A REVIEW: MICROEMULSION-BASED POLYMER MATRIX TRANSDERMAL PATCH FOR THE TREATMENT OF INFLAMMATION

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Abstract

The inflammation is the Immunogenic response when a foreign particle or material or any antigen is entered in the body. The topical delivery or a transdermal delivery is defined as it is a route of administration of a drug via skin or to protect the drug from the metabolism process. The topical formulations are of different types such as lotion, creams, patches, gels and ointments. The transdermal patches are the system where the medicine is diffused from the matrix of polymer and penetrates the skin and the drug shows the therapeutic benefit to the patient. Microemulsion patches are the novel delivery system in which the drug is in micron size ranges and then easily penetrates the skin and becomes a more successful drug delivery over the conventional patches. The microemulsions are the thermodynamically stable biphasic seen as a clear solution in which the drug is entrapped in a dispersed phase and the continuous phase is work as the vehicle for the administration of the dose. There are some tests like entrapment efficiency and Invitro drug release testing for determination of its efficacy. There are some characterization tests like electro conductivity study, rheological properties and centrifugation study has also performed the folding endurance surface pH and the water content and the stability testing has been performed. The microemulsion patch drug delivery system has been found to have more bioavailability and duration of action than the conventional patches or the topical formulation.

Keywords: Inflammation, Transdermal Patches, Microemulsions, Matrix System, Analgesics, Skin.

INTRODUCTION

The medicine distribution using pores and skin offers a greater and more attractive technique of administering pills over the parenteral and oral drug delivery. It bypasses the hepatic first-pass metabolism and avoids the limits of oral drug distribution such as GI degradation, hepatic clearance, etc. At the same time, it is a non-invasive and comfy mode of remedy shipping as a result favoured over the parenteral route[1].

In spite of such benefits, the skin administration of medicines has a range of constraints such as low drug permeability and poor bioavailability due to the presence of pores and skin barrier (stratum corneum)[2,3].

As the skin is the predominant shield protecting the body, it considers all the medication and excipients as external factors and restricts its entry within the body. This difficulty is a widespread obstacle to cutaneous drug administration.

The human skin consists of three layers epidermis, dermis, and subcutaneous tissues. The dermis is the top piece of the skin made out of 5 layers; 1) layer corneum, 2) layer lucidum, 3)stratum granulosum, 4) layer spinosum and 5) layer germinativum gradually from outdoor to inside. This layer accommodates keratinocytes, answerable for the union of keratin. The dermis is the mid layer composed of collagen filaments. It comprises the sebaceous organ, hair follicles, sweat organ, sensitive spots, and veins. This layer ends in the subcutaneous tissues including fat globules and fat tissues[4-7].

Among all the pores and skin layers, the layer corneum is the vast limitation for remedy assimilation. Nonetheless, there are unique courses for transmission of ordinary cloth through the pores and skin which includes the intercellular, follicular and intracellular pathway. The intracellular pathway is successful for the transmission of hydrophilic remedial substances. The
follicular or transappendageal channel approves the on the spot and fast conveyance of substances to the infundibulum district whilst the intracellular vehicle advances the entrance of lipophilic medicament atoms[8]

Figure. 1.Construction of skin uncovering the fundamental parts of the epidermis, dermis, and hypodermis (adjusted from Alexander et al. 2012).
Figure 2. The photos portray numerous ways of medication infiltration by means of various layers of skin including intracellular, intercellular and follicular pathways. (adjusted from Tripti et al. 2018)

The inflammation is defined as at the point when your body comes in contact with an offending substance (for example viruses, bacteria and dangerous chemicals) or your immune system is activated after a wound. Inflammatory cells and cytokines are among the initial immune system responses (substances that activate more inflammatory cells).

To be able to capture microorganisms and other hazardous things or to start the restoration procedures for wounded tissue, these cells trigger an inflammatory reaction. As a result, you may experience pain, swelling, bruising, and redness. Inflammation, on the other hand, has unobservable effects on physiological systems[10].

Chronic inflammation can concentrate on a second rate strength incendiary reaction that is ordinarily as of now not clear of course can be distinguished through extended assembling of cytokines, chemokines, prostaglandins, nitric oxide, proteases and unique fiery middle people at the tissue and plasma recognition. Ongoing irritation can't be related to the guide of methods of intense disease[11].
Types of Inflammation[10]

1) Acute Inflammation

2) Chronic Inflammation

The body's response to a sudden injury, such as cutting your finger, is acute inflammation. To aid in the healing of the injury, inflammatory cells from your body are sent to it. Such cells are where the recovery procedure begins.

When the body sends the inflammatory cells even since there is no external threat, this is known as chronic inflammation. Inflammatory cells and chemicals attack joint tissues in rheumatoid arthritis, for example, generating a flare-up of inflammation that can cause substantial joint damage, such as pain and deformity.

Acute inflammation can result in flushed skin at the injury site.

Tenderness or pain.

Swelling. Heat

It's likely that chronic inflammation symptoms are more difficult to identify than acute inflammation symptoms. Chronic inflammation can express itself in a variety of ways, including:

Pain in the abdomen. Pain in the chest. Fatigue. (For instance, systemic lupus) Fever. (For instance, TB). Joint stiffness or discomfort. (For instance, rheumatoid arthritis). Sores in the mouth. (For instance, HIV infection). A rash on the skin. (For instance, psoriasis)

A transdermal patch is a local use of a drug to healthy skin, either for specific curing of the local portion under the surface or for full-body therapy. There are many advantages of employing a transdermal patch vs standard formulation and controlled-release oral systems.
The utilization of a topical delivery ensures predictable plasma levels, escapes hepatic metabolism processing, works on tolerating consistency, and takes away part dumping[12,13].

Table 1: Ideal Properties of Drug for Transdermal Drug Delivery System [14]

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Less than 20mg/day</td>
</tr>
<tr>
<td>Half life</td>
<td>&lt; 10 hrs</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt;400 Daltons</td>
</tr>
<tr>
<td>Melting point</td>
<td>&lt;200°C</td>
</tr>
<tr>
<td>watery dissolvability</td>
<td>&gt;1mg/mL</td>
</tr>
<tr>
<td>pH of the watery immersed arrangement</td>
<td>5-9</td>
</tr>
<tr>
<td>Skin Penetrability Coefficient</td>
<td>&gt;0.5x10^{-3} cm/h</td>
</tr>
<tr>
<td>Skin Response</td>
<td>Nonirritating and non-sensitizing</td>
</tr>
<tr>
<td>Oral Bioavailability</td>
<td>Low</td>
</tr>
</tbody>
</table>

Due to the substantial obstruction to infiltration over the skin, which is fundamentally linked with the epidermis’ farthest layer cornum layer, epidermal transportation of a more expanded scope of medications is constrained. As indicated by the activity’s objective site, skin details can be isolated into two kinds. After prescription take-up from the cutaneous microvascular network, one makes foundational impacts, while the other has neighborhood impacts in the skin. Transdermal medication organization can almost rough sluggish intravenous imburement without the dangers, and it likewise has the additional advantage of letting the consumers to quit taking the medicine by just eliminating the fix at the picked time assuming that poisonousness happens.[15]

Microemulsions are fluid frameworks that are straightforward, optically isotropic, and thermodynamically steady, with drop sizes going from 10 to 100 nanometers[16]

Microemulsions have been infinitely better than traditional definitions and have been viewed as magnificent with regards to dissolvability, ingestion, and dissemination. Moreover, they make skin organization simpler by coordinating the dynamic moiety into gels, forestalling the hepatic first-pass impact, corruption of the dynamic moiety in salivary and stomach contents, and other unfavorable consequences. Oil, surfactant, cosurfactant (e.g., sorbiton monooleate, propylene glycol), and watery stage coincide in a solitary stage in microemulsions to increment prescription bioavailability after effective and foundational conveyance. Hoar and Schulman were quick to propose the idea of microemulsion in the mid 1940s.

Table 2: Types of Microemulsions on the basis of Emulsifier used

<table>
<thead>
<tr>
<th>Nature of emulsifier</th>
<th>Structure of the system</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonionic surfactants</td>
<td>O/W, W/O emulsions</td>
<td>[17]</td>
</tr>
<tr>
<td>Ionic surfactants</td>
<td>Micellar emulsions</td>
<td>[17]</td>
</tr>
<tr>
<td>Surfactant mixtures</td>
<td>Microemulsions</td>
<td>[18]</td>
</tr>
<tr>
<td>Polyelectrolytes</td>
<td>Bilayer droplets</td>
<td>[19]</td>
</tr>
<tr>
<td>Mixed polymers and surfactants</td>
<td>Double and multiple emulsions</td>
<td>[20]</td>
</tr>
<tr>
<td>Liquid crystalline phases</td>
<td>Mixed emulsions</td>
<td>[21]</td>
</tr>
<tr>
<td>(Pickering emulsions)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-steroidal calming medications (Non - steroidal enemy of) are usually used to make transdermal patch systems for the treatment of irritation & distress. NSAID patches are a more secure and more helpful option in contrast to the oral structure. Rheumatoid joint inflammation patients were given different NSAID pills. The utilization of NSAID transdermal patches limits incidental effects, for example, stomach dying, expanded causticity, and ulcers. A NSAID pain relieving patch can be applied to the site of an injury, sprain, or strain. At the point when these patches are set topically as a transdermal fix, the medicine enters into Â the epidermis, subcutaneous adipose tissue, and muscle at enough dose to have local remedial benefits without arriving at increased plasma drug concentrations. So as a consequence, NSAIDs give the advantage of further developed nearby prescription conveyance to burdened tissues while decreasing the gamble of foundational secondary effects. Patients with Rheumatoid Arthritis are urged to involve NSAIDs for a more drawn out timeframe, albeit the fundamental contraindications of NSAIDs prescriptions incorporate foundational harmfulness and GIT bothering[22,23]
Diclofenac sodium is a non-steroidal mitigating medicine i.e. commonly used for symptomatic therapy for pain and inflammation in musculoskeletal disorders, arthritis, toothaches, and other conditions. Topical applications of diclofenac sodium have been reported. Only about half of the drug’s prescribed dose reaches systemic circulation due to extensive hepatic first-pass metabolism.

NSAIDs are recommended for those patients with rheumatoid arthritis, although Diclofenac sodium has a large list of negative impacts, including systemic toxicity, Gastrointestinal irritation, nausea, vomiting, gastrointestinal erosion, and headache. It is a good candidate for formulation into a transdermal patch device with a sustained release matrix, because to its own small biological half-life and repeated dosage. The study’s main purpose is to create a Diclofenac sodium transdermal patch Reducing dose frequency while increasing medicine dosage release rate will help patients adhere to their treatment regimens more effectively for faster To prevent GIT-related bioavailability, delay drug oral delivery until after the initiation of action, and increase drug availability regionally to the site of action in arthritis[24].

Table 3: Drug Description of Diclofenac sodium

<table>
<thead>
<tr>
<th>IUPAC NAME</th>
<th>sodium;2-[2-(2,6-dichloroaniline)phenyl]acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>In the temperature scope of 293.15 to 313.15 K, the solvency of Diclofenac sodium in CH3)2CO, ethyl acetic acid derivation, and dimethyl sulfoxide. The dissolvability of the prescription increases with temperature in all solvents, true to form, yet this effect is more in dimethyl sulfoxide.</td>
</tr>
<tr>
<td>Molar formula</td>
<td>C14H10Cl2NNa2</td>
</tr>
<tr>
<td>Molar mass</td>
<td>318.1 g/mol</td>
</tr>
<tr>
<td>Melting point</td>
<td>284.0 °C</td>
</tr>
</tbody>
</table>

FORMULATION OF MICROEMULSION MATRIX BASED TRANSDERMAL PATCH

Preparation of w/o Microemulsion

Drug was mixed with the oil phase and the surfactant and co surfactant was added. The water is added drop by drop with continuous stirring with gentle heat. The clear oil phase was formed.

Preparation of Drug containing Microemulsion hydrogel

The microemulsion hydrogel was Prepared by adding the aqueous polymer solution in the microemulsion with continuous stirring.

preparation of Microemulsion based Patches: The polymer solution is spread in the mould of required size and forms an even layer. the layer is dried for some time, the hydrogel was spread on the membrane and than the required amount of permeation enhancer and cosolvent was added. Then it is sealed with the polymeric solution and it is then freeze dried. and the patch was obtained.
Figure 4: Formulation of Microemulsion based Transdermal patches (Original Flow diagram)

EVALUATION PARAMETERS

Centrifugation study:

Any changes in homogeneity were noted after centrifuging the ME-based formulations for 30 minutes at 25 °C using a Microliter Centrifuge (Heraeus Biofuge Pico) at 10,000 round per minute and a relative radial force (RRF) of 8960 grams[25].

Particle size measurement:

A Zetasizer Nano-DTS 1060 was used to measure the particle size at 25°C and a fixed angle of 173°. (Malvern Instruments Ltd, UK). After the formulations had been suitably diluted in double-distilled water, the samples were maintained in disposable cuvettes, and the observations were made three times. As a statistic for the quality of droplet-size distribution, the polydispersity index (PDI) was used[26].

Rheological studies:

A Brookfield DV-III Ultra viscometer was utilized to assess the microemulsions' thickness. Shaft number 21 was turned at 150 cycles each moment with a 30 second interruption. The formulations were offered a reprieve at room temperature for 10 minutes before the perceptions. The rheological boundaries of the Microemulsion - based gel were estimated utilizing a Malvern Rheometer (kinexus) with an equal plate.

Entrapment efficiency:

The amount of drug entrapped in the formulation is assessed by percentage drug entrapment. The produced microemulsion was ultra centrifuged (REMI, India) at 20,000 rpm for the measurement of percentage drug entrapment. The isolated supernatant oil phase was diluted in methanol and spectrophotometrically measured for Diclofenac Sodium at 280 nm after dilution. The percentage of drugs entrapped was determined as follows.

\[ \% \text{ Entrapment (E)} = \frac{C_{\text{final}}}{C_{\text{initial}}} \]
Zeta Potential:

This research is beneficial because it offers information on the surface charge of microemulsions, which is important in assessing formulation stability. The zeta potential was determined by using Malvern Zetastester nano ZS-90 (Malvern Instruments Ltd., UK). The zeta potential cell was filled with a predetermined amount of sample and inserted close to the lids for analysis, with its inbuilt gold electrodes.

In vitro Drug release test:

A modified diffusion cell (region 2.5 cm²) with a treated cellophane layer was utilized to assess the in-vitro arrival of medicine from a few ideal plans. The contributor and receptor compartments of the cells were then braced along with the layer. The receptor arrangement consisted of 20 mL of Phosphate buffer pH 7.4 that was kept at 37±0.5°C utilizing a thermostatic water shower and attractively fomented at 600rpm during the examination. 1 g of material was in the contributor chamber. The 0.7 ml aliquots elminated from the receptor compartment at 0.5 hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 12 hr, 18 hr, and 24 hr spans were then supplanted with new receptor arrangement. The samples were quickly spectrophotometrically assessed for concentration at 277 nm.

Skin sensitivity study

The irritation test was carried out to investigate localized reactivity of the skin to microemulsion and microemulsion-based hydrogel. A single dose of 101 of optimized MEDS, and HMEDS was administered in Swiss Albino mice's left ear for this purpose, using the right ear as the control. The Utelly test was used to track the progression of erythema over the course of three days.

The following formula, Eq. (1), was used to compute irritation potential:

\[
\text{The following indices are produced: } \frac{A}{B} \times \frac{1}{\text{Number of observation days}} (1)
\]

where, respectively, A and B stand for the erythema value and corresponding day.

Pharmacodynamic studies

The anti-inflammatory efficacy was once studied using a water plethysmometer to check changes in paw volumes in a carrageenan-induced rat paw oedema model. (Italy, Ugo Basile Model No. 7140). Female Charles Foster albino rats weighing between one hundred and 130 grams divided into seven groups, each having six animals. One day earlier than experiment, they employed an electric powered clipper to do away with the hair on their backs. On the backs of the rats, 100 milligrammes of the dosage structure was once positioned at some point of a place of 8-10 cm². No applications had been delivered to the control group. Oedema used to be precipitated one hour after drug cure by way of injecting 0.05 ml of a 0.5 percent w/v carrageenan suspension in saline subcutaneously beneath the plantar surface of the left hind paw the use of a 26 gauge needle. The plethysmometer used to be used to measure the oedema extent straight away after the carrageenan challenge, as properly as three and 5 hours later. The extent of each rat's left and proper paws was once measured right away after the carrageenan venture and deducted from the extent of the corresponding paws at the end of the third hour following carrageenan injection. For each rat in a group, the amplification in saline paw volume used to be deducted from the upward thrust in carrageenan paw quantity to generate an internet make bigger in bigger paw volume, i.e. oedema. The rats' paw volume increases were then averaged for every group. The average paw swelling of drug-treated rats (Vt) was in contrast to that of managed rats (Vc) (Vc) (Vc). The formula (1- \( Vt / Vc \) x one hundred was used to measure the proportion inhibition of oedema formation. Similarly, the proportion inhibition of oedema at the give up of the 5th hour after carrageenan injection, i.e. the sixth hour after drug packed method administration, was once calculated.

Evaluation for the transdermal patch system

Physical appearance

Color, clarity, flexibility, and smoothness were all checked visually on all of the prepared patches.
Thickness of the patch

A screw gauge micrometer has been used to determine the thickness of the drug-loaded patches at three different spots on the patches. For each drug-loaded patch, the average and probable error values of 3 observations were determined.

Uniformity of weight

After measuring all of the patches on an electronic weight machine, the patches were exposed to a weight variation test. For each formulation, the tests were done in triplicate. After that, the mean mass and standard error were determined.

Flatness study

A flatness test was done to guarantee that the transdermal patches manufactured had an easy texture and would not cave in with time. At three wonderful places on the film, three longitudinal strips were cut. Each strip's size used to be measured, and the difference in size attributable to non-uniformity in flatness used to be determined by the usage of percent constriction, with zero percent constriction equaling a hundred percent flatness.

\( \frac{(l_1 - l_2)}{l_1} \times 100 \) was used to determine the percentage restriction. The initial length of every strip is \( l_1 \), but the give up size of every strip is \( l_2 \).

Folding endurance

This check was carried out to examine how advantageous the plasticizer was or how sturdy the patch created from polymeric composites was. The number of folds necessary to rupture any polymer patch is known as folding endurance. Manual folding staying power was assessed through folding a little piece of film (2x2 cm) in the same area until it broke. The value of folding persistence was decided by the number of instances the patch may want to be folded in the identical place barring breaking or cracking. The examination comprised three patches of each kind.

Water vapor transmission

The amount of dampness moved by means of unit surface area of film in time \( t \) is known as the water fume transmission rate (WVTR) (WVTR). As transmission cells, glass vials of equivalent volume and width were used. The cells were painstakingly washed and dried in the broiler. The fix was then put over the edge of the vial with the assistance of sticky tape, and about 1 g of anhydrous melded calcium chloride was poured in every vial. These vials were then gauged and placed in desiccators with an immersed potassium chloride answer for keep an overall dampness of 84%. After the first, second, third, fourth, fifth, 6th, and seventh days, the cells were taken from the desiccators and gauged. The pace of water fume transmission was assessed as follows:

\[
\text{W} = \frac{W \times L}{S \times W} \text{ V.T.}
\]

Where \( W \) is the heaviness of water fumes moved, \( L \) is the thickness of fix and \( S \) is the surface region uncovered in square centimeters.

Surface pH

In glass tubes, patches were set in touch with 0.5 ml of twofold refined water for 1 hour and permitted to grow. Following a one-minute equilibration span, pH readings were taken with a blend glass terminal set close to the fix's surface.

Drug content determination

Every sort of plan was cut into 2x 2 pieces and put in 100 cc phosphate cushioned saline pH 7.4 arrangement, For 2 hours, the items were attractively upset. From that point onward, the arrangement was sifted utilizing Whatman channel paper (0.45) and weakened with phosphate cushion saline pH 7.4 to the fitting fixation. The arrangement's absorbance at 289 nm was then tried utilizing a fake treatment fix as a control. The medication content was resolved utilizing the absorbance readings.
Recent Advances in transdermal Drug delivery system

1. Transdermal films of non-steroidal moderating cure diclofenac sodium the usage of mercury substrate approach and examined for physicochemical impediments like thickness, weight variety, sogginess take-up, soddenness content, falling steadiness, and cure content material qualities. Three transdermal patches had coordinated the usage of specific centralizations of ethyl cellulose with the guide of dissolvable projecting technique. They contemplated that as the union of polymers would draw out the thickness of fix, weight consistency and give way eagerness rises, rate moistness content material fabric and rate sogginess take-up diminishes with development in polymer center.

2. A transdermal film of indomethacin the utilization of patchouli oil as a property enhancer to increase transdermal immersion of the cure from the cross section contraption all by rat epidermis. the transdermal progress done of the exceptional thought of patchouli oil will routinely decorate with creating point of convergence of the oil and the top notch transdermal movement of 61.92 ± 0.89 μg/cm2/hr was once when gotten with methodology f7 (counting 1% w/v of patchouli oil). They contemplated a feasible overhauling effect of patchouli oil on the transdermal entrance of the model drug medication indomethacin and may moreover likewise similarly be utilized as expected invasion sponsor in transdermal restorative medication transport structures.

3. A transdermal therapeutic drug giving over (tdds) of metformin hydrochloride (mfh) making usage of mixes of polyvinyl pyrrolidone k30 and hydroxypropylmethylcellulose e50 in a number extents through dissolvable scattering approach. PVA used to be utilized to develop the supporting layer and dibutyl phthalate as plasticizer. They guessed that metformin hydrochloride that shipped off from the transdermal patches of f7 (pvp k30-hpmc e50 2.5:1) are superb legitimate for daily medication transport.

4. An ethosomal definition of glimepiride then deliberate transdermal film to provide decreased drug point of view impact, multiplied discharge behaviors and continue to be away from first forget about with the help of impact. Four aspects had been simplified for their penalties for vesicle trouble (y1), entanglement effectivity (y2) and vesicle adaptability (y3) (y3) (y3). The accelerated ethosomal recipe validated hooked up values for y1, y2 and y3 of sixty one nm, 97.12% and 54.03, respectively. Ethosomal method would probably want to be regarded as a suited remedy conveyance framework for the most phase when piled into transdermal automobiles with achievable lessen in aftereffects and managing the remedy discharge.

5. A transdermal patches of cefdinir utilizing a scope of polymers like cellulose subsidiaries, polyvinyl liquor, polyethylene, polypropylene, polyvinylpyrrolidone and polymethyl methacrylate with their excellent consideration thru the dissolvable vanishing approach by means of the utilization of peg-400 as plasticizer. They reasoned that amongst a lot of polymers hpmc k100m used to be located to be the incredible polymer employed to layout transdermal patches.

CONCLUSION

After the review it is concluded that micro emulsion patch is thermodynamically stable, increased drug solubility and easily formulated. The invivo Â and invivo drug permeation determines that the drug easily penetrates from the skin and might shows its efficacy. The micro emulsion can be used for the enhancement of the efficacy of the drug. The efficacy of the microemulsion patches is more than the conventional transdermal patches, so that it might be used in the treatment of many skin and peripheral diseases.

CONFLICT OF INTEREST:

The authors have no conflict of interest regarding this investigation.

REFERENCES


10. https://my.clevelandclinic.org/health/symptoms/21660-inflammation


47. kumar et al. Robbins Basic Physiology 8th edition, Elsevier.