union pharmaceuticals

Table 3: Patented formulation [51-55]

S. No.	Formulation	Patent no.
1	Gel-microemulsion formulation	US20030083314 A1
2	Microemulsion gel preparation of oxiconazole nitrate	CN102423293 B
3	Composition for microemulsion gel having bleaching and antiseptic properties	US5336432 A1
4	Microemulsion based gel	EP0760651 B1
5	Granisetron HCL Microemulsion based gel	CN101933902 A

CONCLUSION :

Microemulsion is a potential drug delivery system, mostly used for the delivery of hydrophilic and lipophilic drug. Microemulsion have good characteristics such as improved drug solubilization, longer shelf life and improvement of bioavailability of poorly soluble drugs. According to the literature evidence the oil, surfactant and cosurfactant present in the microemulsion show their effect on microemulsion, i.e. type of oil, concentration and molecular volume influence the area of microemulsion and droplet size. Surfactants with a single chain increase the microemulsion region. Type of surfactant like ionic and nonionic extends the microemulsion region compared to other types of surfactants. The ratio of surfactant shows its effect on microemulsion penetration. Cosurfactant with medium chain length gives good microemulsion and cosurfactant reduces surfactant effective HLB value within the range of required microemulsion formulation.

REFERENCES

1. Kale SN, Deore SL. Emulsion microemulsion and nano emulsion: a review. Syst Rev Pharm. 2016;8(1):39-47. doi: 10.5530/srp.2017.1.8
2. Sah SK, Badola A, Nayak BK. Emulgel: magnifying the application of topical drug

delivery. Indian J Pharm Biol Res. 2017;5(1):25-33. doi: 10.30750/ijpbr.5.1.4.
3. Akbari S, Nour AH. Emulsion types, stability mechanisms and rheology: a review. IJIRSS. 2018;1(1):11-7. doi: 10.53894/ijirss.v1i1.4.
4. Madaan V, Chanana A, Kataria MK, Bilandi A. Emulsion technology and recent trends in emulsion applications. Int Res J Pharm 2014;5(7):533-42. doi: 10.7897/2230-8407.0507108.
5. Yadav SK, Mishra MK, Tiwari A, Shukla A. Emulgel: a new approach for enhanced topical drug delivery. Int J Curr Pharm Sci. 2017;9(1):15-9. doi: 10.22159/ijcpr.2017v9i1.16628.
6. Vijayanta Dhawas DD, Shaktipal Patil. Emulgel: Acomprehensive review for novel topical drug delivery system. Int J Recent Sci Res. 2020. doi: 10.24327/ijrsr.2020.1104.5247.
7. Goswami P, Choudhury A, Kumar Dey B. Microemulsion– a potential carrier for improved bioavailability. International Journal of Pharmaceutical and Biological Archives. 2019;10(2):69-77.
8. Patel V, Kukadiya H, Mashru R, Surti N, Mandal S. Development of microemulsion for solubility enhancement of clopidogrel. Iran J Pharm Res. 2010;9(4):327-34. PMID 24381597.
9. Yadav S, Kawtikwar PS, Sakarkar DM, Gholse YN, Ghajbhiye SD. Microemulsion: a review. Res J Pharm Technol. 2009:441-8.
10. Udmale AR, Jain PN, Choudhary MV. Microemulgel as a novel approach for enhancing topical drug delivery: a review. Indo Am J Pharm Sci. 2019;6(2):4803-9.
11. Zingade SG, Nagoba Shivappa N, Avinash ASGS B. Formulation and evaluation of topical microemulgel containing terbinafine hydrochloride. J Pharm Res Int. 2021;33(47A):794-803. doi: 10.9734/JPRI2021/v33i47A33075.
12. Shaikh NM, Nagoba SN. A review on current trends of nanoemulsion. Indo Am J Pharm Sci. 2019;6(1):721-32. doi: 10.5281zenodo.253678.
13. Raj ELPSoosai. Sangameswaran Balakrishnan. Short review–emulgel. J Compr Pharm Rev Article. 2016;3(1):34-7. doi: 10.37483/jcp.2016.3105.
14. Kumar D, Jasbir Singh MA, Kumar V. Emulgel-novel topical drug delivery system–a comprehensive review. International Journal of Pharmaceutical Sciences and Research. 2016;7(12):4733-42. doi: 10.13040/IJPSR.0975-8232.
15. Koh Kai Seng. Wongvoonloong introductory chapter: from microemulsions to nanoemulsions Books>nanoemulsions-Properties, Fabrications and Applications; 2019.
16. Chaudhary A, Gaur PK, Barman M, Mishra R, Singh M. A review on microemulsion a promising optimising technique used as a novel drug delivery system. Int Res J Pharm 2018;9(7):47-52. doi: 10.7897/2230-8407.097124.
17. Patel TB, Soni TG, Suhagia BN. Preparation and characterization of oxcarbazepinemicroemulsion. Egypt Pharmaceut J. 2016;15(3):173-80. doi: 10.4103/1687-4315.197586.
18. Dixit GR, Shende AB. Formulation and evaluation of anthralinmicroemulsion gel using karanj oil. Int J Pharm Sci Res. 2014;5(5):2014-50. doi: 10.13040/IJPSR.0975-8232.5(5).2014-50.
19. Kale SN, Deore SL. Emulsion microemulsion and nanoemulsion: a review. Syst Rev Pharm. 2016;8(1):39-47. doi: 10.5530/srp.2017.1.8.
20. Talegaonkar S, Azeem A, Ahmad FJ, Khar RK, Pathan SA, Khan ZI. Microemulsions: A novel approach to enhanced drug delivery. Recent Pat Drug Deliv Formul. 2008;2(3):238-57. doi: 10.2174/187221108786241679, PMID 19075911.
21. Mehta SK, Kaur G. Microemulsions as carriers for therapeutic molecules. Recent Pat Drug Deliv Formul. 2010;4(1):35-48. doi: 10.2174/187221110789957282, PMID 19807681.
22. Russell Jones G, Himes R. Water-in-oil microemulsions for effective transdermal delivery of proteins. Expert Opin Drug Deliv. 2011;8(4):537-46. doi: 10.1517/17425247.2011.559458, PMID 21413905.
23. Furlanetto S, Cirri M, Piepel G, Mennini N, Mura P. Mixture experiment methodsin the development and optimization of microemulsion formulations. J Pharm and Biomedical Analylsis. 2011;55(4):610-7. doi: 10.1016/j.jpba.2011.01.008. PMID: 21295935.
24. Hathout RM, Woodman TJ. Applications of NMR in the characterization of pharmaceutical microemulsions. J Control Release. 2012;161(1):62-72. doi: 10.1016/j.jconrel.2012.04.032. PMID 22579644.
25. Kushwah P, Kumar Sharma P, Koka S, Gupta A, Sharma R, Darwhekar GN. Microemulgel: a novel approach for topical drug delivery. J Appl Pharm Res. 2021;9(3):14-20.
26. Ashara KC, Paun JS, Soniwala MM, Chavda JR, Mendapara VP, Mori NM. Microemulgel: an overwhelming approach to improve

therapeutic action of drug moiety. Saudi Pharm J. 2016;24(4):452-7. doi: 10.1016/j.jsps.2014.08.002. PMID 27330376.
27. Wani RR, Patil MP, Dhurjad P, Chaudhari CA, Kshirsagar SJ. Microemulsion-based gel: A novel approach in the delivery of hydrophobic drugs. Int J Pharm Res Scholars (IJPRS). 2015;4(I-2):397-410.
28. Pawbake GR, Shirodkar SV. Microemulgel: a promising approach to improve the therapeutic efficacy of drug. Crit Rev. 2020;7(14).
29. Mehta DP, Rathod HJ, Shah DP, Shah CN. A review on microemulsion-based gel: A recent approach for topical drug delivery system. Res J Pharm Technol. 2015 Feb;8(2):118. doi: 10.5958/0974-360X.2015.00021.9.
30. Deshmukh PD, Salunkhe KS, Patil WS, Chaudhari SR, Davange RM, Varpe UD. Microemulsion: A novel approach for drug delivery system. J Adv Drug Delivery. 2016;3:54-61.
31. Jha SK, Dey S, Karki R. Microemulsions-potential carrier for improved drug delivery. Asian J Biomed Pharm Science. 2011;1:5-9. doi: 10.15272/AJBPS.V1I1.2.
32. Sisak MAA, Daik R, Ramli S. Study on the effect of oil phase and co-surfactant on microemulsion systems. Malays J Anal Sci. 2017;21(6):1409-16. doi: 10.17576/mjas-2017-2106-23.
33. Sarheed O, Dibi M, Ramesh KVRNS. Studies on the effect of oil and surfactant on the formation of alginate-based O/W lidocaine nanocarriers using nanoemulsion template. Pharmaceutics. 2020;12(12). doi: 10.3390/pharmaceutics12121223, PMID 33348692.
34. Huang CT, Tsai MJ, Lin YH, Fu YS, Huang YB, Tsai YH. Effect of microemulsions on transdermal delivery of citalopram: optimization studies using mixture design and response surface methodology. Int J Nanomedicine. 2013;8:2295-304. doi:10.2147/IJN.S43474. PMID 23919086.
35. Al Abood RM, Talegaonkar S, Tariq M, Ahmad FJ. Microemulsion as a tool for the transdermal delivery of ondansetron for the treatment of chemotherapy-induced nausea and vomiting. Colloids Surf B Biointerfaces. 2013;101:143-51. doi: 10.1016/j.colsurfb.2012.06.015, PMID 22796784.
36. Djekic L, Primorac M. The influence of cosurfactants and oils on the formation of pharmaceutical microemulsions based on PEG-8 caprylic/capric glycerides. Int J Pharm. 2008;352(1-2):231-9. PMID 18068919/j.ijpharm.2007.10.041.
37. Dhaval M, Devani J, Parmar R, Soniwala MM, Chavda J. Formulation and optimization of microemulsion based sparfloxacin *in situ* gel for ocular delivery: *in vitro* and *ex vivo* characterization. J Drug Deliv Sci Technol. 2020;55:101-373. doi: 10.1016/j.jddst.2019.101373.
38. Patel RB, Patel MR, Bhatt KK, Patel BG. Formulation consideration and characterization of microemulsion drug delivery system for trans nasal administration of carbamazepine. Bull Fac Pharm Cairo Univ. 2013;51(2):243-53. doi: 10.1016/j.bfopcu.2013.07.002.
39. Abd-Allah FI, Dawaba HM, Ahmed AMS. Development of a micro emulsion-based formulation to improve the availability of poorly water-soluble drug. Drug Discov Ther. 2010;4(4):257-66. PMID 22491208.
40. Chen L, Tan F, Wang J, Liu F. Assessment of the percutaneous penetration of indomethacin from soybean oil microemulsion: effects of the HLB value of mixed surfactants. Liangmei Chen. 2011.
41. Muhammad AS, Daik R, Ramli S. Study on the effect of oil phase and co-surfactant on microemulsion systems. MJAS. 2017;21(6):1406-16. doi: 10.17576/mjas-2017-2106-23.
42. Muzaffar Faizi, Singh UK, Chauhan L. Review on microemulsion as futuristic drug delivery. Int J Pharm Pharm Sci. 2013;5(3):39-53.
43. Jha SK, Dey S, Karki R. Microemulsions-potential carrier for improved drug delivery. Int Pharm Sci. 2011;1(2):25-31.
44. Singh PK, KashifIqubal Mohd, Shukla VK, Shuaib Mohd. Microemulsions: current trends in novel drug delivery systems. J Pharm Chem Biol Sci. February 2014;1(1):39-51.
45. Shrestha S, Sabita Pokhrel SS, Manandhar M, Irshad Alam. Formulation and evaluation of topical microemulgel loaded with terbinafinehclmicroemulsion. Int J Pharm Sci Res. 2017;8(11):4716-23. doi: 10.1304/IJPSR.0975-8232.8(11).4716-23.
46. Dixit GR, Shende AB. Formulation and evaluation of anthralinmicroemulsion gel using karanj oil. Int J Pharm Sci Res. 2014;5(5):2014-50. doi: 10.13040/IJPSR.0975-8232.5(5).2014-50.
47. Tole K, Deshmukh G. Design and characterization of microemulsion gel for transdermal drug delivery system of duloxetine hydrochloride. Asian J Pharm Clin Res 2018;11(11). doi: 10.22159/ajpcr.2018.v11i11.27552.
48. Shah M, Modi D, Shah D. Formulation, design and evaluation of microemulsion and micro-

emulgel of itraconazole for topical application. Int J Pharm Pharm Res. 2017;9(2):124-59.
49. Basheer HS, Noordin MI, Mowafaq M Ghareeb. Characterization of microemulsions Prepared using isopropyl palmitate with various Surfactants and Cosurfactants. Trop J Pharm Res. June 2013;12(3):305-10. doi: 10.4314/tjpr.v12i33.5.
50. Anindya Hanairadhati, Mahdi Jufri. Formulation and physical stability test of griseofulvinmicroemulsion gel. Int J Appl Pharm. 2017;9Suppl 1. doi: 10.22159/ijap.2017.v9s1.22.
51. Yiv Seang, Li Mingshu, D'Cruz O, Fatih Uckun. Gelmicroemulsion formulations. United States Patents US20030083314 A1; 2003.
52. Jianping T, Tanran C. Jiang Lixin, Z Zhiwen. Microemulsion gel preparation of oxiconazole nitrate. Canadian Patents CN. 102423293 B; 2013.
53. Petchul J, Gaudreault R. Composition for microemulsion gel having bleaching and antiseptic properties. United States Patents US5336432 A1; 1994.
54. Backlund S, Eriksson F, Rantala M. Pertti Rantala, Kari Varho. Pharmaceutical compositions derived from microelmulsion-based gels, the method for their preparation and new micro emulsion-based gels. European Patents EP. 2001;B1:0760651.
55. YuYu, Xuemei Zhang. Granisetron hydrochloride micro emulsion-based gel and preparation method thereof. Canadian Patents CN. 101933902 A; 2011.