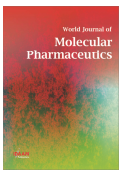

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REVIEW ARTICLE

A Review on Microemulsion Based Hydrogel for Topical Drug Delivery

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ABSTRACT

A hydrogel is a network of polymer chains that don't dissolve in water. It can also be found as a liquid gel in water. Hydrogels are superabsorbent materials that come from nature or are made in a lab. They can hold over 99 percent water. Because the medicine gets into the lower layers of the skin or mucous membranes, it has affects that are only felt at the place where it is applied. Microemulsions are colloidal dispersions that are thermodynamically stable, fluid, transparent (or translucent), and made up of an oil phase, an aqueous phase, a surfactant, and a co-surfactant in the right amounts to form a single optically isotropic solution with droplet sizes that are usually between 10 and 100 nanometers. Transparency, low viscosity, and, most importantly, the ability to make micro-emulsions that naturally split from regular emulsions. As a way to put medicine on the skin, micro-emulsions are better than creams, gels, and liquids in a number of ways. Based on microemulsion, the Hydrogel technology will be able to keep the effective dose at the site of action while also making the drug more bioavailable. This study looks at how microemulsion-based hydrogel is made, how it is characterised, how it is evaluated, and how stable it is.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are discrete or complete dose forms that, when applied to intact skin, transfer a predetermined amount of medication to systemic circulation at a slow rate through skin. These methods are regarded as some of the best ones for delivering restricted substances. These are dosage form created to evenly distribute a medicinally active dose of medication in skin of a patient [1, 2].

TDDS primary goal is to transport medications into the bloodstream by the skin at a set rate with little inter as well as intra patient fluctuation [3, 4]. One of the most promising drug delivery techniques at the moment is transdermal [5, 6]. It eases the strain that regular oral medicine administration has on the liver and digestive system. It expands patient compliance, decreases dangerous drug adverse effects brought on through brief overdoses, and is practical for transdermal drugs that only need a single weak application [7, 8].

This will enhance various effect [9, 10]. In contrast to conventional oral dosage forms, that causes a decrease in plasma life after last dose. Transdermal drug delivery has a number of benefits, including limiting hepatic first pass metabolism, refining beneficial efficacy, and maintaining a constant plasma level of medication [11, 12].

It is thought that administering medicines through the skin would be a preferable option than taking it orally. Patients frequently forget to take their medications, particularly if they need to take them several times daily. Systems for transdermal medication administration may be created for once-daily use. Transdermal medication delivery devices would avoid the GI tract, eliminating GI discomfort and first pass metabolism. Systems for transdermal medication delivery provide consistent, progressive absorption. The blood level peaks and valleys caused by oral dosage forms are typically

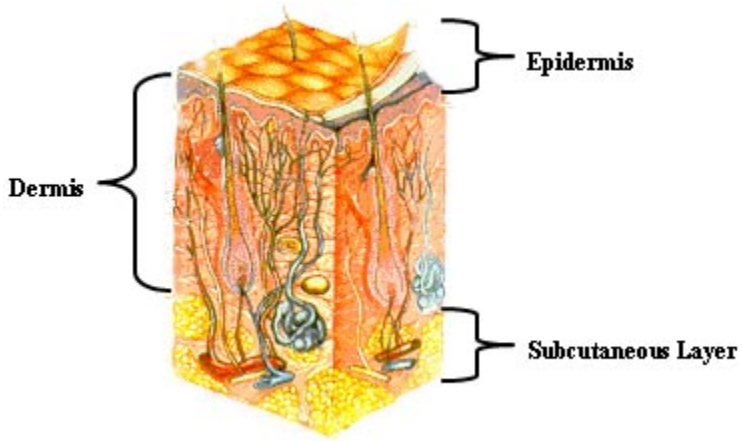

Figure 1: Anatomy of Skin

preferred to the steady state absorption of drugs over hours or days.

Manufacturing of novel pharmaceuticals for transdermal drug delivery systems was restricted by industrial restrictions and delivery challenges since they needed to meet requirements for molecular weight, lipophilicity, and potency [13].

Human Skin and Its Structure:
Human skin is made up of three interdependent layers:

- Epidermis
- Dermis
- Hypodermis [14].

Epidermis
The stratified epithelium of the skin, which consists of five layers, creates the epidermis of the skin [15, 16].

The absence of blood vessels in the epidermis is its most significant characteristic. The dermis's capillaries supply the nutrients. The epidermis, the top layer of skin, is made up of a stratified, keratinizing squamous epithelium. Keratinocytes, which are in charge of the skin's barrier activities, make up more than 90% of the cells in the skin [17].

Dermis
Collagen, elastin, and fibrillin make up the majority of the dermis, the skin's next layer, giving it strength and flexibility. The ground material, also known as mucopolysaccharides, is present in the dermis, a vascularized connective tissue that is rich in collagen [18].

Hypodermis:
The hypodermis is the skin's innermost layer. Sebaceous glands, sweat glands all originate in the dermis but are enclosed in the epidermis. A thin salt solution is injected into the skin's surface by sweat glands. In order to regulate body and skin temperatures, the evaporation of this diluted salt solution cools the skin. The body contains sweet glands all around. Environment heat, the quantity of skeletal muscle activity that produces heat, and a number of emotional factors all have an impact on how much dilutions (sweat) produced. An oily substance called sebum enters hair follicles before exiting and making its way to the skin's surface [19, 20].

Microemulsion
Schulman invented microemulsions for the first time in 1943. Microemulsions have received extensive research due to their wide range of applications in various industries. Oil, water, and a surfactant are often combined with a cosurfactant to create transparent, stable, isotropic microemulsions. Microemulsions are adaptable carriers with a number of exceptional qualities, including increased bioavailability of unwell soluble medications, great absorption and penetration due to less surface tension and minor droplet size, as well as a practical cost-saving strategy [21, 22]. A careful and exact selection of the constituents, their proper ratios, and the application of a cosurfactant that provides flexibility at the water/oil interface can frequently meet this need [23]. In contrast to regular emulsions or macroemulsions, microemulsions can form by just mixing the ingredients together without the high shear

conditions that are generally needed to create classic emulsions [24].

Microemulsions need a lot of energy to create are not thermodynamically steady and eventually start to degrade or show phase separation (coalescence). Due to the high energy consumption, production costs are high, formulation development is difficult, and shelf life is shortened. Benefits of using microemulsions to deliver API is the ability to incorporate other classes of analgesic into formulation, this enhances the skin's thermodynamic activity and permits a variety of concentrations to be applied to the skin from the microemulsion carrier [25]. Non-steroidal anti-inflammatory medicines have less solubility in vehicles, can be delivered using this [26]. Due to the similar effects of components for boosting medication delivery and therapeutic efficacy, using microemulsions also improves drug penetration. Emulsions and microemulsions differ from one another [27].

Advantages of Microemulsion [28, 29]

- Thermodynamically stable entities necessitate a minimal amount of energy for their production.
- In order to enhance the dermal absorption of both lipophilic and hydrophilic medications in comparison to traditional formulations, (emulsions, pure oils, aqueous solutions).
- Compared to solvents without the surfactant system, it is easy to make and has high diffusion and absorption rates.
- Microemulsion creation is reversible. Although they can become unstable at either low or high temperatures, the microemulsion will rebuild when the temperature returns to its stable range.
- Drugs that are thermo-labile are easily incorporated without the risk of degradation.
- Microemulsions serve as a drug's super solvent. They are effective in dissolving pharmaceuticals that are both water- and fat-soluble, even those that are poorly soluble in water. Benefits include drug targeting and controlled release, and the technique has several applications in colloidal drug delivery systems.
- A large amount of drug can be incorporated in the formulation due to the high solubilizing capacity that might increase thermodynamic activity towards the skin.
- Because they operate as penetration enhancers, the surfactant and co-surfactant in the microemulsions could make the stratum corneum less effective as a barrier to the diffusion of substances.
- A low surface tension allows for a more comfortable and effective touch with the skin. Additionally, the dispersed phase has the ability to function as a reservoir, which makes it feasible to keep an almost constant concentration gradient throughout the skin for an extended period of time.

Disadvantages of Microemulsion:

- The nanodroplets' stability is ensured by the high concentrations of surfactant and co-surfactant used.
- Limited solubilizing capacity for high-melting substances.
- When used in pharmaceuticals, the surfactant must not pose any health risks..
- Environmental factors, such as temperature and pH, affect the stability of microemulsions. These parameters change upon microemulsion delivery to patients.

Method of preparation of Microemulsion [27]

1. Phase Titration Method:

Microemulsions are made using the spontaneous emulsification technique (phase titration technique), and their formation may be shown graphically with the use of phase diagrams. Building a phase diagram is a great way to investigate the chain of reactions that can take place when substances are combined. The chemical content and concentration of each component determine the association structure created during the formation of a microemulsion, which can be any of several different types (emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion). Phase equilibria and phase boundary delineation are major concerns in this investigation.

Pseudo ternary phase diagrams, in which each corner of the figure represents 100% of the component, are typically produced to locate the different zones, including the microemulsion zone, because quaternary phase diagrams (four component systems) are time-consuming and difficult to read. Based on its composition—whether it is oil-rich or water-rich—the area can be classified as a w/o or o/w microemulsion. Careful observation is required to exclude the metastable systems.

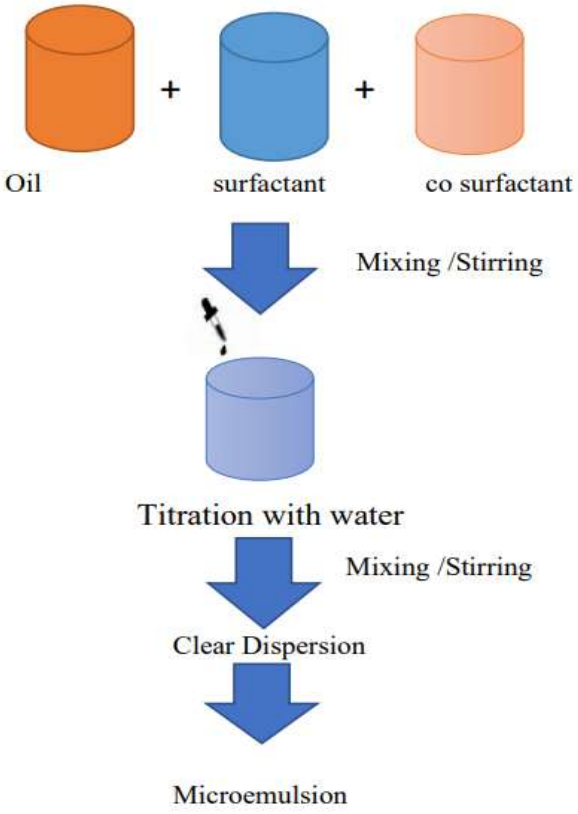

Figure 2: Phase Titration Method

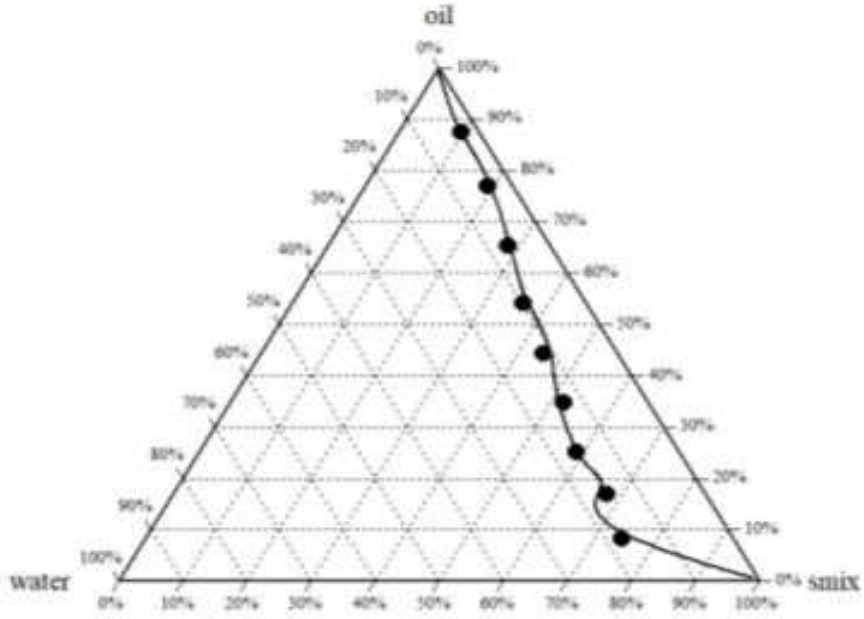

Figure 3: Ternary Phase Diagrams

Construction of Ternary Phase Diagrams [27, 28]:
Using titration, pseudoternary phase diagrams were created to determine microemulsion area. The oil and S/Cos mixtures were titrated with double-distilled water at room temperature under moderate magnetic stirring. After equilibration, mixtures were visually examined and classified as microemulsions, emulsions, or gels.

2. *Phase Inversion Method* [28]:

Microemulsions undergo phase inversion when an excess of the dispersed phase is added, or when the temperature changes. Changes in particle size and other physical properties can impact drug release *in vivo* and *in vitro*, and both can occur during phase inversion. This method is referred to as phase inversion temperature (PIT) method.

It is possible to take into account additional factors besides temperature, such as salt content or pH value. Altering the water volume fraction also results in a change in the spontaneous radius of curvature. When water is added to oil one drop at a time, droplets develop in the oil. When the water content is increased, the inversion locus shifts from stabilizing a water-in-oil (w/o) microemulsion to an oil-in-water (o/w) microemulsion due to the surfactant's spontaneous curvature.
Controlled addition of lesser alcohols (butanol, pentanol, and hexanol) to milky emulsions yields clear solutions with nanometer- or colloidal-scale dispersions of water-in-oil (w/o) or oil-in-water (o/w) (100 nm).

Microemulsions also have industrial applications, one of them being the synthesis of polymers. Microemulsion polymerization is a complex heterogeneous process where transport of monomers, free radicals, and other species (such as chain transfer agent, co-surfactant, and inhibitors) between the aqueous and organic phases, takes place. Compared with other heterogeneous polymerization processes (suspension or emulsion) microemulsion polymerization is a more complicated system. Polymerization rate is controlled by monomer partitioning between the phases, particle nucleation, and adsorption and desorption of radicals. Particle stability is affected by the amount and type of surfactant and pH of dispersing medium.

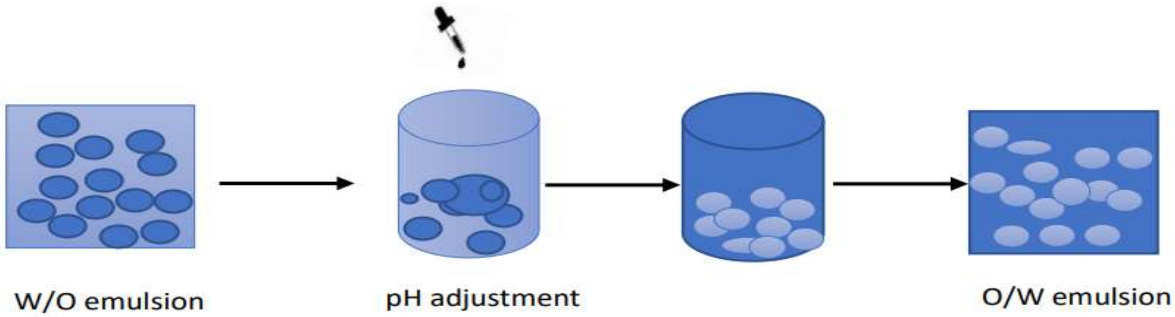

Figure 4: Phase Inversion Method

Types of Microemulsions [29, 30]

1. O/W Microemulsion
2. W/O Microemulsion
3. Bi-continuous Microemulsion

1. *Oil in Water Microemulsion:*

Continuous watery phase disperses oil droplets. Interesting o/w systems solubilize hydrophobic drugs in internal oil droplets, making them more soluble in aqueous systems. Most weakly water-soluble medicines prefer small/medium molecular volume oils over hydrocarbon oils due to their polarity

2. *Water in Oil Microemulsions:*

Continuous oil disperses water droplets. Water-in-oil microemulsions have oil continuous phases around water droplets. These are called "reverse-micelles," with the surfactant's polar head groups facing water droplets and the fatty acid tails facing oil.

3. *Bi-continuous Microemulsions:*

Micro domains of oil and water are interspersed within the system. A bicontinuous microemulsion system both water and oil exist as a continuous phase. Irregular channels of oil and water are intertwined, resulting in what looks like a “sponge-phase.

Hydrogels

A hydrophilic gelling agent appropriately gels an aqueous dispersion medium to form hydrogels, a particular type of gel [31]. Sodium alginate, carbapol, and other hydrophilic polymers including hydroxypropyl methylcellulose (HPMC), have all been studied as gelling agents in the past [32]. Chemical or physical crosslinks can be used to create hydrogels. Entanglements, crystallites, Van der Waals interactions, and hydrogen bonds are a few examples of these physical crosslinks. ''Reversible'' or ''physical'' hydrogels are crosslinked hydrogels made via physical processes [33]. ''Chemical'' or ''permanent'' hydrogels, on the other hand, are made of crosslinked networks that are covalently bound [34].

Diffusion and chemical stimulation are two different ways that drugs can be released from hydrogels. Erosion of the hydrogel in bulk or movement through the polymer matrix, both control diffusion. Chemically stimulated gels efficiently open their pores to release the medication that is trapped inside them when they swell in response to environmental cues like pH and temperature or enzymatic activity. Only sick tissues can benefit from this kind of mechanism for targeted medication release [35].

Classification of Hydrogel [30, 34, 35]:

1. Based on the Type of Networked Connections.

a. Permanent/Chemical Gels:

Crosslinked covalent networks (replacing the hydrogen bond with a stronger and more durable covalent bond) networks are dubbed 'permanent' or 'chemical' gels. They attain equilibrium expansion based on polymer-water interaction parameters and crosslinking density.

b. Reversible/Physical Gels:

Networked 'reversible' or 'physical' gels are kept together by molecular and/or secondary forces such ionic hydrogen bonding or hydrophobic interactions. Physical interactions between polymers inhibit dissolution chains in crosslinked gels. Changes and reverses can disturb all these connections stress or physical conditions.

2. Based on The Origin:

a. Natural Polymer:

Biocompatible, Biodegradable, Supports Cellular Activities do not have enough mechanical properties. It may contain pathogens. It caused immunity and inflammation feedback.

Examples: Proteins such as collagen and gelatine, polysaccharides such as alginate and agarose.

b. Synthetic Polymer:

Inherent bioactive properties are absent.

Examples: Acrylic Acid - Hydroxyethyl Methacrylate (HEMA), Vinyl Acetate, Methacrylic acid (MAA).

3. Based on The Preparation:

a. Homo polymer

Polymer networks made from one monomer called homopolymers. The infrastructure unit is any polymer network. Depending on the monomer and polymerization method, homopolymers may contain crosslinked skeletons. Crosslinked homopolymers are employed in contact lenses and medicine delivery.

b. Co-polymer

Co-polymeric hydrogels are comprised of two or more different monomer species with at least one hydraulic component, randomly designed, constraint or alternative configuration together the polymer network chain.

c. Red Semi Interpenetrate

If one polymer is linear and penetrates another interconnected network without any other chemical bonds between them, is called a semi-penetrating network.

Is a close mixture of two polymers, at least one of which is interpenetrating and synthesised or cross-linked in its presence. This is commonly generated by immersing prefiltered hydrogen in monomer and polymerization starting solutions. IPN can overcome thermodynamic incompatibility induced by permanent network segment connection and restricted phase separation. IPNs' key benefit is the ability to make thick hydrogel matrices with harder and tougher mechanical characteristics, controllable bodily traits, and better drug loading than other hydrogels.

Microemulsion Based Hydrogel:

Microemulsion consist of an oil phase, water phase, and surfactant mixture (S_{mix}), which is an isotropic, transparent, and thermodynamically stable colloidal system with particle sizes

between 10 nm and 200 nm [36, 37]. Water-insoluble pharmaceutical compounds may be effectively dissolved in the oil phase and/or absorbed at the oil-water interface of a microemulsion (ME). This enables a greater capacity for drug loading in the ME formulation and boosts the driving force for drug penetration through the skin [38, 39]. Furthermore, it has been shown that some components included in the ME formulation had the ability to promote penetration, hence overcoming the barrier functions of the skin. Nevertheless, despite the inherent benefits of microemulsions (MEs), their practical use in clinical environments has often encountered obstacles due to their limited viscosity. Therefore, there has been a significant interest in the use of ME-based hydrogels (MEHs) as a viable option for topical drug delivery systems. Typically, microemulsions (MEHs) with appropriate viscosity and favourable biocompatibility have the capacity to extend the duration of medication retention on the skin while mitigating the likelihood of skin irritation subsequent to their topical administration [40, 41].

Onchomycosis, fungal infection that affects the nail plate and nail bed, psoriasis, rheumatoid arthritis, allergic rhinitis AR [Fexofenatidine], and other topical infections are successfully treated with MBH formulations, which also have antibacterial, antifungal, immunosuppressive, and anti-inflammatory properties [42, 43].

Advantages [44, 45]:

- When applied topically, reduces the risk of upper GIT haemorrhage when NSAIDS are used by older people to provide an immediate anti-inflammatory benefit without any negative side effects.
- In comparison to standard formulations, MBH exhibits improved drug solubility as well as penetration, good thermodynamic stability, ease of manufacture, and optical clarity.
- Increased bioavailability, rate of absorption, and biocompatibility all contribute to the solubilization of lipophilic medicines while using low energy.

Disadvantages [46]:

- Iontophoresis has shown that drug penetration from MBH into body cavities like nails is an expensive and unsuccessful process.
- It has been discovered that topical gels and solutions used to treat fungal infections are poorly soluble in lipophilic medications.
- Corticosteroids like betamethasone dipropionate are weakly permeable through skin due to the stratum conium, a barrier function of the skin, which decreases therapeutic efficiency at the target region. Appropriate dermal vehicles should be incorporated into these formulations to address this drawback.

Basic Components of MBH Formulations:

In MBH systems, the primary ingredients are oils, surfactants, and co- surfactants; however, Due to their toxicity, risk for irritation, and unclear method of action, their use is restricted. Utilising the right concentration range of biocompatible, non-toxic, and clinically acceptable materials will produce a moderate, non-aggressive MBH.

1. **Oil Phase:** Oleic acid is employed as the ME's oil phase since it has a high solubilizing capacity. As in the case of the MBH system of Ibuprofen, camphor and menthol are occasionally utilised as an oil phase in a eutectic combination. MBH also uses ethyl oleate, lauryl alcohols, and isopropyl myristate. The drug's solubility in the aqueous phase is the main consideration when choosing an oil phase to administer dose of the medication in an encapsulated form in the MBH system [47, 48].

2. **Surfactants:** The surfactant should be able to generate a flexible film that easily deforms into droplets, low to a very low value that enables dispersion during MBH formation, and have the proper lipophilic character providing the necessary curvature at the interfacial area [41-48].

3. **Co - surfactants:** Due to the co surfactants' presence, the interfacial film has the flexibility it needs to adopt the many curvatures needed to produce micro emulsions over a wide range of composition. In a certain micro emulsion, a variety of nonionic surfactant and alcohol types can function as cosurfactants. Typically, a high HLB surfactant is paired with a low HLB co-surfactant [47, 48].

4. **Aqueous Phase:** Normally, distilled water is used as the aqueous phase [47, 48].

5. **Gelling Agent:** Various polymers make up its composition. These are the agents used to increase the consistency of any dosage form and can also be used as a thickening agent [49, 50].

Method of Preparation of Microemulsion Based Hydrogel:

The construction of the microemulsion-based hydrogel involved the utilization of a gel matrix with the aim of enhancing the viscosity of the microemulsion intended for topical administration. The hydrogel and microemulsion were combined gradually while being subjected to stirring [49, 50].

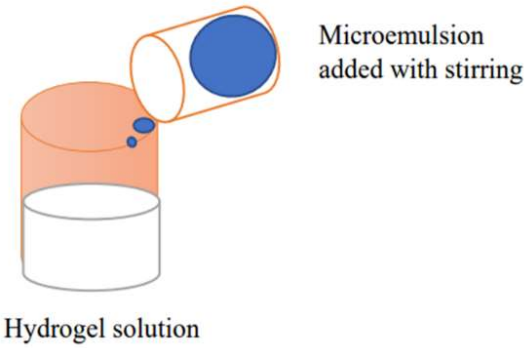

Figure 5: Preparation of Microemulsion Based Hydrogel

Characterization of the Microemulsions Based Hydrogel

Determination of physical parameter [51]:

Gel compositions were tested for visual colour, homogeneity; consistency, texture, and application feel, including grittiness, greasiness, stickiness, and smoothness. Checked formulation colour against white and black backdrop and hydrogel consistency was tested on skin.

pH Evaluation [52]:

pH assessment is crucial for topical formulations. The pH of hydrogel should be 5.8–6 to imitate skin. Patient irritation may result from acidic or basic hydrogel pH. By dipping the glass electrode into the hydrogel, a digital pH metre assessed its pH. The pH of each formulation was measured three times and averaged.

Viscosity [53]:

Brookfield Hydrogel viscosity was measured with a viscometer. Hydrogel formulation was poured to the beaker and settled for 30 minutes at 25-30 °C to determine viscosity. Position the spindle so it does not touch the bottom of the jar and revolve at 100 RPM for 10 minutes. The viscosity was recorded.

Spreadability [54]:

Modified laboratory equipment is used to measure spreadability. Two glass slides and a wooden block with a pulley at one end tested gel spreadability based on Slip and Drag. A ground glass slide was fixed on this block. 1 gramme of various formulation gels was put on the ground slide. Gel was placed between this slide and a fixed ground slide-sized glass slide. Extra gel was scraped off the edges. The top plate was pulled 50gms. Reduced slide separation time improves spreadability."

Spreadability is calculated by using the following formula:

$$S = M \times L/T$$

Where, S is the spreadability,
M is the weight in the pan (weight tied to the upper slide),
L = is the length moved by the glass slide,
T = time taken to separate the slide completely from each.

Drug Content Determination [55]:

For drug content determination, about 1 g of microemulsion based hydrogel was weighed in a 10 ml volumetric flask and dissolved it in methanol and diluted properly. Methanol was taken as blank and analyzed spectrophotometrically at specific λ_{max}.

Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor.

***In vitro* drug diffusion study [56-65]:**

It was done *in vitro* with cellophane membrane, activated cellophane membrane in glycerine for 4 h. This cellophane membrane was put on Franz diffusion cell using feviquick adhesive at the donor compartment edge to prevent test sample leakage. The receiver chamber was covered with cellophane and the donor chamber fastened. The diffusion medium was 30 ml of phosphate buffer pH 7.4 in the receiver chamber. The assembly was magnetically stirred. 1 gm of microemulsion-based hydrogel was placed on the cellophane membrane and stirred with a timer. At predefined intervals, samples were removed from the receiver solution and replaced with buffer solution to their designated volumes. The

receiver compartment solution was carefully added to avoid air trapping. The samples were filtered and %drug release was estimated by measuring absorbance at λ_{max}.

Stability Study [66]:

One month of stability investigations at different temperatures were performed on optimized microemulsion-based hydrogel formulations. Formulations were stored at 5 ± 3°C, 25 ± 2°C, and 45 ± 2°C. According to ICH recommendations, samples are taken every 10 days and analysed for appearance, pH, medication content, release profile, etc.

Skin irritation Test [67]:

White male rabbits (n=3) were used in the skin irritation investigation after receiving consent from the Animal Ethical Committee. After using an electric shaver to remove hair from the rabbits' dorsal sides, a sample of the test item weighing about 4 gm was introduced under a double gauze layer to a skin region of about 1" 1" (2.54× 2.54 cm^2) at each site (two sites per rabbit). Rabbits had their skin treated with the gelled emulsion. We put the animals back in their cages. The gellified emulsion is discarded after being exposed for 24 hours. Any remaining gel at the test locations was removed by rinsing with running water. Three days of visual observation were used to track the progression of erythema/edema.

CONCLUSION

The microemulsion gel system is the most convenient, effective, and efficient topical administration method. Gels are becoming increasingly popular due of their stability and regulated release. Its non-greasy gel-like texture and lack of oily bases enable improved medication release compared to other topical drug delivery systems. Incorporating microemulsion into gel creates a controlled release mechanism, addressing issues including phase separation and creaming, and improving stability. Microemulsion gels containing particular medications are useful for treating fungal and arthritic problems, making them a promising drug delivery strategy.

REFERENCES

[1] Tanwar H and Sachdeva R: Transdermal Drug Delivery System: A Review. Int J Pharm Sci Res 2016; 7(6): 2274-90.

[2] Mulla JS, Khazi IM. Influence of Process Variables on Particle Size of Solid Lipid Nanoparticles. Indian Journal of Novel Drug Delivery2009; 1(1): 47-49.

[3] Kumar A, Pullankandam N, Prabhu SL, Gopal V. Transdermal drug delivery system: an overview. Int. J Pharm Sci. Review Res. 2010;3(2):49-54.

[4] Mulla JAS and Karande BS. Microemulsion Based Hydrogel Formulation for Topical Drug Delivery - A Concise Review. Indian Journal of Novel Drug Delivery. 2021Apr-Jun; 13(2): 63-69.

[5] Rani S, Saroha K, Syan N, Mathur P. Transdermal patches a successful tool in transdermal drug delivery system. Plegia Res. Lib. 2011;2(5):17-29.

[6] Mabrouk M, Chejara DR, Mulla JAS, Badhe RV, Choonara YE, Kumar P, du Toit LC, Pillay V. Design of a novel crosslinked HEC-PAA porous hydrogel composite for dissolution rate and solubility enhancement of efavirenz. International journal of pharmaceutics. 2015; 490 (1-2): 429-437.

[7] Dhawan S, Aggarwal G. Development, fabrication and evaluation of transdermal drug delivery system- a review. Pharm info.net. 2009:1-25.

[8] Chejara DR, Mabrouk M, Badhe RV, Mulla JA, Kumar P, Choonara YE, du Toit LC, Pillay V. A bio-injectable algin-aminocaproic acid thixogel with tri-stimuli responsiveness. Carbohydrate polymers. 2016 Jan 1;135:324-33.

[9] Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. The Pharm Innovation. 2012;1(4):66-75.

[10] Jamakandi VG, Mulla JS, Vinay BL, Shivakumar HN. Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug. Asian Journal of Pharmaceutics. 2009; 3(1): 59-65.

[11] Jadhav VU, Jamakandi VG, Mulla JA, Borkar SN, Karpe P, Suresh R, Dama GY, Sanap GS, Chatap VK. Reservoir Type Nicorandil Transdermal Delivery System By Using Permeation Enhancers. Indian Drugs. 2009; 46(9): 23-31.

[12] Jalwal P, Jangra A, Dhaiya L, Sangwan Y, Saroha R. A review on transdermal patches. Pharm Res. J. 2010; 3:139-149.
[13] Gennaro, AR, Ed., Remington's Practice of Pharmacy, 20th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2000 p. 836.
[14] Narasimhulu A, Tzammulferdous S, M. Niranjan Babu. A Review on Transdermal Drug Delivery System. Asian J Res in Biological and P'ceutical Scie.2015; 2:59 - 65.
[15] Lakshmi P K , Samarth K, D. Prasanthi B. Veeresh, Chennuri A. Oils As Penetration Enhancers For Improved Transdermal Drug Delivery: A Review. Int. Res. J. Pharm 2017; 8(4):9-17.
[16] Sajid A, Maryam S, Nabeel S. The Structure of Skin and Transdermal Drug Delivery System- A Review. Res J. Pharm. and Tech 2015;8(2):103-109.
[17] Asija R, Asija S, Sharma D, Dhakar PC, Nama N: Topical ointment: an updated review. Drug Discovery T'peutics. 2015; 3(25): 47-51.
[18] Chandel A, Parashar B, Gupta N, Kumar A, Sharma V. An Overview On The Gel Formulation. Int Journal Pharm Rev Rese2013; 2(1): 18-22.
[19] Sowmya J, Gowda DV, Srivastava A.Topical Gels: A Recent Approach for Novel Drug Delivery. Int.J Health Scie and Rese2015; 5(10): 305-312.
[20] Steinstrasser I, Merkle HP. Dermal metabolism of topically applied drugs: Pathways and models reconsidered. Pharmaceutica Acta Helvetiae 1995; 70:3–24.
[21] Jain NK, Controlled and novel drug delivery. 1st Ed., CBS Publisher and Distributors, New Delhi. 2001:100-129.
[22] Goodarzi, F. & Zendehboudi, S. Effects of Salt and Surfactant on Interfacial Characteristics of Water/Oil Systems: Molecular Dynamic Simulations and Dissipative Particle Dynamics. Ind. Eng. *Chem. Res.* 58, 8817–8834 (2019).
[23] Mu, J., Motokawa, R., Akutsu, K., Nishitsuji, S. & Masters, A. J. A Novel Microemulsion Phase Transition: Toward the Elucidation of Third-Phase Formation in Spent Nuclear Fuel Reprocessing. J. Phys. Chem. B 122, 1439–1452 (2018).
[24] Paliwal, H., Solanki, R. S., Chauhan, C. S. & Dwivedi, J. Pharmaceutical Considerations of Microemulsion as a Drug Delivery System. 9, 661–665 (2019)
[25] Deng, Y. *et al.* Improving the skin penetration and antifebrile activity of ibuprofen by preparing nanoparticles using emulsion solvent evaporation method. Eur. J. Pharm. Sci. 114, 293–302 (2018).
[26] Shakeel, F. *et al.* Nanoemulsions as vehicles for transdermal delivery of aceclofenac. AAPS Pharm Sci Tech. 8, 191 (2007).
[27] Heuschkel, S.; Goebel, A.; Neubert, R.H. Microemulsions—Modern colloidal carrier for dermal and transdermal drug delivery. J. Pharm. Sci. 2008, 97, 603–631.
[28] Cabaleiro-Lago, C.; Garcia-Rio, L.; Hervella, P. The effect of changing the microstructure of a microemulsion on chemical reactivity. Langmuir. 2007; 23: 9586–9595.
[29] Pepe, D.; Phelps, J.; Lewis, K.; Dujack, J.; Scarlett, K.; Jahan, S.; Bonnier, E.; Milic-Pasetto, T.; Hass, M.A.; Lopes, L.B. Decylglucoside-based microemulsions for cutaneous localization of lycopene and ascorbic acid. Int. J. Pharm.2012, 434, 420–428.
[30] Khurram Rehman and Mohd Hanif Zulfakar. Recent advances in gel technologies for topical and transdermal drug Delivery. Drug DevInd Pharm, 2014; 40(4): 433–440
[31] Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulation. Eur J Pharm Biopharm 2000;50:27–46.
[32] Martinez RMA, Julian LVG, Maria MdB, et al. Rheological behavior of gels and meloxicam release. Int J Pharm 2007;333: 17–23
[33] Davide C, Patrick D, Marco R, et al. Semisynthetic resorbable materials from hyaluronan esterification. Biomaterial 1998;19: 2101–27.
[34] Allan SH. Hydrogels for biomedical applications. Adv Drug Deliv Rev 2012;64:18–23.
[35] Naryan B, Jonathan G, Miqin Z. Chitosan-based hydrogels for controlled, localized drug delivery. Adv Drug Deliv Rev 2010;62: 83–99.
[36] Zhu W, Guo C, Yu A, Gao Y, Cao F, Zhai G. Microemulsion-based hydrogel formulation of penciclovir for topical delivery. Int J Pharm 2009;378:152e8.
[37] Kansagra H, Mallick S. Microemulsion-based antifungal gel of luliconazole for dermatophyte infections: formulation,

characterization and efficacy studies. J Pharm Invest 2016;46:21e8

[38] Sah AK, Jain SK, Pandey RS. Microemulsion based hydrogel formulation of methoxsalen for the effective treatment of psoriasis. Asian J Pharm Clin Res 2011;4:140e5

[39] Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev 2000;45:89e121.

[40] Lee SG, Kang JB, Kim SR, Kim CJ, Yeom DW, Yoon HY, Kwak SS, Choi YW. Enhanced topical delivery of tacrolimus by a carbomer hydrogel formulation with transcutol P. Drug DevInd Pharm 2016;42:1636e42.

[41] Rao S, Barot T, Rajesh K, Jha LL. Formulation, optimization and evaluation of microemulsion based gel of butenafine hydrochloride for topical delivery by using simplex lattice mixture design. J Pharm Invest 2016;46:1e12.

[42] Almoshari, Y. Novel Hydrogels for Topical Applications: An Updated Comprehensive Review Based on Source. Gels 2022, 8, 174.

[43] Hyma. P, Noor Jahan, Raheemunissa, Sreelekha G, Babu K. Microemulsion Based Hydrogel Formulation For Topical Delivery. An International Journal of Advances in Pharmaceutical Sciences. Volume 5, Issue 1, January-February 2014,Pages 1874-1880.

[44] Muzib, Kumari. Study on transmucosal permeation of Diclofenac Diethylamine Micro emulsion Gel. Int.J. of Pharm and biological research IJPBR, 3 3, 2012.

[45] Ujwala Shinde, Sharda Pokharkar and Sheela Modani. Design and evaluation of Micro emulsion Gel system of Nadifloxacin. Indian J. Pharm Sci. 74 3, 237-247, 2012

[46] Vidya Sabale and Sejal Vora. Formulation and evaluation of MBH for topical delivery of Bifanazole. Int.J.Pharm.Investig. 2 3, 140-149, 2011.

[47] Yongmei Yin, Fude Cui, Chaofeng Mu, Suk-Jae Chung, Chang-Koo Shim, Dae-Duk Kim. Improved solubility of docetaxel using a microemulsion delivery system: formulation optimization and evaluation. Asian Journal of Pharmaceutical Sciences, 4 6: 331-339, 2009.

[48] Hong-Mei Piao, Prabagar Balakrishnan, Hyun Jong Cho, Hyunjun Kim. Preparation and evaluation of fexofenadine microemulsion for intranasal delivery, 2010.

[49] Lee EA, Balakrishnan P, Chng Kil Song CK, Choi JH, Noh GY, Park CG, Choi AJ, Chung SJ, Shim CK, Kim DD. Microemulsion based hydrogel formulation of itraconazole for topical delivery. J Pharm Invest 2010;40:305-11.

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

[51] Reddy K, Smitha E, Vandana P, Mohanambal E, Raja S, Umadevi S. Formulation of nimesulide microemulsion based hydrogel for topical delivery: *in vitro* and *ex vivo* characterization. Scientia J Res Pharm 2011; 2: 15-23.

[52] Deepak Chandra Sharma et al. "Desin and characterization of apermilast loaded hydrogel for topical treatment-aresearch". International journal of pharmacy and biological sciences 2018, volume 8: 552-562.

[53] Swati Verma, etal. "Formulation and evaluation of ketoconazole nanohydrogel–a research". World journal of pharmacy and pharmaceutical science, 2016, volume 5(2):899-911.

[54] G. Jagadish, Rama Shukla, Purnima Shukla. Formulation and evaluation of microemulsion based gel of posaconazole for topical delivery. EPRA International Journal of Research and Development (IJRD). 2021;6(1): 165-174.

[55] Dadwal M. Hydrogel: A novel approach to topical drug delivery. Sci. J Res Pharm 2013; 4: 847-56.

[56] Hiremath SP, Dasankoppa FS, Nadaf A, Jamakandi VG, Mulla JS, Sholapur HN. Formulation and evaluation of a novel in situ gum based ophthalmic drug delivery system of linezolid. ScientiaPharmaceutica. 2028; 76 (3): 515-532.

[57] Mulla JA, Suresh S, Khazi IA. Formulation, characterization and *in vitro* evaluation of methotrexate solid lipid nanoparticles. Research J. Pharm. and Tech. 2009 Oct;2(4):685-689.

[58] Mulla JA, Dasankoppa FS, Vilas GJ, Sholapur HP. Fast dissolving tablets of promethazine: A novel oral formulation for the treatment of fractionated radiotherapy-

induced nausea and emesis. Indian Drugs. 2008; 45(4):314.

[59] Panchamukhi SI, Mulla JA, Shetty NS, Khazi MI, Khan AY, Kalashetti MB, Khazi IA. Benzothieno [3, 2-e][1, 2, 4] triazolo [4, 3-c] pyrimidines: Synthesis, Characterization, Antimicrobial Activity, and Incorporation into Solid Lipid Nanoparticles. Archiv der Pharmazie. 2011 Jun;344(6):358-65.

[60] Mulla JAS, Hiremath SP, Sharma NK. Repaglinide loaded solid lipid nanoparticles: design and characterization. RGUHS J Pharm Sci 2 (4), 41-9.

[61] Mulla JAS, Shetty NS, Panchamukhi SI, Khazi IAM. Formulation, Characterization and *in vitro* Evaluation of Novel Thienopyrimidines and Triazolothienopyrimidines Loaded Solid Lipid Nanoparticles. International Journal of Research in Ayurveda & Pharmacy. 2010; 1(1): 192-200.

[62] Mulla JA, Khazi MI, Khan AY, Gong YD, Khazi IA. Design, Characterization and *In vitro* Evaluation of Imidazo [2, 1-b][1, 3, 4] thiadiazole Derivative Loaded Solid Lipid Nanoparticles. Drug Invention Today. 2012; 4(8): 420-423.

[63] Mulla JAS, Aralelimath VR, Tipugade O, Shinde SS, Tetgure NG, Mulla AA, Gavali DD. Formulation and Evaluation of Teneligliptin-Loaded Mucoadhesive Microspheres. Indian Journal of Novel Drug Delivery. 2020 Oct-Dec;12(4): 222-227.

[64] Mulla JAs, Chopade UA, Kumbhar SA, Marathe PA, Ware PV. Formulation and Evaluation of Fast Dissolving Oral Films of Domperidone. Indian Journal of Novel Drug Delivery 10 (2), 68-75.

[65] Reddy K, Smitha E, Vandana P, Mohanambal E, Raja S, Umadevi S. Formulation of nimesulide microemulsion based hydrogel for topical delivery: *in vitro* and *ex vivo* characterization. Scientia J Res Pharm 2011; 2: 15-23.

[66] G. Jagadish, Rama Shukla, Purnima Shukla. Formulation and evaluation of microemulsion based gel of posaconazolefor topical delivery. EPRA International Journal of Research and Development. 2021;6(1): 165-174.

[67] Dhruti PM, Hemendrasinh J. R., Dhiren P. S, Chainesh N. Review on Microemulsion Based Gel: A Recent Approach for Topical Drug Delivery System, Research J. Pharm. and Tech.8 (2): February 2015,Page 118-126.