# Effect of various penetration enhancers concentrations on diclafenac sodium release from cellulose acetate phthalate polymeric film

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An investigation was conducted to evaluate the influence of different penetration enhancers in various concentrations on the release of diclofenac sodium (DFS) as a water-soluble drug from Cellulose acetate phthalate polymeric films containing 50% w/w PEG 600 as plasticizer, to choose the most appropriate enhancer and its optimum concentration to be used to achieve the maximum release and permeation of the drug. The addition of various enhancers, as isopropylmyristate (IPM; 0.2_5% w/w), oleic acid (OA; 0.2_5% w/w) and linoleic acid (LOA; 0.2_5% w/w), Tween 80 (T80;1_10% w/w) and transcutol, (TC; 1_10% w/w) enhanced the DFS release from the polymeric films. The enhancement ratio of the penetration enhancers used in the formulation of DFS were found to increase in the order of IPM>LOA>OA>T80>TC. (56.2, 54.1, 50, 48.7 and 48%, respectively). *In vitro* permeation studies were performed using rabbit abdominal skin as the permeating membrane. The results indicated that maximum permeation was obtained at 24hrs (0.5% IPM, 0.2% LOA, 1% OA, 0.5%T80 and 10%TC, increased skin permeation of DFS by 4.46, 4.06, 3.37, 1.65 and 1.49 time, respectively). IPM was found to be the most efficient enhancer. The results obtained from ANOVA test indicate that the difference in drug permeation rates is highly significant compared to the control formulation ($P<0.05$). The mechanism of drug release from the polymeric films obey Higuchi's model.

**Key words:** *In vitro release study, penetration enhancers, percutaneous absorption, polymeric films, ransdermal patch, skin and permeation study, transdermal*

## INTRODUCTION

Transdermal drug delivery system attracts many scientists around the world. There has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery (transdermal delivery) of drugs. The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches. There are a number of routes by which a molecule can cross the stratum corneum; these are intercellular, transcellular and appendageal but the intercellular route is considered to be the major pathway for permeation of most drugs across the stratum corneum.[1]

Transdermal delivery of drugs promises many advantages over oral or intravenous administration. Some of the potential advantages include: avoidance of first-pass metabolism, elimination of gastrointestinal irritation resulting from some drugs, reduced dosing frequency and rapid termination of drug action. However, the success of a transdermal drug delivery system depends on the ability of the drug to penetrate the skin in sufficient quantities to maintain therapeutic level. The principal barrier to most transdermal drug delivery is the stratum corneum. Many strategies have been suggested in order to overcome the low permeability of drugs through the skin.

Transdermal therapy also has some disadvantages, like, higher molecular weight candidates (>500 Da) fail to penetrate the stratum corneum without modifying

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the nature of stratum corneum, drugs with very low or high partition coefficient fail to reach systemic circulation and high melting drugs, due to their low solubility both in water and fat[1,2]

The effective barrier properties of the skin may prevent the entry of drug molecules from the external environment. Molecules may activate allergic responses and the drug may be metabolized by mircoflora on the surface of skin or by enzymes in the skin.[3,4]

Many strategies have been suggested in order to overcome the low permeability of drugs through the skin. A popular approach is the use of penetration enhancers which enhance the permeability of the stratum corneum such as terpenes,[5] nonionic surfactants,[6] Azone[7] and IPM[8]

Diclofenac sodium (DFS) is nonsteroidal anti-inflammatory drugs used to relieve the inflammation, swelling, stiffness and joint pain associated with rheumatoid arthritis, osteoarthritis (the most common form of arthritis) and ankylosing spondylitis (arthritis and stiffness of the spine). It is extensively metabolized in the liver and because of its short biological half life the drug has to be given frequently but it has been known to cause peptic ulcers and bleeding with prolonged administration Therefore, developing a therapeutic system to provide a transdermal delivery is beneficial.

The objective of this study was to investigate the effect of some penetration enhancers on the release of DFS as a model of water-soluble drug from polymeric films and its permeation through abdominal rat skin, also to study physicochemical and physicomechanical characteristics of the prepared films.

## MATERIALS AND METHODS

### Chemicals
DFS kindly supplied by Egyptian International Pharmaceutical Industries Co., (EIPICO, Egypt), cellulose acetate phthalate (CAP), kindly supplied by El kahira Pharmaceutical Industries Co., Egypt, polyethylene glycol 600 (PEG 600), (Fluka Chemical, Switzerland), transcutol, (TC), isopropylmyristate (IPM), oleic acid (OA), linoleic acid (LOA) and carrageenan (Sigma Chemical Co., St. Louis, MO, USA), tween 80, (T80) from (Merck Shape and Dohmn, Germany), acetone, potassium chloride, potassium dihydrogenphosphate, disodium monohydrogenphosphate from (EL-Nasr company For Pharmaceutical and Chemical Co., Abozabal).

### Preparation of films
Films of CAP polymer were prepared employing casting technique[9] 4% w/v polymer solution was prepared using acetone as solvent. PEG 600 as a plasticizer was incorporated at a concentration of 50% w/w of dry polymer weight. Briefly, polymer solution containing drug (12.5 mg per film 2×3cm),

polymer, plasticizer and penetration enhancers in different concentrations was poured on Petri dish (8 cm in diameter). The rate of evaporation of solvent was controlled by placing an inverted funnel over the Petri dish. The choice of penetration enhancers concentration depend on preliminary experiments from which we can select the suitable concentration. The patches did not bear a rate-controlling membrane. This served as a matrix-type transdermal delivery system [Table 1].

### Determination of partition coefficient of DFS
The partition coefficient of the drug was determined by shaking equal volumes of octanol and the aqueous phase in a separating funnel.[10]

A drug solution of 70 $\mu$g/ml was prepared in distilled water and 5 ml of this solution was taken in a separating funnel and shaken with an equal volume of octanol for 10min and allowed to stand for 24 hrs with intermittent shaking. Then, the aqueous phase was assayed before and after partitioning using a UV spectrophotometer to get the partition coefficient values. Partition coefficient of DFS in octanol/water system was determined in absence and presence of 5% OA, 5% LOA and 5% IPM according to Hanan[11]

### Characterization of the transdermal patches
*Physical appearance*
All the transdermal patches were visually inspected for color, clarity, flexibility and smoothness

### Thickness of the films
The thicknesses of the drug-loaded polymeric films were measured at five different points using a digital micrometer (Mitutoyo, Japan).[12,13]

The average and standard deviation of five readings were calculated for each batch of the drug-loaded films.

### Weight uniformity
The films of different batches were dried at 60°C for 4hrs before testing. Five patches from each batch were accurately weighed in a digital balance.[14] The average weight and the standard deviation values were calculated from the individual weights.

**Table 1: Composition of CAP polymeric films containing DFS and different concentration of penetration enhancers**

| Polymer (4% w/v) | Plasticizer (50% w/w of dry polymer weight) | Penetration enhancer | Concentration (% w/w of dry polymer weight) |
|---|---|---|---|
| CAP | PEG 600 | IPM | 0.2, 0.5, 1, 2, 3 |
| CAP | PEG 600 | OA | 0.2,0.5, 1, 2, 3 |
| CAP | PEG 600 | LOA | 0.2, 0.5, 1, 2, 3 |
| CAP | PEG 600 | T80 | 0.5,1, 2, 4, 6, 8, 10 |
| CAP | PEG 600 | TC | 1, 3, 5, 10 |
| CAP | PEG 600 | – | – |

## Content uniformity of films

To ensure uniform distribution of DFS in the film, a content uniformity test was performed. Ten samples each $1\times1$ cm representing different regions within film were cut and weighed, and DFS was extracted with 10 ml methanol twice for 12hrs each time at ambient room temperature using shaker water bath operating at 100rpm. These extracts were diluted with distilled water (pH 6) and estimated spectrophotometrically at 276 nm. Such determinations were carried out for each formulation. Blank experiment was made using drug-free samples.[15]

## Film transparency

Strips of film $8\times40$mm were used for this test. Each strip was mounted on the cell holder of spectrophotometer and light transmittance at 600 nm was determined. Three strips of each film formulation were used and the mean percent transmittance was calculated.[16]

## Tensile strength and percentage elongation

The tensile strength and percentage elongation were measured using JJ load cell instrument 100 N, J.J. Lioyd instruments limited (Warash, Southampton, England) according to Venkateshwari,[17] weight was gradually increased so as to increase the pulling force till the patch broke. The force required to break the patch consider as a tensile strength and it was calculated as Kg/cm$^2$

## Moisture uptake

The weighed films were kept in a desiccator at room temperature for 24hrs. They were taken out and exposed to 84% relative humidity using saturated solution of potassium chloride. After equilibrium was attained, the films were taken out from the chamber and weighed. The moisture uptake was calculated based on the change in weight with respect to the initial weight of the film

%Moisture uptake $=100$ (Ww - Wd) / Wd
Where Ww $=$ weight of wet film
Wd $=$ weight of dry film.

## Stability studies

CAP polymeric films which showed the highest *in vitro* drug release patterns were selected and subjected to stability study by storing the films at different storage conditions. The films were stored for 6 months at different temperatures, ambient room temperature(25°C), 37°C and 40°C and for one month at relative humidity of 96% and 75% at ambient room temperature. The stability study was conducted with drug release, physicomechanical and physicochemical characteristics.

## Evaluation of transdermal patches
### Drug content

Transdermal system of specified area (1cm$^2$) was cut into small pieces and DFS was extracted as before. The solutions were filtered and the absorbance was measured at 276 nm.

## In vitro drug release studies

A Paddle -over-disc assembly (USP 23, Apparatus 2) was used for the assessment of release of drug.[18] The TDDS patch was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 ml phosphate buffer of pH 7.4. The apparatus was equilibrated to $37\pm0.5$°C and operated at 50 rpm. The samples (5-ml aliquots) were withdrawn at appropriate time intervals up to 8hrs and analyzed on a UV spectrophotometer at 276 nm.

## In vitro skin permeation studies

Preparation of the skin barrier: Fresh full-thickness (75-80 mcm) rabbit skin was used for the study. The skin was immersed in water at 60°C for a period of 5 minutes. The epidermis was peeled from the dermis. The isolated epidermis ($25\pm5$ mcm thick) was rapidly rinsed with hexane to remove surface lipids and then rinsed with water and used immediately.

The *in vitro* skin permeation[19-21] from the prepared polymeric patches across the abdominal rabbit skin barrier was studied using a Keshary Chien diffusion cell. Fifty-four milliliters of phosphate buffer of pH 7.4 was used as an elution medium. The patches which studied were placed in between the donor and the receptor compartment in such a way that the drug releasing surface faced toward the receptor compartment. The elution medium was magnetically stirred for uniform drug distribution at a speed of 60 rpm. The temperature of the whole assembly was maintained at $37\pm1$°C by thermostatic arrangements. An aliquot of 3 ml was withdrawn at a suitable interval and an equivalent volume of fresh buffer was replaced. The amount of drug permeated across the skin was determined at 276 nm. The flux (mcg/cm$^2$) was calculated from the slope of the plot of the cumulative amount of drug permeated per cm$^2$ of skin at steady state against time using linear regression analysis. The data were fitted into various classical equations to characterize the kinetics and mechanism of diffusion.

## Skin irritation test

Skin irritation test was performed on six healthy adult albino rabbits weighing between 2.0 and 3.5 kg. Aqueous solution of formalin 0.8% was used as the standard irritant. Drug-free polymeric patches of 4.874 cm$^2$ were used as test patches. Standard irritant was applied on the left dorsal surface of each rabbit and drug-free patches were applied on the right dorsal surface of the rabbit. The patches were removed after a period of 24hrs with the help of an alcohol swab. The skin was examined for erythema/edema. The skin irritation was performed according to International Organization for Standardization (ISO) specification 10993-10 (no erythema 0, very slight erythema 1, well-defined erythema 2, moderate-to-severe erythema 3, severe erythema to slight Escher formation 4; no edema 0, very slight edema 1, well-defined edema 2, moderate edema 3, severe edema 4).

### Carrageenan-induced rat hind paw edema

The anti-inflammatory activity of DFS formulae which showed the highest permeation rate through rabbit skin were tested in rats using carrageenan induced rat hind paw edema method described by Winter *et al*.[22]

The rats were divided into five groups, each consisting of six rats (n=6). The first group served as control and received phosphate buffer saline (PBS) orally using feeding canula. Second group administered plain DFS dissolved in PBS orally using feeding canula as a standard group in the dose equivalent to (1.8 mg/kg). Third group received marketed formulation (Voltaren® tablets 25 mg) as a reference group. Fourth group subjected to the application of CAP polymeric film (CAP 4% W/V, 50% w/w PEG 600 of dry polymer weight and 0.5%w/w IPM of dry polymer weight) containing dose equivalent to (1.8 mg/kg). Fifth group subjected to the application of CAP polymeric film containing 1% w/w OA of dry polymer weight containing dose equivalent to (1.8 mg/kg). The DFS polymeric films were applied to the shaved abdominal surface after cleaning with a piece of cotton to remove dust and dirt from the skin and covered with a piece of adhesive tape. One hour after drug pretreatment, edema was induced in the right hind paw of each rat by injecting 0.1 ml of 1% carrageenan suspension in sterile 0.9% Nacl S.C in the planter tissue. The thickness of injected paw of rats was measured immediately at zero time (Ti) and after 1/2, 1, 2, 4, 6, 8 and 24hrs of carrageenan injection (Tf). Measuring the paw thickness was performed applying micrometer.

The percentage edema and the percentage inhibition were calculated from the mean effect in control and treated animals according to the following formulae.[23]

$$\% \text{ edema} = \frac{Tf - Ti}{Ti} \times 100$$

$$\% \text{ edema} = \frac{Tf - Ti}{Ti} \times 100$$

$$\% \text{ Inhibition} = \left(1 - \frac{\% \text{ swelling of drug-treated group}}{\% \text{ swelling of control group}}\right) \times 100$$

## RESULTS AND DISCUSSION

### Physicomechanical and physicochemical characters

Matrix-type transdermal patches of DFS were prepared using CAP polymeric films containing 50% w/w PEG 600 and penetration enhancers in different concentrations to get the desired drug release profile. The prepared patches were subjected to content uniformity, thickness of the film, weight uniformity, drug content, percentage elongation and tensile strength, percentage moisture content and film transparency their values are shown in [Table 2].

From the data shown one can conclude that:
Drug was distributed uniformly throughout the film as revealed from the data of content uniformity and this is in a good agreement with that mentioned by Dhanikula and Panchagnula.[14]

All films have uniform thickness as shown from the values of film thickness Dhanikula and Panchagnula.[14]

- The addition of penetration enhancers increased moisture uptake Wu *et al*.[24]
  Data of tensile strength and % elongation indicated that the resulted films are flexible and elastic, the addition of penetration enhancers increased both parameters Wu *et al*.[24]
- All prepared films were transparent as revealed from the data of high transmittance present in table 2 except IPM which is slightly turbid Heng *et al*.[25]
- The weight of selected patches for each film formulation indicated that the prepared films have uniform weight Verma and Murthy.[26]

The drug content of selected patches was not less than 98% which indicate that complete solubility of the drug in the polymer matrix Verma and Murthy.[26]

**Table 2: Physicochemical and physicomechanical characters of CAP films**

| Enhancer | Conc. of enhancer (%) | Drug content (%)±S.E | Content uniformity (mg)±S.E | Moisture uptake (%) | Film transparency (%) *n*=4 | Tensile strength (N/mm²) | % elongation | Weight (gm) | Thickness (mm)±S.E |
|---|---|---|---|---|---|---|---|---|---|
| Control | 0 | 99.30 ±1.50 | 2.073 ±0.008 | 11.4 | 70.8±1.14 | 7.0 | 40 | 0.172 ±0.011 | 0.215 ±0.009 |
| IPM | 0.5 | 99.70 ±0.48 | 2.073 ±0.007 | 13.0 | 55.0±0.31 | 8.5 | 44 | 0.174 ±0.015 | 0.215 ±0.005 |
| OA | 1 | 99.60 ±0.17 | 2.081 ±0.009 | 14.7 | 69.0±1.68 | 8.0 | 42 | 0.173 ±0.012 | 0.215 ±0.008 |
| LOA | 0.2 | 98.50 ±0.45 | 2.073 ±0.003 | 18.1 | 70.0±2.64 | 9.0 | 45 | 0.176 ±0.006 | 0.215 ±0.005 |
| T 80 | 0.5 | 100.0 ±2.20 | 2.081 ±0.006 | 16.5 | 70.8±4.45 | 9.5 | 47 | 0.175 ±0.010 | 0.215 ±0.003 |
| Tc | 10 | 98.30 ±1.70 | 2.081 ±0.003 | 15.3 | 70.4±1.77 | 10.0 | 51 | 0.172 ±0.006 | 0.215 ±0.010 |

*Control: No enhancers; **Others: the best concentrations of enhancers

Partition coefficient of DFS in the octanol/water system was found to be 13.97. Partition coefficient of DFS were evaluated in presence of different types of enhancers IPM, OA and LOA (5%); it was 17.75, 14.00 and 14.45 consequently.

### *In vitro* drug release studies

Drug release from polymer matrix and drug dissolution follows Higuchi diffusion model ($r^2 = 0.998$) and ensures sustained reproducibility of rate and duration of drug release.

The effect of IPM was found to be significantly ($P < 0.05$) greater at a concentration of 0.5% w/w than the other studied concentrations (0.2, 3 and 5%) [Figure 1]; it was 56.2% as shown in Figure 1 IPM is an aliphatic ester which is widely used as a safe penetration enhancer. Its mechanism of action may be due to its intermediate polar nature, its PKa 17.75; IPM is being portioned as a result into both the lipid and polar phase.[27]

The effect of both OA and LOA on the drug release is shown in Figures 2 and 3. The effect of 1% OA and 0.2% LOA increased drug release significantly more than other concentrations studied for OA 48% and 54.1% for LOA. The mechanism of enhancing was ascribed to formation of a complex between amino group of DFS and carboxylic group of fatty acids by charge interaction or hydrogen bonding. This complex dissolve in the hydrophobic matrix of the film more than pure DFS and upon film hydration this complex dissociate and DFS partition into the hydrophilic dissolution medium. This is in a good agreement with that mentioned by Saunders *et al*.[28]

The effect of T80 on the drug release is shown in Figure 4. 0.5% w/w T80 increased drug release significantly ($P < 0.05$) more than the other concentrations used (1, 2, 6, 8 and 10%) [Figure 4], it was 50%, this may be attributed to the increasing of film hydrophilicity and also the surfactant solubilized hydrophilic drug in hydrophobic polymer.[29]

In addition increasing concentration of enhancers, the drug release decreased and this may be attributed to micellar complexation.[30]

The effect of TC was found to be significantly ($P < 0.05$) greater at a concentration of 10% w/w than the other studied concentrations (1, 3 and 5%)

The percent release was 48.7%. As shown in Figure 5, TC is a powerful solubilizing agent which increased solubility of the drug in polymer matrix and consequently DFS concentration gradient increased, in addition to its plasticizing effect.[31]

### *In vitro* permeation studies

Drug delivery to or via skin has provided an effective route for local or systemic administration of therapeutically active agents.[30] However, skin and in particular stratum corneum provide an efficient protective barrier for drug absorption.

A useful approach for increasing percutaneous absorption of drugs is to employ permeation enhancers.

The formulations which showed the highest *in vitro* release pattern were selected and subjected to permeation through excised rabbit skin. Figure 6 demonstrates the release and permeation of DFS through rabbit skin. It was found that there is a correlation between the *in vitro* release of DFS from polymeric films to dissolution medium and its permeation through rabbit skin. The enhancement effect of penetration enhancers used in the formulation of DFS films was found to increase in the order of IPM >LOA >OA>T80>TC.

The results obtained from ANOVA test of significance indicate that the difference in drug permeation rates of the used formulations is highly significant compared to the control formulation (significance at $P < 0.05$) as follows: 0.5% IPM, 0.2% LOA, 1% OA, 0.5% T80, and 10% TC, increased skin permeation of DFS by 4.46, 4.06, 3.37, 1.65 and 1.49 time, respectively, in comparison with control.

The enhancing mechanism may be attributed to increasing the solubility (TC and T80), increase the flowability of stratum corneum bilayers (OA, LOA and T80)[24] and disrupts the order and arrangement of lipid bilayers of stratum corneum hence improves drug permeation into this layer (IPM)[32]

## STABILITY STUDIES

### Temperature
*Physical properties*
All tested formulations showed high stability upon storage at ambient room temperature, 37°C and 40°C and all physical characteristics have the same values as fresh samples.

### *In vitro* release studies
CAP polymeric films containing 0.5% IPM, 10% TC, 1% OA and 0.5% T80 showed high stability when stored for 6 months at room temperature, 37°C and 40°C. While CAP films containing 0.2% LOA suffered from poor stability as after storage for 6 months at all temperatures the amount of DFS released from the film was significantly decreased. This can be attributed to oxidation of LOA with the formation of peroxides that may hinder the release of the drug.
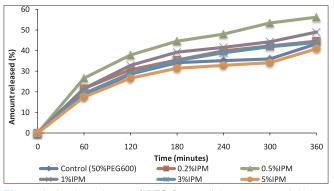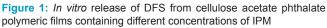
### Humidity
*Physical properties*
a) Tensile strength and percent elongation for all tested formulations increased. The effect was more pronounced in case of samples which stored at 96% relative humidity where the tensile strength and percent elongation showed higher values than those at 75% relative humidity. These results can be attributed to increase film elasticity as a result of increased film porosity due to moisture absorption.

b) Films containing 10% TC showed a slight increase in their weights in comparison to other formulations where no significant weight change was observed.

c) No significant change in drug content, content uniformity, thickness and drug release % was observed for all tested formulations.

### In vitro release studies

All selected formulations showed high stability upon storage at ambient room temperature and relative humidity 96 and 75%. The release of DFS from selected formulations increased but it is nonsignificant in comparison to the control formulation.

## IN VIVO PHARMACOLOGICAL STUDIES

### Carrageenan-induced rat hind paw edema

Both DFS polymeric films and plain DFS solution significantly inhibit swelling compared to the control as shown in Figure 7. The anti-inflammatory activity of DFS in polymeric films is found to be enhanced and prolonged.

It was observed that both the standard group (group treated with plain drug oral solution) and reference group (group treated with Voltaren® 25 mg tablet) produced maximum percent edema inhibition at 4hrs and then the effect reduced



**Figure 1:** *In vitro* release of DFS from cellulose acetate phthalate polymeric films containing different concentrations of IPM



**Figure 2:** *In vitro* release of DFS from cellulose acetate phthalate polymeric films containing different concentrations of OA



**Figure 3:** *In vitro* release of DFS from cellulose acetate phthalate polymeric films containing different concentrations of LOA
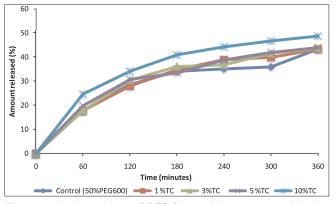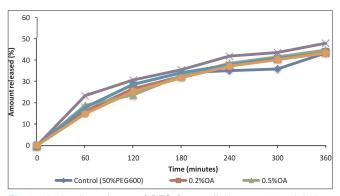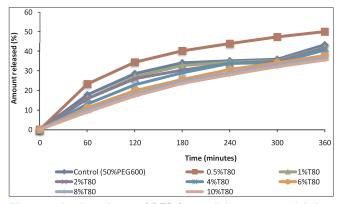


**Figure 4:** *In vitro* release of DFS from cellulose acetate phthalate polymeric films containing different concentrations of T80



**Figure 5:** *In vitro* release of DFS from cellulose acetate phthalate polymeric films containing different concentrations of TC
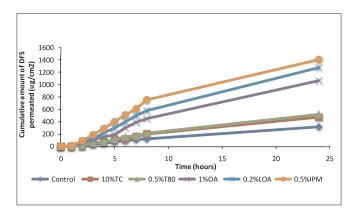


**Figure 6:** *In vitro* permeation of diclofenac sodium through abdominal rabbit skin
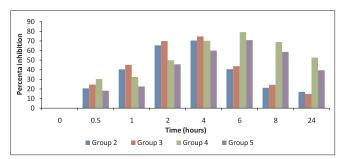
**Figure 7:** Percent edema inhibition by administration of different formulae containing DFS (*n*=6); Gr1: Control group. (no inhibition); Gr2: Standard group; Gr3: Reference group; Gr4: Test group receive 0.5%w/w IPM +1.8 mg/kg DFS; Gr5: Test group receive 1% w/w OA +1.8 mg/kg DFS

gradually with time up to 24hrs, while in case of groups 4 and 5 (groups treated with polymeric films with selected penetration enhancers) produced maximum percent edema inhibition after 6hrs and then continued for 24hrs. The reason for high initial percent edema inhibition at 4hrs and then gradual decrease in the percent edema inhibition up to 24hrs with standard and reference groups may be due to the rapid release of drug from the solution which responsible for faster absorption and excretion of the drug from the body. Slow and gradual release of the drug from polymeric films may have resulted in gradual increase in the percent edema inhibition up to 24hrs.

## Acute skin irritation study

The polymeric films which showed the highest drug release rate and subjected to permeation through rabbit skin were subjected to acute skin irritation test to study their safety upon application to patient skin.

The scores of the Draize test were 0 in every determination both for the edema and for the erythema evaluation in all tested rabbit, indicating that primary irritation was absent

## CONCLUSION

CAP films containing DFS with and without penetration enhancers showed uniform thickness, weight, drug content and homogeneous distribution of the drug. Data of tensile strength and % elongation revealed that all formulations were elastic, flexible. Percentage transmittance proved that all resultant films were transparent. The release rate of drug from films follows Higuchi equation in which the amount of drug released is linear to square root of time. All used enhancers enhanced the DFS in the following descending order: IPM > LOA > OA > T80 >TC

All formulations were stable upon storage at different temperatures and different humilities except that contain OA. No skin irritation was observed. The polymeric film formulations of DFS improved the systemic anti-inflammatory activity compared to the plain drug solution and marketed tablet formulations although the high dose of voltaren.

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## FORM IV

*Statement about ownership and other particulars about newspaper* **(Asian Journal of Pharmaceutics)** *to be published in the first issue every year after the last day of February*

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| 6. | Names and addresses of individuals who own the newspaper and partners or shareholders holding More than one per cent of the total capital. | : | B. R. Nahata Smriti Sansthan, Mandsaur |

I, **Narendra Nahata**, hereby declare that the particulars given above are true to the best of my knowledge and belief.

Date: ???          **Mr. Narendra Nahata**     **Dr. V B Gupta**