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Study of skeletal muscle relaxant effect of baclofen loaded transdermal patch in mice

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ABSTRACT

Treatment of musculoskeletal pain is a challenging condition affecting approximately 47% of the general population. The objective of this investigation was to prepare transdermal patches of baclofen and assess its skeletal muscle relaxant potential. The patches were prepared using HPMC-Eudragit or Eudragit-Ethylcellulose as the polymeric matrix. The patches were found to have significant skeletal muscle relaxant action compared to control group. The patches prepared using Eudragit-Ethylcellulose were able to produce significant effect compared to pure drug baclofen. The study led us to conclude that transdermal patch is an effective alternative to oral delivery of baclofen, helpful in reducing the dose and associated side effects of the drug.

Keywords: *Skeletal muscle relaxant, baclofen, rotarod, cylinder climbing, latency*

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1. INTRODUCTION

Musculoskeletal disorders (MSDs) are injuries or pain in the human musculoskeletal system, including the joints, ligaments, muscles, nerves, tendons, and structures that support limbs, neck, and back. MSDs can arise from a sudden exertion (e.g., lifting a heavy object), or they can arise from making the same motions repeatedly repetitive strain, or from repeated exposure to force, vibration, or awkward posture [1]. Musculoskeletal pain is a challenging condition for both patients and physicians. Many adults have experienced one or more episodes of musculoskeletal pain at some time of their lives, regardless of age, gender, or economic status. It affects approximately 47% of the general population. Of those, about 39–45% have long lasting problems that require medical consultation. Inadequately managed musculoskeletal pain can adversely affect quality of life and impose significant socioeconomic problems. A combination of pharmacological and non-pharmacological interventions are important, and they may be used together to manage a patient's pain. For patients with chronic MSK pain, clinicians and patients should initially select non-pharmacologic treatment, including home exercises and multidisciplinary rehabilitation protocols. In patients with chronic MSK pain who have had an inadequate response to non-pharmacologic therapy, pharmacologic treatment with NSAIDs should be considered as first-line therapy with or without adjuvant therapy [2].

Oral baclofen is predominantly utilized for spasticity, where it is FDA-approved for relieving associated pain, particularly in conditions like spinal cord lesions and multiple sclerosis. Beyond its primary indication, baclofen is also employed off-label for various pain conditions. For instance, it serves as a second-line therapy for trigeminal neuralgia, where it has been observed to reduce the frequency of painful episodes and prolong remission, sometimes in combination with other medications like carbamazepine or phenytoin [3]. It has also been explored as an adjunctive treatment for general muscle spasm and musculoskeletal pain, often in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen [4].

To overcome the problems associated with baclofen (a short elimination half-life, which necessitates frequent daily dosing, and the high incidence of bothersome systemic side effects) transdermal patch for delivery of baclofen was prepared. In this work, we have evaluated and compared the effect of the transdermal patches of baclofen prepared using as skeletal muscle relaxant in mice..

2. MATERIAL AND METHODS

Baclofen, HPMC, Eudragit and EC was purchased from Yarrow Pharmaceuticals, Mumbai. Any other reagent, or solvent used was purchased from CDH and used as obtained.

Preparation transdermal patch for the study

Patch T9 was prepared by using 4:1 ratio of HPMC and Eudragit RL100 as the matrix polymers, glycerine as plasticizer and piperine as permeation enhancer. The casting mixture was prepared by dissolving the appropriate amounts of the film forming polymers in chloroform-methanol (1:1) when using HPMC and Eudragit. When Eudragit and EC were used, the polymer were dissolved in dichloromethane: methanol (2:1). The drug and other excipients were then added under continuous stirring. The mixture was then incubated at room temperature for remove bubbles [5].

Patch F1 was prepared by using 8:2 ratio of Eudragit RL100 and Ethylcellulose as the matrix polymers, dibutylphthalate as the plasticizer and dimethylsulfoxide as the permeation enhancer. 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 [6].

The patches were evaluated using standard reported procedures for thickness, weight variation, folding endurance, tensile strength, drug content, moisture content, surface pH and drug release [7,8].

In vivo evaluation of skeletal muscle relaxant activity

Male Albino mice (20-30 g), were housed in clean environment with a 12 hour light /dark cycle. Food and water were provided *ad libitum*. The experimental procedures were approved by Institutional Animal Ethical Committee.

Animals have been acclimatized in the animal house and grouped in 3 groups of 5 animal each.

Group 1: Control (no treatment)

Group 2: Baclofen (2 mg/Kg, p.o)

Group 3: Baclofen transdermal patch

Rotarod Test [9]

The animal were trained prior to testing. All the animal had free access to food and water. The protocol followed involved placing mice in separate lanes on the rod rotating at 5 RPM, allowed them to walk forward to maintain balance. After 60 seconds, returned mice to their home cage. Cleaned the Rotarod with diluted ethanol between training rounds. Performed a total of three repetitions with a 5-minute interval. If a mouse fell off before completing 60 seconds, the round was repeated, but total rounds was kept fixed to four. The treatment protocol was followed once the training of animal was completed. Briefly, the Rotarod was allowed to accelerate from 4 to 40 RPM over 300 seconds. The trial began with the start of acceleration and ended when a mouse fell off the rod. If a mouse clang to the rod and completed a full passive rotation, the timer for that mouse was stopped. Returned any fallen mice to their home cage, ensuring minimal disturbance to others still in the trial. A repeated trial was conducted if the mouse passively rotates or fell off within 5 seconds of the trial start. Cleaned the apparatus with ethanol between trials. Repeated the procedure for a total of three trials with a 10-minute interval between trials. The latency to fall and the speed of rod during fall were recorded.

Cylinder Test [10]

The cylinders were 30 cm long Pyrex glass cylinders with internal diameter of 28 mm. The cylinders were 30 cm long Pyrex glass cylinders. The animal were trained prior to testing. All the animal had free access to food and water. Brieflu, a mouse with its head forward was introduced near the end of the tube, near the mark. The tube is shifted to a vertical position when the mouse reaches the other end of the tube, which it is pushed towards with a rod if necessary. The time it took the mouse to climb backwards out of the cylinder at the top was recorded. Each mouse was given three chances to climb backwards, each with a one-minute break between them. Mice that climbed backwards in 30 sec were used in the experiment. The mice's inability to climb backwards out of the tube within 30 sec was used as the endpoint for determining muscle relaxant action. The treatment protocol was followed once the training of animal was completed and the testing of the effect of treatment was done and the muscle relaxant activity was measured after 30 min, 1, 2 and 4 h after drug administration.

3. STATISTICAL ANALYSIS

Statistical analysis was done by using graphpad prism version 5.01. Data were expressed as mean ± S.E.M. differences between vehicle, control and treatment groups were tested using one-way ANOVA followed by multiple comparisons by the post hoc Dunnett's test (for comparison with control group. A p values less than 0.05 were considered statistically significant.

4. RESULTS AND DISCUSSION

Transdermal patch formulation

Transdermal patches containing baclofen were prepared using Hydroxy propyl methyl cellulose (HPMC) as the hydrophilic matrix and ethyl cellulose (EC) or Eudragit RL100 as the lipophilic component using PVA 2.5%w/v as the backing membrane (Figure 1). The elasticity of the patches was attained using glycerine (40% polymeric weight) or DPB (20% polymeric weight) as the plasticizer and piperine (10% polymer weight) or DMSO (8% polymer weight) was used as the permeation enhancer to assist permeation of drug into the dermis.

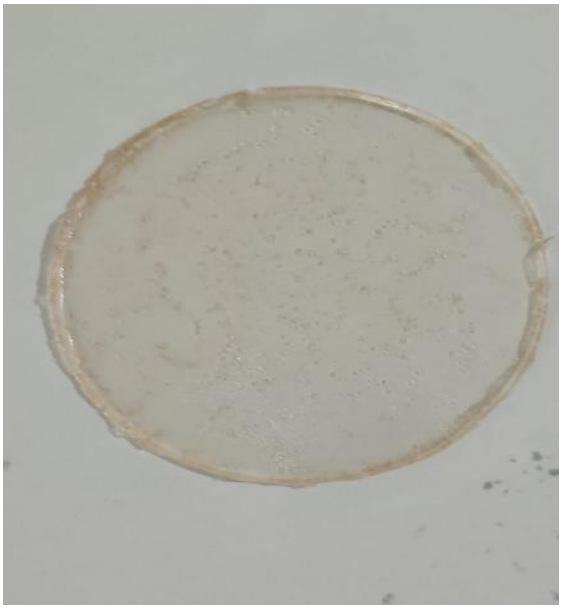

Figure 1Transdermal Patch formulation

The patch T9 revealed thickness of 0.591 cm, average weight of 104 mg, moisture loss of 10.31%, drug content of 94.30%, folding endurance corresponding to 52 folds, surface pH 5.59, tensile strength 7.52 Kg/cm^2 and drug release of 82.07% in 24 h. The patch F1 revealed thickness of 0.354 cm, average weight of 163 mg, moisture loss of 7.37%, drug content of 97.80%, folding endurance corresponding to 82 folds, surface pH 5.54, tensile strength 7.54 Kg/cm^2 and drug release of 88.03% in 24 h.

Pharmacological evaluation

The skeletal muscle relaxant activity of the patch was studied using rotarod and cylinder climbing animal models. The activity of the patch was compared to control animals and standard drug baclofen.

The time taken by the mice to fall from the rotating rod depicts the loss of grip suggesting numbness of the muscle or relaxant activity of the drug. It was visible from the results that the pure drug and the patch were able to significantly decrease the walk time in comparison to the control group (Table 1). It was also evident that the HPMC-ERL patches were not able to produce relaxant effect as effectively as the ERL-EC patches.

Table 1 Time of fall from rotating rod

	30 min	60 min	120 min	240 min
Group	Time of fall (sec)	Time of fall (sec)	Time of fall (sec)	Time of fall (sec)
Control	214.83 ± 4.535	209.5 ± 9.181	207.66 ± 7.447	211.66 ± 7.633
Baclofen	57.00 ± 2.000	49.33 ± 2.338	46.66 ± 1.632	57.16 ± 3.430
T9 Patch	177.33 ± 3.326	151.33 ± 3.723	132.50 ± 1.974	105.66 ± 3.204
F1 Patch	159.50 ± 3.781	125.50 ± 4.549	114.50 ± 4.230	79.16 ± 6.823

As shown in Table 6.10, the response time taken by a group of animals treated with baclofen was significantly higher than the control group at all recording times. The response time taken by the animals treated with patch was also found to be significantly higher at all times post administration. At 240 min post administration the response time by baclofen and the patch was found to be almost similar to each other suggesting that the patch produces sustained release and its efficacy is constantly improving (Table 2). The results also revealed that the ERL-EC patches were more effective in producing skeletal muscle relaxation as compared to the HPMC-EC patches.

Table 2 Latency to climb the cylinder

	30 min	60 min	120 min	240 min
Group	Response Time (sec)	Response Time (sec)	Response Time (sec)	Response Time (sec)
Control	4.16 ± 0.408	5.00 ± 1.032	4.83 ± 0.983	5.00 ± 0.632
Baclofen	11.83 ± 0.752	12.66 ± 1.032	14.50 ± 0.836	14.66 ± 0.816
T9 Patch	6.16 ± 0.752	8.50 ± 0.836	10.83 ± 0.752	11.16 ± 0.752
F1 Patch	9.00 ± 0.632	10.83 ± 0.983	12.33 ± 1.211	14.50 ± 0.547

5. CONCLUSION

The objective of this investigation was to prepare transdermal patches of baclofen and assess its skeletal muscle relaxant potential. The patches were prepared using HPMC-Eudragit or Eudragit-Ethylcellulose as the polymeric matrix. The patches were found to have significant skeletal muscle relaxant action compared to control group. The patches prepared using Eudragit-Ethylcellulose were able to produce significant effect compared to pure drug baclofen. The study led us to conclude that transdermal patch is an effective alternative to oral delivery of baclofen, helpful in reducing the dose and associated side effects of the drug.

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