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Research Article

Formulation & Development of Baclofen microemulsion incorporated into Transdermal patch

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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

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[2,3]

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

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[16]

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, the order of baclofen solubility in different vehicles is Because baclofen is only slightly soluble in methanol, distilled water in an acidic medium was selected as a solubilizer in the formulation of baclofen. controlled release microemulsion transdermal formulation. Methanol, propylene glycol, castor oil, and baclofen are other possible solubilizers.

Determining the oils to use and the HLB value for O/W microemulsions [17]

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

$$HLB = E/5,$$

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.

$$HLB= 20(1-S/A),$$

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

For selecting oils, A 25 ml beaker containing up to 10 g of oil was precisely weighed, and 100 mg of baclofen then was added. The drug was then thoroughly dissolved by stirring at a moderate speed with a magnetic stirrer. When the drug had completely dissolved, another 10 mg of baclofen was added. Up until the saturated solution was attained, the drug was added continuously. At 220 nm, a UV spectrophotometer was used to calculate the total amount of drug consumed when it was determined that the most amount of baclofen had been absorbed by castor oil, it was determined to use it as the vehicle for the microemulsion oil phase.

Preparing a microemulsion of baclofen[18]

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

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.

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

BACLOFEN MICROEMULSION CHARACTERIZATION[19]

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 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:[20]

Baclofen microemulsion patch's physical characteristics[21]

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[22]

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[23]

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[24]

An electronic balance was used to weigh three patches of each formulation (3.77 cm^2), and the mean was calculated as an initial weight. The weighed patches were then left at room temperature in desiccator with anhydrous $CaCl_2$ 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[25]

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[26,27]

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 into 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^{0}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

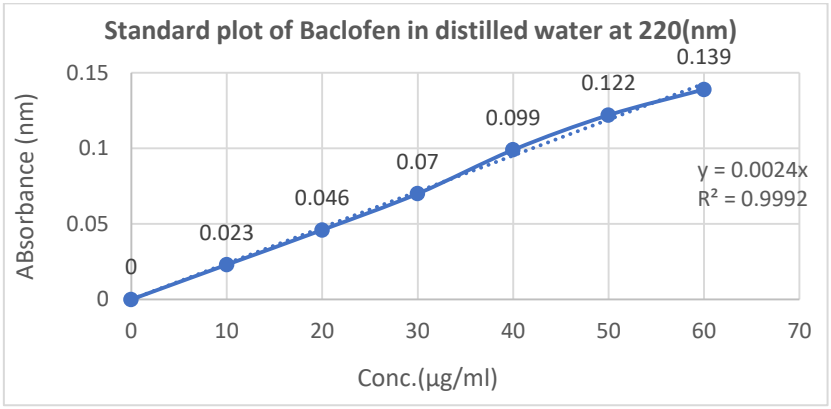

Figure 1: Standard plot of Baclofen in distilled water at 220(nm)

FTIR of baclofen

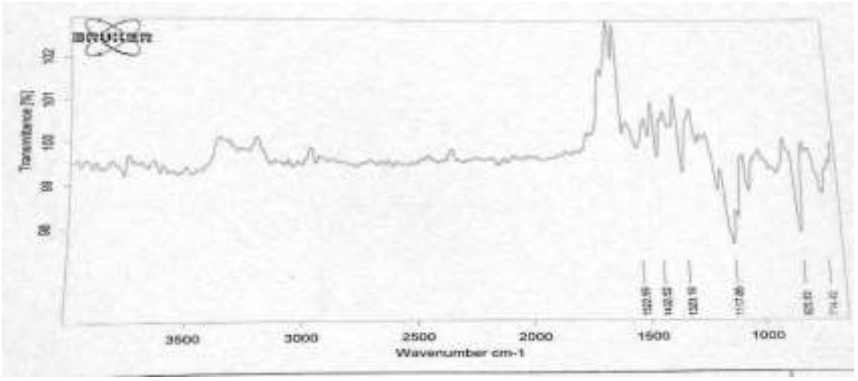

Figure 2: FTIR of baclofen

FTIR of baclofen microemulsion

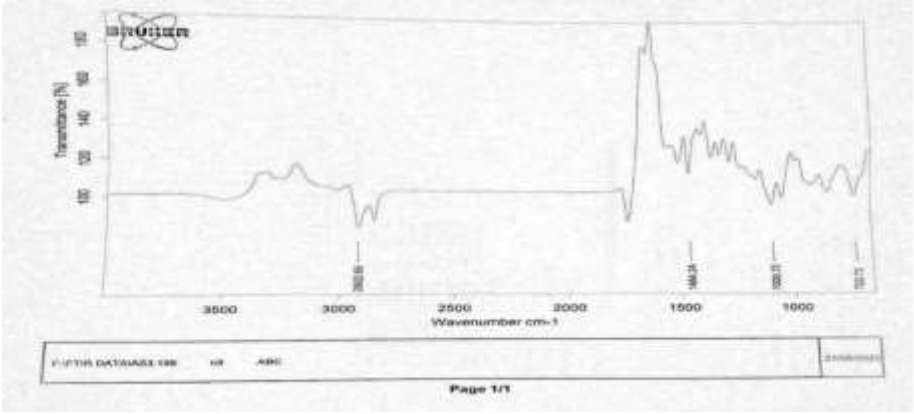

Figure 3: FTIR of baclofen microemulsion

Results of HLB value of selected components of the microemulsion

Table 5: 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.

Table 6: Selecting the oils at 25°C

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:

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.

Table 8: Baclofen microemulsion pH & viscosity

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.

Table 9: The uniform drug content

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

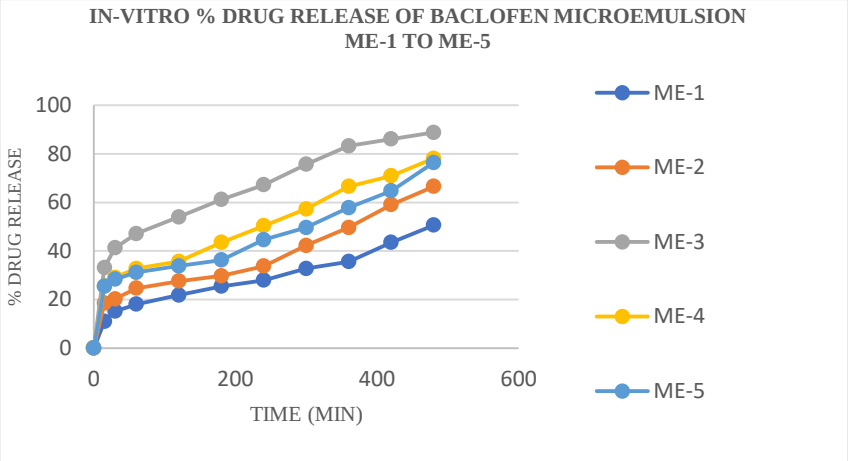

Figure 4: In-Vitro % drug release of baclofen microemulsion ME-1 to ME-5

Figure 5: Baclofen microemulsion ME-3

Baclofen microemulsion patch's physical appearance

Table 11: Microemulsion patch physical appearance

Formulation	Appearance
ME-3	Transparent, colorless, homogenous

Figure 6: Baclofen microemulsion incorporated into a transdermal patch

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

Baclofen microemulsion patch's (%) moisture absorption

When compared to moisture loss, the results of the moisture absorption tests were found to be minimal, ranging from 10 to 20 % (ME-3) shown in Table 14.

Table 14: ME-3 (%) moisture absorption

Formulation	Moisture absorption (%)
ME-3	10

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

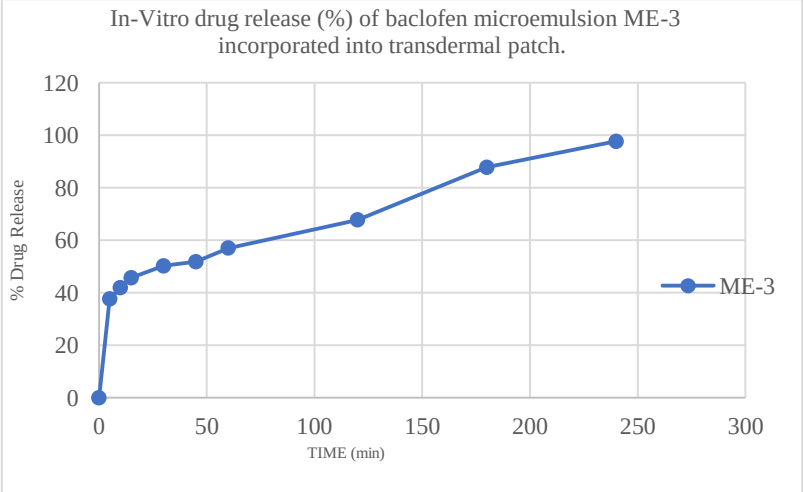

Figure 7: In-Vitro drug release (%) of baclofen microemulsion ME-3 incorporated into transdermal patch.

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	Korsmeyer-peppas Model
	R^2	R^2	R^2	R^2
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.

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