INTRODUCTION:

Transdermal delivery is a very effective alternative approach. A typical adult’s skin is penetrated by one-third of the blood that circulates through their body, with a surface area of about 2m. It is necessary to have some information about the skin because they administer the drug by use of the skin’s transdermal layer.\(^1\)\(^2\)

The transdermal approach has the advantage because increasing the permeability of the drug, the formulation is applied directly to the skin. Transdermal drug delivery approaches can avoid the drawbacks of an oral route. A specialized drug delivery method promotes patient compliance. An injury to biological tissue results in a local defense mechanism.\(^3\)\(^4\)

The need for a microemulsion as a vehicle may improve transdermal penetration through a variety of mechanisms. Additionally, a variety of substances or solubilized in microemulsions cause a change in the drug’s thermodynamic activity, adapting their partition coefficient and promoting penetration of the stratum corneum.\(^4\) Further, its constituent surfactant inhibits, although there are several ways to administer a dose of medication using microemulsion and its gel, transdermal microemulsion application has drawn more attention transdermal release of several drugs has been enhanced using microemulsion gel over traditional preparations like emulsion.\(^5\)\(^6\) Using a transdermal microemulsion approach, baclofen is delivered transdermally in this situation. The drug’s permeability is enhanced and its solubility is improved due to the microemulsion transdermal approach.\(^7\)\(^8\)

Baclofen is a mostly odorless crystalline powder with a molecular weight of 213.66 g/mol and white (or off-white). GABA-B receptors are stimulated by baclofen.\(^9\) It is used to lessen muscle spasms and pain, especially in spinal cord injuries in conditions like paraplegia and multiple sclerosis.\(^10\) Recently, the skin’s lymphocytes, monocytes, and neutrophils were stimulated by the drug baclofen, which also significantly reduced inflammation-related symptoms.\(^11\)\(^12\)

Baclofen has significant pharmacokinetic drawbacks when taken orally because it has a short biological half-life of 3–4 hours and is absorbed in the upper small intestine. Making its duration of action limited. Patient failure to comply results from the requirement that it be taken often.\(^13\) Recent studies attempted to develop oral dosage forms of sustained release in response to all the prior restrictions of oral baclofen, but the efforts failed for a variety of reasons, including dose dumping.\(^14\)\(^15\) Baclofen is a great choice for transdermal drug delivery because of its excellent physical - chemical and biological data, which were obtained from the best sources.

In this study, various polymers, penetration enhancers, and plasticizers were used to develop transdermal patches containing baclofen microemulsion. Studying the compliance of drugs made with various film-forming polymers was done. Also, the optimal formulation’s in-vitro drug release was

Formulation & Development of Baclofen microemulsion incorporated into Transdermal patch

Anshul Panghal*1, Monika Sachdeva 2, Vijay Agarwal 2

1 Raj Kumar Goel Institute of Technology (Pharmacy) 5th KM Stone Delhi Meerut Road, Ghaziabad, Uttar Pradesh, India.
2 Raj Kumar Goel Institute of Technology, Faculty of Pharmacy, Ghaziabad, Uttar Pradesh, India

Abstract

The current study aims at developing formulations based on microemulsions for the transdermal patch of Baclofen. Castor oil was used in the oil phase, Tween-20 was used as a surfactant, propylene glycol(PG) worked as a cosurfactant, and water worked as an aqueous phase in the formation of microemulsions. Using Franz diffusion cells, in vitro permeation tests were conducted. At the conclusion of 8 hours, the in vitro permeation release of ME-3 was determined to be 88.79%, and baclofen microemulsion was later put into the transdermal patch. The most effective composition was ME-3, which included dimethyl sulfoxide as a penetration enhancer, propylene glycol as a plasticizer, and carbopol 940 as a bio-adhesive polymer. The formulation with the best penetration enhancement exhibited a 39-fold increase and contained 0.1% DMSO. It was discovered that ME-3 Patch has a 97.67% in vitro permeation release rate. According to a study, baclofen may be produced into transdermal patches with an acceptable appearance and an appropriate drug release time of 4 hours.

Keywords: (ME-)Microemulsion, HPMC, Transdermal patch, Baclofen, Carbopol- 940
looked at. Physical observation of the prepared patches was done to check for factors like moisture content, drug content, in-vitro drug release, and the results of the kinetic study of drug release.

**MATERIALS AND METHODS:**

Received baclofen sample purchased from Yarrow Chem Maharashtra. The following ingredients came from Central Drug House in New Delhi: Pluronic F127, HPMC K15, soy lecithin, isopropyl palmitate, sorbic acid, potassium sorbate, and ethanol. The materials were all of an analytical calibrated.

**Research methodology of microemulsion**

**Drug Solubility Analysis**

A magnetic stirrer was used to mix the suspension for 24 hours at room temperature. A further 0.45m membrane filter was used to filter the sample. Baclofen content was measured spectrophotometrically at 220nm. Various solvents, including distilled water temp. 60°C, Tween 20, castor oil, propylene glycol, DMSO, and methanol, have been used to dissolve the drug. The baclofen’s solubility was greatest. 60°C for distilled water temp.

**Developing transdermal baclofen patches using HPMC as the forming polymer:**

The appropriate volume of hot distilled water (80-100°C) was used to dissolve HPMC (3% w/v) with constant stirring. The solution was then cooled. The cooled HPMC solution was gradually supplied with the mixture of plasticizer, DMSO as a penetration enhancer, and baclofen microemulsion. The required amount of bio-adhesive polymer was next added while stirring and the final volume was then adjusted with distilled water to reach 10 ml. then was made in the same method shown in Table 2.

**Determining the oils to use and the HLB value for O/W microemulsions**

| S.no | Content | Baclofen (mg) | Castor oil (%w/v) | Tween-20 (%w/v) | PG (%w/v) | Distilled water (%w/v) | Final vol. |
|------|---------|--------------|-------------------|-----------------|----------|----------------------|-----------|
| 1    | ME-1    | 10           | 2                 | 6               | 3        | 19                   | 30        |
| 2    | ME-2    | 10           | 4                 | 6               | 3        | 17                   | 30        |
| 3    | ME-3    | 10           | 6                 | 6               | 3        | 15                   | 30        |
| 4    | ME-4    | 10           | 8                 | 6               | 3        | 13                   | 30        |
| 5    | ME-5    | 10           | 10                | 6               | 3        | 11                   | 30        |

**The formation of transdermal patches incorporating baclofen microemulsion**

Developing transdermal baclofen patches using HPMC as the film-forming polymer:

The appropriate volume of hot distilled water (80-100°C) was used to dissolve HPMC (3% w/v) with constant stirring. The solution was then cooled. The cooled HPMC solution was gradually supplied with the mixture of plasticizer, DMSO as a penetration enhancer, and baclofen microemulsion. The required amount of bio-adhesive polymer was next added while stirring and the final volume was then adjusted with distilled water to reach 10 ml. then was made in the same method shown in Table 2.

**Preventing microemulsion of baclofen**

To make a baclofen microemulsion, castor oil and baclofen were mixed in a correctly optimized ratio (1:2) and added drop by drop. This was followed by continuous magnetic stirring with tween-20 and propylene glycol (1:1). The monophasic formulations spontaneously developed at room temperature for an hour at 3000 rpm. With better microemulsion, dilution research was also carried out & shown in Table 1.

**Table 1: Formulation of baclofen microemulsion**

**Table 2: formation of transdermal patch incorporating baclofen microemulsion**

| Film-forming polymer-HPMC (mg) | Bio-adhesive polymer-Carbopol 940 (mg) | Plasticizer-Propylene glycol (ml) | Penetration enhancer-DMSO dimethyl sulfoxide (ml) |
|--------------------------------|--------------------------------------|----------------------------------|-----------------------------------------------|
| 100                            | 50                                   | 0.25                             | 0.5                                           |

**A non-ionic surfactant with main hydrophilic component is poly-oxyethylene is measured using the formula to determine its HLB.**

\[
HLB = \frac{E}{S}
\]

where E represents the ethylene oxide weight %. Using the formula, one may determine how many fatty acid esters there are in polyhydric alcohols, including glyceryl monostearate.

\[
HLB = \frac{20(1-S/A)}{E}
\]

where A is an ester's acid number and S is its saponification number.
BACLOFEN MICROEMULSION CHARACTERIZATION

Microemulsion optical transparency
To evaluate the formulation's optical transparency, the sample was viewed in front of a lit, black-and-white background while being viewed in a transparent, clear container under good lighting and covered against reflection in the eyes.

Microemulsion pH & viscosity determination
The pH of the microemulsion obtained was measured using a digital pH meter and calibrated with phosphate buffer. For greater accuracy, every reading was obtained in triplicate, and the estimate of the triplicates was obtained. & the viscosity measurement Spindle, S-4 was used to measure the viscosity using a (DV-E viscometer LV) Brookfield Viscometer. After putting the samples in the beaker, the spindle was then placed inside the beaker.

Baclofen microemulsion's drug content
Baclofen Microemulsion Formulations 1 ml were added to a beaker having 10 ml methanol. The beaker's contents were stirred for 30 minutes, then left alone for 24 hours. After 24 hours, after being transferred to the centrifuge tube, the beaker's contents were shaken at 3000 rpm for 10 minutes. The excess was divided and filtered. After that, the drug concentration of 0.1 ml of the residue was spectrophotometrically measured after being properly diluted by Phosphate Buffer Saline (PBS) pH 7.4.

Baclofen microemulsion in vitro drug release
A cellophane membrane-based modified in vitro release mechanism, pH 7.4 phosphate buffer, and the study's dissolution medium was utilized to perform an in vitro drug release analysis of drug ME-1 to ME-5 baclofen microemulsion formulations. The pH 7.4 phosphate buffer was used to soak the cellophane membrane for the test for the entire night. The middle portion of cellophane membrane with the microemulsion on it was precisely weighed and fastened to one of the open ends of the hollow glass cylinder with string. The metal shaft was then connected to the glass cylinder, which was then immersed in the 20 ml of pH 7.4 phosphate buffer that was kept in the beaker until the membrane was just above the top. Throughout the study, the dissolving medium was stirred with a magnetic stirrer at 50 rpm while being maintained at a temperature of 37 ± 0.5 °C, and this condition was maintained until the completion of the study. The receptor media sample was divided into three 3 ml aliquots, each of which was filtered. Each filtered sample was diluted before having the absorbance at 220 nm of a UV spectrometer measured.

Characterization of the transdermal patch incorporating baclofen microemulsions

Baclofen microemulsion patch's physical characteristics
The prepared patches were examined and evaluated visually for factors like color, smoothness, homogeneity, stickiness, texture, uniformity, smoothness, elasticity, transparency, or the presence of tiny air bubbles. These qualities significantly influence patient compliance and acceptance, physical resistance during preparation and storage, and therapeutic efficacy. The analysis did not include samples that had air bubbles, splits, precipitates, or uniform surfaces.

Baclofen microemulsion patch's uniform drug content
A volumetric flask containing 250 ml of phosphate buffer (pH 7.4) and baclofen microemulsion patch units (3.77 cm²) of each formulation was added, and it was constantly stirred. The solution was then filtered and, if necessary, adjusted dilute with the same medium. Determining the amount of Baclofen in the microemulsion required a UV spectrophotometer with a maximum 220 nm calibration. The average of three patch measurements was used to determine the baclofen concentrations, which were then converted to percentages in Microsoft Excel using a standard curve prepared.

Baclofen microemulsion patch's folding resistance
3 patches of each formula were manually divided and cut to size (1 cm x 2 cm) for the different patches that were prepared. A strip was folded at the same spot repeatedly until it broke, or a strip was folded up to 39 times at the breakpoint to determine the film's fold strength.

The baclofen microemulsion patch's present moisture content
An electronic balance was used to weigh three patches of each formulation (3.77 cm²), and the mean was calculated as an initial weight. The weighed patches were then left at room temperature in desiccator with anhydrous CaCl₂ powder for 24 hrs. After 24 hours, the patches were weighed again for the final time. The calculation was used to determine the percent moisture loss.

Baclofen microemulsion patch moisture absorption percentage
In a desiccator with a potassium chloride solution, the films were dried for 24 hours. The final weight was then recorded after 24 hours when the weight was no longer changing. The equation was used to estimate and determine the percentage of moisture and absorption.

Baclofen microemulsion patch in vitro drug release
A cellophane membrane and a modified Franz diffusion cell apparatus are used in an in vitro study. Phosphate buffer (PBS) pH 7.4 is the dissolving solvent used in the test. The patch accurately weighed before being put on the cellophane membrane's central portion. The opening end of the made specifically hollow glass cylinder was then connected to this cellophane membrane. The glass cylinder was attached to the metal shaft and dipped into a 20 ml beaker of pH 7.4 phosphate buffer until the membrane was just above the top. Throughout the testing, the dissolving solvent was continuously stirred with the help of magnetic stirrer at 50 rpm while being maintained at a temperature up to 37±0.5°C. The experiment continued under certain conditions until it was over. The 3 ml sample of receptor media was divided into aliquots and filtered over a specific duration. After dilution, the abs. of each filtered patch was determined using a UV spectrometer at 220 nm.

Result & discussion of baclofen microemulsion patch:

Results of solubility of the baclofen
the most significant components of a microemulsion. A study of solubility in various solvents is shown in the table below. Castor oil is the ideal oil to use while preparing the drug because it dissolves when mixed with distilled water as a solvent. A solubility study found that Tween 20 is more soluble. Given that it provided the highest drug solubility, The co-surfactant selected for further study is propylene glycol. study on drug solubility is listed in Table 3 for baclofen.
Table 3: Different solvents in which baclofen is soluble

| S.no. | Solvents                | Solubility (mg/ml) |
|-------|-------------------------|--------------------|
| 1     | Distilled water at temp. 60°C | 2.508              |
| 2     | Methanol                | 3.453              |
| 3     | Tween-20                | 3.341              |
| 4     | Castor oil              | 3.75               |
| 5     | Propylene glycol        | 0.112              |
| 6     | DMSO                    | 13.70              |

A standard plot of baclofen in distilled water

Absorption maxima of Baclofen in distilled water:

Table 4: standard plot of baclofen in distilled water

| S.no. | Concentration (µg/ml) | Absorbance (nm) |
|-------|-----------------------|-----------------|
| 0     | 0                     | 0               |
| 1     | 10                    | 0.023           |
| 2     | 20                    | 0.046           |
| 3     | 30                    | 0.070           |
| 4     | 40                    | 0.099           |
| 5     | 50                    | 0.122           |
| 6     | 60                    | 0.139           |

Standard graph plot of loxoprofen in distilled water

Figure 1: Standard plot of Baclofen in distilled water at 220(nm)

FTIR of baclofen

Figure 2: FTIR of baclofen

FTIR of baclofen microemulsion

Figure 3: FTIR of baclofen microemulsion
Results of HLB value of selected components of the microemulsion

| S.no. | Substance   | HLB value |
|-------|-------------|-----------|
| 1     | Span-80     | 4.7       |
| 2     | Span-20     | 8.3       |
| 3     | Tween-80    | 17        |
| 4     | Tween-20    | 16.9      |
| 5     | Sodium oleate | 16      |

Selecting the oils

To determine the best oil for a microemulsion's oil phase that will improve baclofen skin penetration. At 25°C, the solubility of baclofen in a selection of oils was measured, along with oleic acid, castor oil, isopropyl myristate, and isopropyl palmitate. The solubility of oleic acid, castor oil, isopropyl myristate, and isopropyl palmitate in oily mixtures was also examined and shown in Table 6.

| S.no. | Drug solubility (in mg/10 g of oil) | Oils              |
|-------|-------------------------------------|-------------------|
| 1     | 120                                 | Olive oil         |
| 2     | 140                                 | Isopropyl-myristate|
| 3     | 120                                 | Isopropyl-palmitate|

Selection of surfactants

Because they are very friendly with both cationic and anionic substances, non-ionic surfactants like Tween-20 (1:1) and co-surfactants like propylene glycol (2:1) do not ionize to a large extent in solution. shows clear appearance shown in Table 7.

Baclofen microemulsion optical transparency:

| S.no. | Formulations | Appearance |
|-------|--------------|------------|
| 1     | ME-1         | Cloudy     |
| 2     | ME-2         | Pearlescent|
| 3     | ME-3         | Clear      |
| 4     | ME-4         | Cloudy     |
| 5     | ME-5         | Cloudy     |

Microemulsion pH & viscosity determination

All microemulsions were found in the pH range up to 6.6 to 6.8 after the pH of microemulsion was calculated using a digital pH meter. Thus, the developed formulations’ obtained pH is a good match for the pH of the skin. The viscosities of all developed microemulsions were determined using spindle S-4 at 25 °C and 60 rpm. The presence of more oil phase in the ME-5 formulation may have contributed to its higher viscosity of 109.2 cps. The ME-1 formulation had the lowest viscosity, measuring 53.5cps. The correlation between viscosity and oil concentration and S/Cos was inversely shown in Table 8.

| S.no. | Formulations | pH* | Viscosity (cps) |
|-------|--------------|-----|-----------------|
| 1     | ME-1         | 6.2 | 53.5            |
| 2     | ME-2         | 5.6 | 76.9            |
| 3     | ME-3         | 6.4 | 93.5            |
| 4     | ME-4         | 5.6 | 101.5           |
| 5     | ME-5         | 5.2 | 109.2           |

Baclofen microemulsion drug content

The baclofen microemulsion formulation’s drug content was calculated through a study of it. The drug content is measured using a range of 90.02% to 96.36%. According to the data, formulation ME-1 has the least drug, whereas formulation ME-3 contains the highest amount shown in Table 9.

| Formulation | Drug content (%) |
|-------------|------------------|
| ME-1        | 90.02            |
| ME-2        | 93.54            |
| ME-3        | 96.36            |
| ME-4        | 94.21            |
| ME-5        | 95.79            |

In-Vitro (%) drug release of baclofen microemulsion ME-1 to ME-5

Analysis of the in-vitro release of baclofen microemulsion in all its forms. The research was performed over a cellophane membrane for 8 hours using a modified in vitro Franz diffusion cell apparatus. Formulation ME-1 showed a release of 50.63 %, Formulation ME-2 showed a release of 66.56 %, Formulation ME-3 showed a release of 88.79 %, and Formulation ME-4 showed a release of 78.13 %, and Formulation ME-5 demonstrated a release of 76.40 %, show in Table 10.
Table 10: In-Vitro (%) drug release of baclofen microemulsion ME-1 to ME-5

| TIME | ME-1  | ME-2  | ME-3  | ME-4  | ME-5  |
|------|-------|-------|-------|-------|-------|
| 0    | 0     | 0     | 0     | 0     | 0     |
| 15   | 10.09 | 18.52 | 33.12 | 25.44 | 25.41 |
| 30   | 15.14 | 20.25 | 41.24 | 29.05 | 28.36 |
| 60   | 18.02 | 24.65 | 47.14 | 32.72 | 31.14 |
| 120  | 21.80 | 27.53 | 53.98 | 35.68 | 33.80 |
| 180  | 25.44 | 29.73 | 61.19 | 43.53 | 36.22 |
| 240  | 27.96 | 33.77 | 67.24 | 50.34 | 44.61 |
| 300  | 32.76 | 42.23 | 75.68 | 57.30 | 49.65 |
| 360  | 35.57 | 49.62 | 83.24 | 66.56 | 57.80 |
| 420  | 43.53 | 59.03 | 86.12 | 70.92 | 64.76 |
| 480  | 50.63 | 66.56 | 88.79 | 78.13 | 76.40 |

Figure 4: In-Vitro % drug release of baclofen microemulsion ME-1 to ME-5

Baclofen microemulsion patch’s physical appearance

| Formulation | Appearance                        |
|-------------|-----------------------------------|
| ME-3        | Transparent, colorless, homogenous |
Baclofen microemulsion patch’s folding resistance

The patch showed appropriate physical and mechanical characteristics, as indicated in Table 13, and the findings were most satisfactory for a chosen ME-3. In this study, it was found that the patch was flexible and provided resistance to breaking after being folded more than 39 times in the same place. It also showed no cracks, which was the test’s endpoint. Further, it was noted that HPMC-based formulations limited flexibility. The patch grew more fragile and its resistance to folding may have been caused by the high concentration of HPMC, shown in Table 12.

Table 12: ME-3 patch folding endurance

| Formulation | Folding endurance |
|-------------|-------------------|
| ME-3        | 39                |

Baclofen microemulsion patch’s moisture content

Calculations were used to determine the moisture content. The moisture content was found to be at a moderate level of 20%. As the amount of PG increased, no moisture content was visible, showing that the results were due to a plasticizer, shown in Table 13.

Table 13: ME-3 (%) moisture content

| Formulation | Moisture content (%) |
|-------------|----------------------|
| ME-3        | 20                   |

In vitro drug release from a baclofen microemulsion patch

The physical and chemical properties of the microemulsion Baclofen ME-3 allowed it to be selected as an applicant for the transdermal patch. ME-3 was the satisfactorily control release in the in vitro release research when HPMC was used as the film-forming polymer, offered strong physical qualities, appearing as flexible films that were translucent. It was determined that ME-3 contains PG, a plasticizer that adds flexibility, as well as DMSO, a penetration enhancer. Finally, it was determined that ME-3 released baclofen with a regulated release rate for 4 hours. Similarly, 97.67% release is shown in Table 15.

Table 15: ME-3 In-vitro drug release

| TIME  | ME-3 |
|-------|------|
| 5     | 37.69|
| 10    | 41.93|
| 15    | 45.74|
| 30    | 50.24|
| 45    | 51.86|
| 60    | 57.05|
| 120   | 67.79|
| 180   | 87.85|
| 240   | 97.67|

Figure 6: Baclofen microemulsion incorporated into a transdermal patch

Figure 7: In-Vitro drug release (%) of baclofen microemulsion ME-3 incorporated into transdermal patch.
Kinetic models of the three best baclofen microemulsion formulations ME-3, ME-4 & ME-5

Table 16: Kinetic models of the three best baclofen microemulsion formulations ME-3, ME-4 & ME-5

| Formulation | Zero order | First order | Higuchi model | Kostrmeyer-peppas Model |
|-------------|------------|-------------|---------------|-------------------------|
| ME-3        | 0.8294     | 0.9866      | 0.9536        | 0.9806                  |
| ME-4        | 0.9113     | 0.9699      | 0.9606        | 0.9601                  |
| ME-5        | 0.8929     | 0.898       | 0.9186        | 0.8466                  |

Stability studies of baclofen microemulsion patch formulation

Table 17: Stability studies of baclofen microemulsion patch formulation

| S.no. | Formulation ME-3 | Before storage | Stored at 40°C ± 2°C and 75%±5% RH |
|-------|-------------------|----------------|-------------------------------------|
|       |                   |                | 1 month                              |
| 1     | Drug content (%)  | 88.79          | 87.22                                |
| 2     | pH                | 6.4            | 6.4                                  |
| 3     | Viscosity (cps)   | 93.5           | 93.5                                 |

CONCLUSION:

The Baclofen Microemulsion with Castor Oil was chosen as the vehicle for the phase of the microemulsion’s oil since the study shows that it consumed the greatest quantity of baclofen. Tween-20 and Propylene Glycol were selected in the optimal ratios as the ideal co-surfactant and surfactant. Baclofen Microemulsion reduces the side effects caused by regular oral doses because it is formulated as a controlled release dosage form that lasts for 24 hours. Evaluation of the chosen ME-3 formulation with castor oil (6%), Tween-20/propylene glycol (30%), and other ingredients showed that it was stable after centrifuge stress testing that its viscosity made it suitable for the transdermal application, and that its pH value was within the range of physiological values. The formulation contains 96.36% active ingredients. This study focused on the performance of baclofen ME-3 in enhancing in vitro drug release. ME-3 shows 88.79%. The formulation is in accordance with fits the Korsmeyer-Peppas model, and after that for the microemulsion, the physical and chemical characteristics of Baclofen ME-3 allowed it to be chosen as a candidate for the transdermal patch. ME-3 was the successfully controlled release in the in vitro release study.

REFERENCES:

1. Prausnitz Mark R., Mitragotri Samir; Langer Robert. Current status and future potential of transdermal drug delivery. Nature Reviews Drug Discovery volume. Published online February 1, 2004:115-124. https://doi.org/10.1038/nrd1304

2. Verma S, Vaiikshv Y, Verma S, Jha A. Anhydrous Nanoemulsion: An Advanced Drug Delivery System for Poorly Aqueous Soluble Drugs. Current Nanomedicine. 2017; 7(1):36-46. https://doi.org/10.2174/2468187306666160926124713

3. Biswal Biswajit. Formulation and Evaluation of Microemulsion Based Topical Hydrogel Containing Lornoxicam. Journal of Applied Pharmaceutical Science. Published online December 30, 2014. https://doi.org/10.7324/JAPS.2014.41214

4. Delgado-Charro MB, Iglesias-Vilas G, Blanco-Méndez J, López-Quintela MA, Marty JP, Guy RH. Delivery of a hydrophilic solute through the skin from novel microemulsion systems. European Journal of Pharmaceutics and Biopharmaceutics. 1997; 43(1):37-42. https://doi.org/10.1016/S0939-6411(96)0016-1

5. Kititsis G. A Study on the In-vitro Percutaneous Absorption of Propranolol from Disperse System. Journal of Pharmacy and Pharmacology. 1998; 50(4):412-418. Accesscd August 21, 2022. https://doi.org/10.1111/j.2042-7158.1998.tb0081x

6. Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. Advanced Drug Delivery Reviews. 2002; 54:577-596. https://doi.org/10.1016/S0169-409X(02)0116-3

7. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Advanced Drug Delivery Reviews. 2000; 45(1):89-121. https://doi.org/10.1016/S0169-409X(00)00103-4

8. Peltola S, Sairinen-Suvolainen P, Kievaara J, Suzuki H, Urni T. Microemulsions for topical delivery of estradiol. International Journal of Pharmaceutics. 2003; 254(2):99-107. https://doi.org/10.1016/S0378-5173(02)00632-4

9. Wisher D. Martiniale: The Complete Drug Reference. 37th ed. J Med Libr Assoc. 2012; 100(1):75-76. https://doi.org/10.1363/1536-5050.100.1.018

10. Dario A, Stefano M.G. Di, Grossi A. Long-term intrathecal baclofen infusion in supraspinal spasticity of adulthood. Acta Neurol Scand. 2002; 105(2):83-87.

11. Dathey B, Hübner A, Diehl S, Boehncke S, Pfuffer J, Boehncke WH. Anti-inflammatory effects of the GABAB receptor agonist baclofen in allergic contact dermatitis. Experimental Dermatology. 2010; 19(7):661-666. https://doi.org/10.1111/j.1600-0625.2010.01076.x

12. Nabi-Neibodi M, Navidi B, Navidi N, Vatanara A, Reza Rouini M, Ramezani H. Optimized double emulsion-solvent evaporation process for production of solid lipid nanoparticles containing baclofen as a lipid insoluble drug. Journal of Drug Delivery Science and Technology. 2013; 23(3):225-230. https://doi.org/10.1016/S1773-2247(13)50034-7
13. S.M. Foroutan, A.R. Shaafati, A. Khodam. Bioequivalence Studies Of Two Formulations Of Baclofen Tablet In Healthy Volunteers. *Iranian Journal of Pharmaceutical Research*. 2003; 2(3):153-155.

14. Delhaas EM, Brouwers J R. Intrathecal baclofen overdose: report of 7 events in 5 patients and review of the literature. *Int J Clin Pharmacol Ther Toxicol*. 1991; 29(7):274-280.

15. Chandrashekar N, Shobha Rani R. Physicochemical and pharmacokinetic parameters in drug selection and loading for transdermal drug delivery. *Indian Journal of Pharmaceutical Sciences*. 2008; 70(1):94. https://doi.org/10.4103/0250-474X.40340

16. Aulton BP, Ahar FAAPS FSP FRPharmS ME, Taylor BPharm FRPharmS KM. Aulton’s Pharmaceutics: The Design and Manufacture of Medicines.; 2018. www.konkur.in

17. Garti N, Aserin A, Tiunova I, Fanun M. A DSC study of water behavior in water-in-oil microemulsions stabilized by sucrose esters and butanol. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*. 2000; 170(1):1-18. https://doi.org/10.1016/S0927-7757(00)00486-6

18. Ghosh PK, Majhihya RJ, Umrethia ML, Murthy RSR. Design and development of microemulsion drug delivery system of acyclovir for improvement of oral bioavailability. *AAPS PharmSciTech*. 2006; 7(3):E172-E177. https://doi.org/10.1208/pt070377

19. Chen H, Chang X, Weng T, et al. A study of microemulsion systems for transdermal delivery of triptolide. *Journal of Controlled Release*. 2004; 98(3):427-436. https://doi.org/10.1016/j.jconrel.2004.06.001

20. Kumar B, Jain SK, Prajapati SK. Effect of Penetration Enhancer DMSO on In-Vitro Skin Permeation of Acyclovir Transdermal Microemulsion Formulation. *International Journal of Drug Delivery*. 2011; 3(1):83-94. https://doi.org/10.5138/ijdd.2010.0975.0215.03057

21. Prajapati ST, Patel CG, Patel CN. Formulation and Evaluation of Transdermal Patch of Regapaglide. *ISRN Pharmaceutics*. 2011; 2011:1-9. https://doi.org/10.5402/2011/651909

22. Ganai Kevin, Shinde Anilkumar. Formulation and in-vitro characterization of monolithic matrix transdermal systems using HPMC/Eudragit S 100 polymer blends. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2009; 1(1).

23. Kusum Devi V, Saisivam S, Maria GR, Deepti PU. Design and Evaluation of Matrix Diffusion Controlled Transdermal Patches of Verapamil Hydrochloride. *Drug Development and Industrial Pharmacy*. 2003; 29(5):495-503. https://doi.org/10.1081/DDC-120018638

24. Gupta R, Mukherjee B. Development and In Vitro Evaluation of Diltiazem Hydrochloride Transdermal Patches Based on Povidone–EthylCellulose Matrices. *Drug Development and Industrial Pharmacy*. 2003; 29(1):1-7. https://doi.org/10.1081/DDC-120016678

25. Minghetti P, Glurzo F, Casiraghi A. Measuring Adhesive Performance in Transdermal Delivery Systems. *American Journal of Drug Delivery*. 2004; 2(3):193-206. https://doi.org/10.2165/00137696-200402030-00004

26. Pierre MBR, Ricci E, Tedesco AC, Bentley MVLB. Oleic Acid as Optimizer of the Skin Delivery of 5-Aminolevulinic Acid in Photodynamic Therapy. *Pharmaceutical Research*. 2006; 23(2):360-366. https://doi.org/10.1007/s11095-005-9261-x

27. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. *European Journal of Pharmaceutical Sciences*. 2001; 13(2):123-133. https://doi.org/10.1016/S0928-0987(01)00095-1