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Formulation and Characterization of Transdermal Patches of Baclofen for Pain Management

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Abstract
Bacofen transdermal patches made using the solvent casting method and composed of the plasticizer dibutylpthalate and the polymers ethyl cellulose and Eudragit RL100 are very stable. The patches had an average weight of 161–167 mg, with a surface area of 1.5 cm2. The patches' thickness varied between 0.267 and 0.354 mm, with the exact value depending on the polymer ratio. In the folding endurance test, the patches withstood 47–83 folds in the same spot. The medication concentrations in all of the formulations ranged from 97-80.9 percent. The medication was released in a range of formulations, from 88.3% to 60.7%. The regression coefficients of the mathematical model's graphical depiction show that the Korsemeyer-Peppas model can describe the release of etodolac from the patches. The phrase describes how the medicine is released from the patches mainly by diffusion control, from the patch's polymeric matrix.
Keywords: *Baclofen, transdermal, patch, pain, controlled release*

INTRODUCTION

The number and types of injuries have been on the rise in recent years due to the increased participation in both competitive and recreational sports [1]. Reducing injury-related pain, edema, inflammation, and muscular spasm is one goal of sports injury treatment. Another is helping the patient regain function so they can return to sports. The type of injury, whether it's chronic or acute, dictates the treatment choice [2]. Although they are only used for the treatment of peripheral pain, ibuprofen and naproxen make up over 60% of all NSAID prescriptions and are most often taken for musculoskeletal ailments. Therapeutic doses do not alleviate skeletal pain to an adequate degree [3]. Skeletal muscle relaxants (SMRs) are an eclectic class of medicines with a wide range of pharmacologic characteristics, adverse effects, and physically distinct active components. Reducing skeletal muscle spasm, aiding in pain alleviation, and increasing mobility of afflicted muscles are the goals of SMR administration. Because of its effects on the central nervous system (CNS), drowsiness and dizziness are the most typical side effects of SMRs. Nausea, vomiting, lack of appetite, and headache are less prevalent side effects associated with joints [4].

For the most part, baclofen is used to treat muscle spasms since it is a muscle relaxant and an analogue of the putative inhibitory neurotransmitter gamma amino butyric acid. Baclofen is commercially accessible as both an oral tablet and an intrathecal injection; it has a high value of distribution throughout the body and is absorbed orally in varying ratios. It travels through the liver's first-pass metabolism and is then passed out in the urine [5]. Because it is absorbed in the upper part of the small intestines when given orally, it has a short biological half-life of 3-4 hours, meaning its duration of effect is brief [6, 7], and patients often fail to comply because of the frequent dosing required. The numerous drawbacks of oral baclofen in the past led to numerous attempts to develop sustained-release oral dosage forms, but these failed for a variety of reasons, including dose dumping [8].

Introducing the medicine into the bloodstream at a set pace is an unconventional method of drug delivery [9]. Adhesive TDDSs have a specific surface area and transport a predetermined amount of medication to the undamaged skin at a preprogrammed rate [10]. Whether it's for systemic therapy or localized treatment of tissues underneath the skin, a transdermal patch is a topical application that distributes chemicals to healthy, intact skin. They prevent dosage dumping, maintain steady blood levels, boost patient compliance, and bypass first-pass metabolism [11].

Hence to overcome the problems associated with baclofen, it was envisioned to prepare and evaluate transdermal patches of baclofen.

MATERIAL AND METHODS

Preformulation Studies

The preformulation studies were carried out in the terms of tests of identification like physical appearance, melting point and λ_{max} [12]. It also includes solubility profile of drug in various solvents (water, HCl, ethanol and acetone) and determination of partition coefficient (butanol-water) [13].

Preparation of Calibration Curve

A stock solution (100 µg/ml) of pure drug was prepared by dissolving 10 mg baclofen in 10 mL of methanol. From this stock solution, the working standard solutions at 10-50 µg/ml concentrations were prepared by suitable dilution. A standard curve was constructed against absorbance and concentration.

Preparation of Transdermal Patches [14]

Various ratios of hydrophobic propionic acid and ethyl cellulose were utilized in the solvent evaporation process to create the balcofen matrix transdermal patches. The backing layer was made by putting a 4% PVA solution into aluminium foil-lined petri dishes, and then drying them in a hot air oven at 60°C for three to four hours.

To begin the formulation process, a mixture of two polymers, ethyleneglycol and eudragit RL100, was dissolved in a mixture of dichloromethane and methanol at a ratio of 2:1. The mixture was then left to fully swell for one hour. Then ethyl cellulose was added while swirling constantly. Following that, the plasticizer (Dibutylphthalate, or DBP) and permeation enhancer (Dimetylsulfoxide, or DMSO) were added and mixed thoroughly for the allotted few minutes. Stirring constantly ensured a thorough mixing of the medication before its incorporation. A backing membrane was used to spread the resulting homogeneous dispersion. After being cut to size, the created films were wrapped in aluminium foil and placed in the desiccator for future research. The ingredients used to make the transdermal patches are detailed in Table 1.

Table 1: Composition of Transdermal patch formulations

Formulation	Ratio of polymer (Eudragit : EC)	Total wt. of Polymers (mg)	Solvent (DCM:methanol, 2:1) (ml)	Plasticizer (DBP) (mg)	Permeation enhancer (DMSO) (mg)	Baclofen (mg)/patch
F1	8:2	1000	30	200	80	10
F2	7:3	1000	30	200	80	10
F3	6:4	1000	30	200	80	10
F4	4:6	1000	30	200	80	10
F5	3:7	1000	30	200	80	10
F6	2:8	1000	30	200	80	10

Evaluation of Transdermal Patches [14,15]

Small patches of 1.5 cm^2 area were cut from the stored films and the evaluation of various parameters was carried out on the patches.

Weight Variation

The patches were subjected to mass variation by individually weighing randomly selected patches. Such determinations were carried out for each formulation.

Thickness

The thickness of each patch was measured by using screw gauge at different positions of the patch and the average was calculated.

Folding endurance

Folding endurance was determined by repeatedly folding one patch from the same place till it broke. The number of times the film could be folded from the same place without breaking/ cracking gave the value of folding endurance.

Percentage moisture content

The prepared transdermal films were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for the duration of 24 hours. After 24 hours, the films were re-weighed and the percentage moisture content was determined

Drug content determination

For determining the drug content, an area of 10 cm^2 of the patch was cut and dissolved in 10 ml of phosphate buffer (pH 7.4). After that, 0.1 ml volume was withdrawn from the solution and diluted with the phosphate buffer to 10 ml in a volumetric flask. The absorbance of the solution was taken at 240 nm by using UV spectrophotometer.

In-Vitro Permeation Study

Applying the patches to a Franz diffusion cell with a receptor compartment capacity of 60 ml allowed for in-vitro permeation investigations. After positioning the 0.64 cm2 designed patch between the donor and dialysis membranes, the donor and receptor compartments of the diffusion cell were connected. There was phosphate buffer saline (pH 6.8) in the receptor compartment of the diffusion cell. The whole setup was fastened to a magnetic stirrer, and magnetic beads were used to continually swirl the solution in the receptor compartment at 50 rpm, while a temperature of 37±0.5°C was maintained. The drug content was measured by UV at 240 nm after 1 ml aliquots were removed at 0, 1, 2, 3, 4, 6, and 24 h intervals. In order to track the amount of medication that permeated each square centimetre of patches over time, the receptor phase was periodically refilled with an equal volume of phosphate buffer (37°C). We computed and recorded the percent drug penetrated and the log percent DRP.

RESULT AND DISCUSSION

Preformulation studies

The first and most important stage in developing dosage forms of a pharmacological substance rationally is preformulation testing. The study looks into the chemical and physical characteristics of the drug material both on its own and in combination with other substances called excipients. Gathering data that can aid the formulator in creating a dosage form that is stable, effective, and safe is the overarching goal of preformulation studies. An organoleptic examination of baclofen has been conducted using the senses of sight, sound, touch, and smell. The open capillary method was used to estimate the melting point, and the results are presented in Table 2 without any correction for environmental conditions.

Table 2 Organoleptic features and melting point of balcofen

S. No.	Characteristic	Observed Results
1	Color and appearance	White, powder
2	Odor	Odorless
3	Melting Point	206-208°C
4	Solubility	Soluble in methanol, acetone; slightly soluble in ethanol; insoluble in water
5	Partition Coefficient	3.49

Calibration curve in phosphate buffer

The calibration curve of baclofen was constructed in phosphate buffer pH 6.8 at concentration range of 1.0-50.0 µg/mL. The λmax was found to be 240 nm and was used for all the analysis of drug (Figure 2).

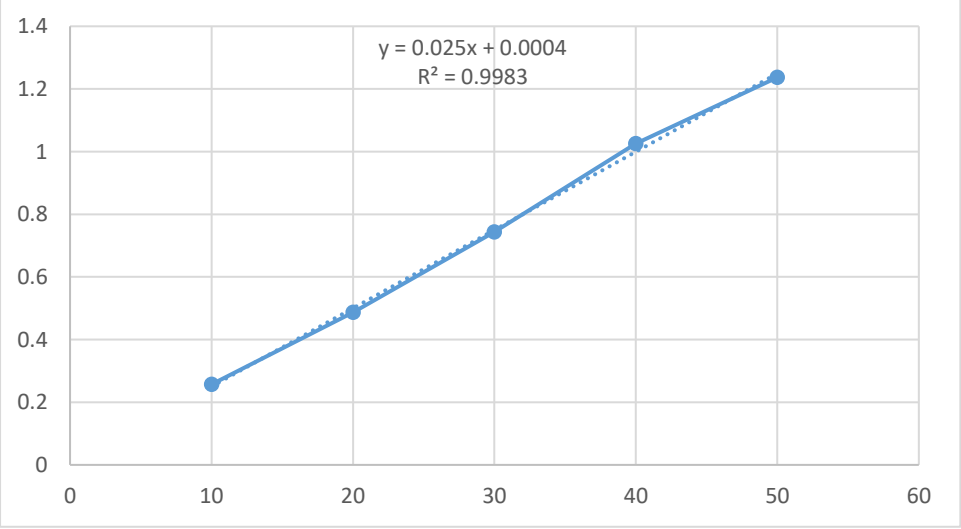

Figure 1 Calibration curve of baclofen in phosphate buffer pH 6.8

Evaluation of transdermal patches

The evaluation of the patch was performed as per reported procedures and the result is reported in table 3.

Table 3 Physiochemical features of Transdermal Patches

	Thickness (mm)	Average weight (mg)	Moisture content (%)	Drug content (%)	Folding Endurance
F1	0.267	163	5.71	97.8	47
F2	0.269	167	6.83	98.1	49
F3	0.271	165	6.97	98.4	51
F4	0.327	161	7.08	98.9	57
F5	0.331	163	7.22	99.1	74
F6	0.354	161	7.37	99.4	82

The patches had an average weight of 161–167 mg, with a surface area of 1.5 cm2. Different patches from the same batch had identical weights. The patches' thickness varied between 0.267 and 0.354 mm, with the exact value depending on the polymer ratio. Patch thickness was shown to be proportional to the concentration of ERL in the polymeric matrix.

The results of the folding endurance test showed that the patches remained intact when placed to the skin and did not break. We discovered that the film patches were more flexible when they were thinner. When tested in the same spot, the patches withstood 47–82 folds. It was also noted that the patches' pliability was enhanced by increasing the concentration of the hydrophilic polymer (ERL). The medication concentrations in all of the formulations ranged from 97-80.9 percent. Because the medicine was fully absorbed by the patches, it could be concluded that the formulation procedure used to make the patches was reliable.

The analysis of moisture content showed that as the concentration of ERL increased, the patches with the highest moisture content were F6 (7.37%), and the patches with the lowest moisture content were F1 (5.71%). The stable patches did not grow brittle and dried out during storage, as shown by their low moisture content [16].

Researchers used the Franz diffusion device to examine the patch-induced baclofen in vitro release profile. The study's results showed that the patches maintained medication release for over 24 hours. The medication was released in a range of formulations, from 88.3% to 60.7%. Researchers observed that drug release reduced with increasing ERL concentration in the formulation. This could be because the hydrophilic matrix of the patch hinders the migration of the poorly soluble medication. The mathematical and graphical exploration of the release data allowed for the evaluation of potential medication follow-up mechanisms from the patches. Models such as zero-order, first-order, Higuchi, and Kosemeyer-Peppas kinetics were applied to the data (Figure 2-5).

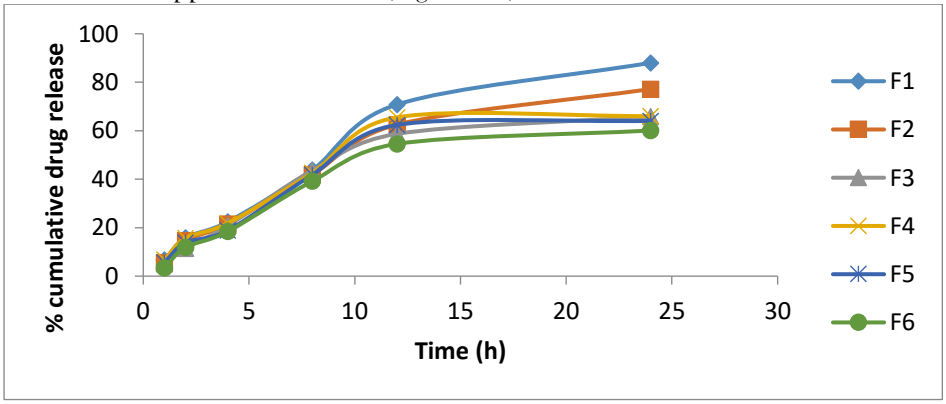

Figure 2 Zero order release plot of baclofen from patches

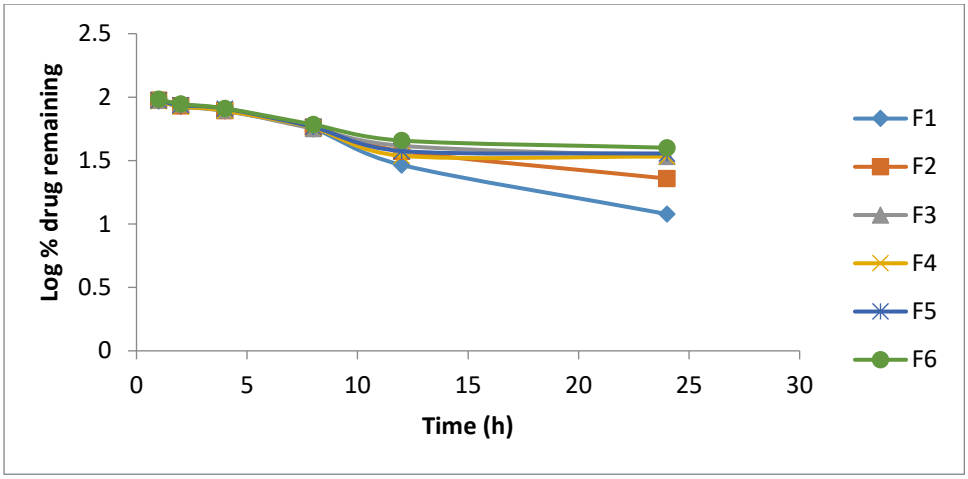

Figure 3 First order release plot of baclofen from patches

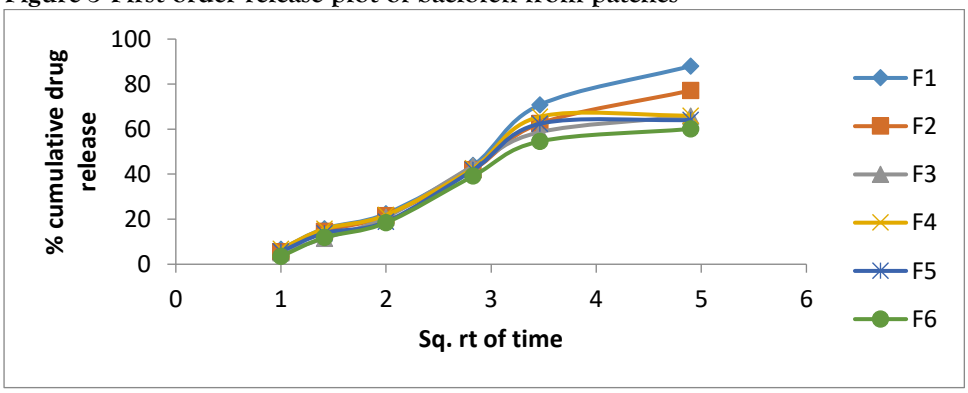

Figure 4 Higuchi release plot of baclofen from patches

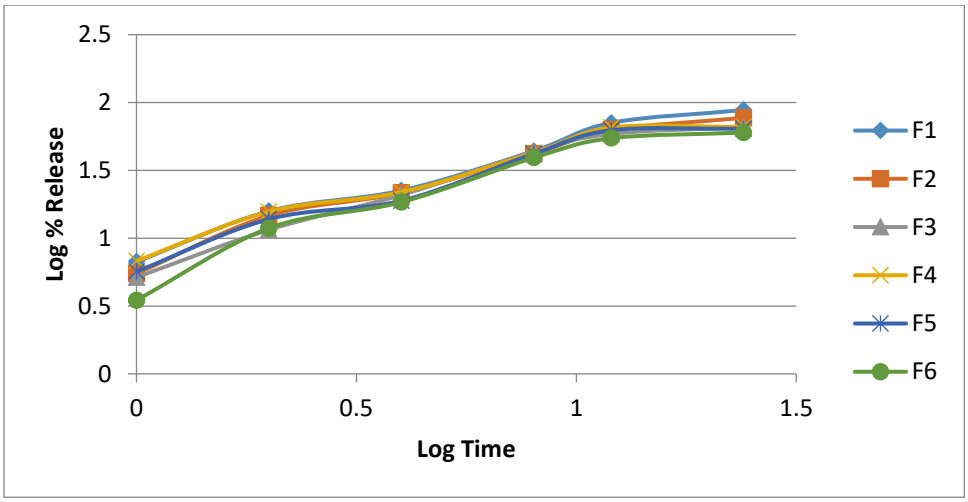

Figure 5 Korsemeyer-Peppas release plot of baclofen from patches

The slope and regression coefficient of the drug released and the various applied kinetic models. The regression coefficients of the graphical representation of the mathematical models reveal that the release of baclofen from the patches can be described by Korsemeyer-Peppas model. The expression relates that the drug released from the patches is due to diffusion of drug from the polymeric matrix of the patch and is primarily diffusion controlled.

CONCLUSION

There are a number of pain problems that could benefit greatly from the transdermal administration of Baclofen. The current study set out to determine whether baclofen transdermal patches could be useful in lowering the drug's dosage frequency. The combination of a lower dose and a longer duration of action suggests that baclofen administered transdermally may improve compliance compared to more traditional methods of medication delivery. When applied topically, baclofen patches can be quite helpful for a variety of pain disorders.

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