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## In Vivo Evaluation of Piroxicam Release In Cellulose Acetate Phthalate Films In and Organogels In Rats

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### ABSTRACT

Three groups of rats each consists of five rats were used for this study. Edema was induced by injecting a solution of carrageenan in saline intradermally. Transdermal cellulose acetate phthalate film (with IPM as penetration enhancer) with highest drug release and organogels formulation (F1: Span 60: 17; Tween 20: 3; Soya bean oil: 40; Drug: 2 and Water: 40) with the highest spreadability, the lowest viscosity and the optimized drug release over 8 h was applied. Results from the in vivo pharmacological study revealed that gel preparation was superior to the patch in reducing the edematous swelling in the rats feet pad over the 1 day of application.

**Keywords:** Organogels, Solution of carrageenan

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## INTRODUCTION

Inflammation is a critical process that maintains normal tissue homeostasis following injury or infection, by removing potential pathogens and beginning the process of wound repair and healing<sup>1</sup>. Inflammation is part of the body's defense mechanism and plays a role in the healing process. Inflammation is body's response to inactivate or destroy the invading organisms, remove irritants, and set stage for tissue repair. Inflammation is triggered by the release of chemicals from the injured tissues and migrating cells. The specific chemical mediators vary with the type of inflammation process and include amines such as histamine, serotonin, lipids such as prostaglandins and small peptides such as kinins<sup>2</sup>.

The inflammatory reaction is readily divided into an acute and chronic response. The acute reaction is characterized by redness, heat, swelling, and pain with an accompanying loss of function. The acute reaction is optimally observed in the skin. The chronic reaction is characterized by persistent pain, swelling, and cellular proliferation with an accompanying chronic and often major loss of function such as that observed in rheumatoid arthritis. In this instance, redness and heat may be conspicuously absent. The mechanisms of acute and chronic inflammatory reactions are complex, vary from tissue to tissue, and are dependent on the etiological agent. Common mechanisms include chemotactic stimuli, phagocytosis, and lysosomal enzyme release as well as activation of the clotting, fibrinolytic, kinin, and complement pathways<sup>3</sup>. Histamine release appears to occur early in the initial stages of inflammation. Bradykinin, a non-peptide, is formed from  $\alpha_2$ - globulins by the release of proteases from an area of polymorphonuclear leukocytes after they migrate to an area of inflammation. Lipases activate many arachidonic acid byproducts such as prostaglandins (PGs), thromboxans (TXs), or leukotrienes (LTs). Platelet activating factors and oxygen-free radicals also are released as chemical mediators of inflammation. The initial steps in these reactions involve a number of different cell types and cellular interactions. Most of these chemical mediators appear to have similar effects in that they dilate capillaries in the area of inflammation, increase capillary permeability causing greater transudation, and heighten leukocyte intracapillary adhesiveness and diapedesis into the interstitium where active phagocytosis occurs<sup>2</sup>.

It has been disclosed that blood monocytes and tissue macrophages are primary sources of many cytokines. One of the cytokines is the polypeptide hormone termed interleukin-1, which not only has a potent effect on the inflammatory response but also enhances the immune response by supporting B lymphocyte proliferation and antibody production as well as T lymphocyte production of lymphokines<sup>3</sup>.

The two most important classes of pharmacological agents that inhibit the acute or chronic inflammatory response are (1) the non steroidal anti-inflammatory drugs (NSAIDs), the prototype of which is aspirin, and w(2) the adrenal glucocorticosteroid hormones (SAIDs), the prototype being hydrocortisone <sup>4</sup>.

Models of acute inflammation, which is induced by formalin into the interstitium where active dextran, histamine, serotonin, bradykinin, prostaglandin and carrageenan used to investigate anti-inflammatory effects of drugs <sup>5</sup>.

Carrageenan-induced inflammation, determine COX; model is a COX-dependent reaction and is used to inhibition. Adhesiveness and diapedesis phagocytosis occurs. It has been disclosed that blood monocytes and tissue macrophages are primary sources of many cytokines. One of the cytokines is the polypeptide hormone termed interleukin-1, which not only has a potent effect on the inflammatory response but also enhances the immune response by supporting B lymphocyte proliferation and antibody production as well as T lymphocyte production of lymphokines <sup>6</sup>.

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class used to relieve the symptoms of painful, inflammatory conditions like arthritis . Piroxicam works by preventing the production of a certain type of body chemical called prostaglandins which are involved in the mediation of pain, stiffness, tenderness and swelling. The medicine is available as capsules, tablets and (not in all countries) as a prescription-free gel 0.5%. It is also available in a betadex formulation, which allows a more rapid absorption of piroxicam from the digestive tract <sup>7</sup>. Moreover, topical dosage forms could provide relatively consistent drug levels for prolonged periods and avoid gastric irritation, as well as the other typical side effects of oral NSAID administration. Penetration depends on ability of drug to penetrate the stratum corneum, enter the systemic circulation and to achieve the therapeutic effect <sup>8</sup>. Carrageenan is a strong chemical that functions in stimulating the release of inflammatory and proinflammatory mediators, including bradykinin, histamine, tachykinins, reactive oxygen, and nitrogen species. Typical signs of inflammation include edema, hyperalgesia, and erythema, which develop immediately following the treatment of carrageenan.

## MATERIALS AND METHOD

1. Carrageenan (Sigma Chemical company, USA)
2. Piroxicam was a gift sample kindly supplied by El-Nile Pharmaceutical Company, Cairo, Egypt.
3. Cellulose Acetate Phthalate (CAP) was obtained from EL Kahira Pharm. & Chem. IND. Co., Cairo, Egypt.

4. Acetone purchased from EL Gomhouria Co., Egypt.
5. Polyethylene glycol 600 (Fluka chemical Switzerland)
6. IPM

### Equipment

1. Electric hair clipper (Oster, Oster Corporation, USA) Detachable blade size 40.
2. Dial Micrometer (Cole-Parmer Instrument Co., Japan)
3. Elasto plast (Adhesive tape, Afri Medical Co., Cairo, Egypt).

### Animals

All research strategies have been accomplished in compliance with local experimental animal care regulation and approved by the institutional ethics committee, Faculty of Veterinary Medicine Zagazig University, Egypt (ZU-IACUC/3/F/86/2020). Fifteen (n=15) male rats were randomly allocated to two different preparations of piroxicam gel (F1 formulation: Span 60 (17), Tween 20 (3); Soya bean oil (40); Piroxicam(2) and water (40)) and patch (piroxicam, PEG (600), cellulose acetate phthalate (polymer) and IPM as a penetration enhancer). Rats were obtained from the animal breeding center, Faculty of Veterinary medicine, Zagazig University, Egypt with an average weight of 230±50 g. Animals were housed in the standardized conditions at the animal house of the Faculty of Pharmacy, Zagazig University, Egypt. All animals were acclimatized and kept under constant temperature (25 ± 2 C). All animals were fasted for 12 h prior to the experiment with free access to water.

### Procedure

#### CARRAGEENAN INDUCED RAT HIND PAW OEDEMA.

Rats were allocated into three groups each consists of five rabbits:

**Group 1** Negative control received water

**Group 2:** Patch (0.2 gm of Piroxicam)

**Group 3:** Gel (0.1 gm of Piroxicam) Edema was induced by injecting a solution of carrageenan in saline intradermally.

After cleaning the plantar surface on the footpad with 70% ethanol. The needle was inserted, then each preparation was applied topically on the edematous area. The edematous volume was measured at 0, 1, 2, 3, 4, 5 and 24d after the start of drug treatment using micrometer.

Organogels (F1 formulation: Span 60 (17), Tween 20 (3); Soya bean oil (40); Piroxicam(2) and water (40)) with the highest spreadability, the lowest viscosity and the optimized drug release over 8 h was applied. Induction of edema footpad injections. The thickness of injected paw of rats was measured immediately at zero time (Ti) and after 1, 2, 4, 6, 8, and 24 hours of carrageenan

injection ( $T_f$ ) by micrometer. The percentage oedema and the percentage inhibition were calculated from, the mean effect in control and treated animals according to the following formulae:

$$Oedema(\%) = \frac{T_f - T_i}{T_i} \times 100$$

$T_f$ : final thickness

$T_i$ : intial thickness

$$Inhibtion(\%) = 1 - \left( \frac{\text{Swelling of the drug treated group}(\%)}{\text{Sewlling of control group}(\%)} \right) \times 100$$

### Statistical analysis

In order to assess the influence of both the gel and patch preparation of Piroxicam, one-way analysis of variance (ANOVA), followed by Tukey's Honestly Significant Difference (Tukey's HSD) test as post hoc test was used. Analysis was done using Statistical Package for Social Sciences version 22.0 (IBM Corp., Armonk, NY, USA). Results are reported in means  $\pm$  SD (Standard deviation). The value of  $P < 0.05$  was used to indicate statistical significance.

## RESULTS AND DISCUSSION

Results from the in vivo pharmacological study revealed that gel preparation was superior to the patch in reducing the edematous swelling in the rats feet pad over the 1 day of application.

**Table 1: Comparison of inhibition% among the different preparations through 24 hours post treatment**

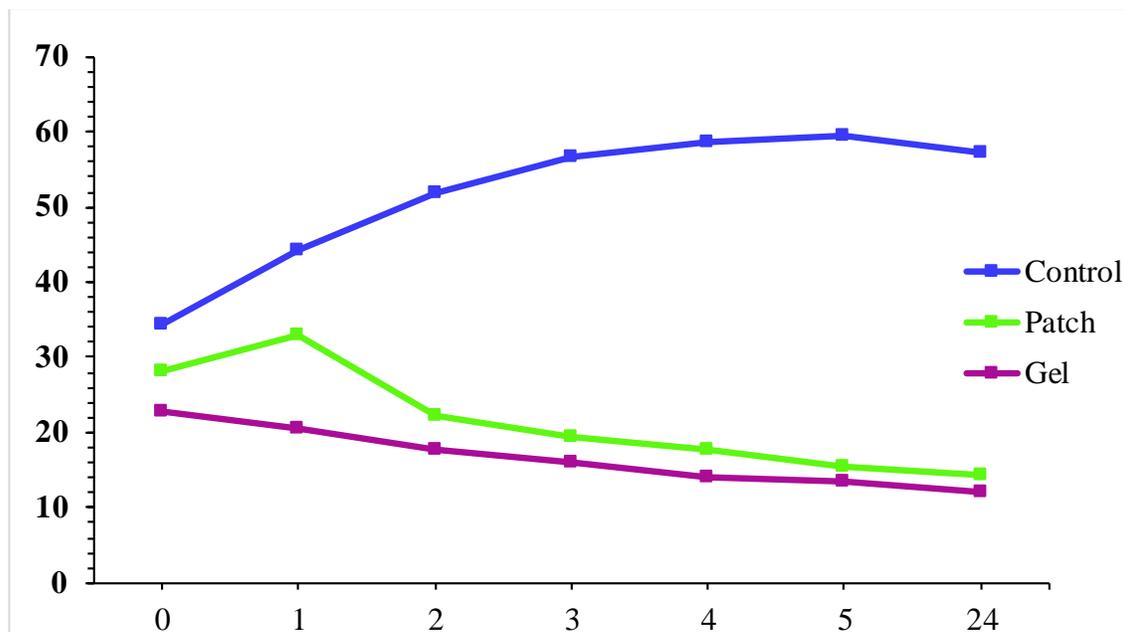
	Control	Patch	Gel
0h	-	18.03 $\pm$ 1.04	34.26 $\pm$ 1.32
1h	-	25.61 $\pm$ 2.02	53.39 $\pm$ 3.11
2h	-	57.34 $\pm$ 3.11	65.83 $\pm$ 5.21
3h	-	65.9 $\pm$ 5.62	71.73 $\pm$ 4.01
4h	-	69.97 $\pm$ 5.75	75.94 $\pm$ 3.02
5h	-	73.99 $\pm$ 4.11	77.52 $\pm$ 6.01
2h	-	74.78 $\pm$ 6.33	78.98 $\pm$ 8.10



**Figure 1: Applying patch and gel preparations**



**Figure 2: Measuring edematous foot pad**



**Figure 3: Comparison of oedema% among the different preparations through 24 hours post treatment 0, 1, 2, 3, 4, 5 and 24**

## CONCLUSION

The oregano gel preparation showed a significantly more efficient performance in terms of the edema inhibition (%).

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