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# DESIGN AND *INVITRO* EVALUATION OF DICLOFENAC-PARACETAMOL DUAL RELEASE TRANSDERMAL PATCH

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**ABSTRACT**

The plan of this current study is to design the dual release transdermal patches (Dual Trans) and to perform the physiochemical and *invitro* evaluation studies for it. The present study proved that Transdermal patch containing two drugs i.e., Diclofenac potassium (Diclo) and Paracetamol (Para) follows simultaneous release pattern of drug without interacting the release of each other and also it focus its effect on chronic pain associated with skeleton-muscular disorders such as Rheumatoid arthritis. In this study Diclo-Para Dual Trans was prepared by solvent evaporation method using different polymer like Ethyl Cellulose, HPMC with varying proportions, Dimethyl Sulfoxide (DMSO) as a skin permeation enhancers and Polyethylene Glycol is used as a plasticizer. The prepared patches were evaluated for its thickness, weight variation, folding endurance, moisture content, drug content uniformity and also taken for *invitro* permeation study, *invitro* release kinetics studies and skin irritation studies. A drug polymer interaction was studied by FTIR. *Invitro* release and permeation studies were performed by using Franz-diffusion cell. The Results shows that patches prepared with HPMC and DMSO showed higher % moisture transmission and desired % drug release of both the drugs Diclofenac and Paracetamol. Also the study reveals that the formulation containing HPMC (with drug and polymer ratio 1:1) has ideal zero-order release kinetics and best fit for Peppa's fitting curve.

**Key Words:-** Dual release transdermal patch, Diclofenac, Paracetamol, HPMC, Transdermal patches, Rheumatoid Arthritis.

## INTRODUCTION

A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. Transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivering to the systemic circulation via skin. The success of transdermal therapeutic system has created much interest in the pharmaceutical industry and has activated research activities related to it (Misra AN *et al*., 1997 & Chien YW *et al.*, 1997). Transdermal delivery has many advantages over conventional modes of drug administration, it avoids hepatic first pass metabolism, potentially decreases side effects and improves patient compliance (Keith AD, 1983). Drug delivery with transdermal patch systems exhibit slow, controlled drug release and absorption. The plasma drug concentration does not vary significantly over time. Transdermal delivery system is a growing market that is expected to expand in the near future with the discovery of new drug treatment applications and technologies (Kunal N Patel, 2010). Diclo-para which have a non-steroid anti-inflammatory drug with analgesic

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and antipyretic action. It inhibits cyclo-oxygenase activity with a reduction in the tissue production of prostaglandins. The aim of present study is to formulate and evaluate dual transdermal drug delivery for controlled release of Diclo-para. Dual Transdermal drug delivery systems are capable of controlling the rate of drug delivery, prolonging the duration of therapeutic activity and targeting the delivery of drug to a tissue. In response to these advances, several transdermal drug delivery systems have been developed to achieve the objective of systemic medication through application on the intact skin surface. The advantage of dual transdermal drug delivery system is that they can provide sustained drug delivery and enhance constant drug concentrations in plasma over a prolonged period of time. Thus it is estimated that Dual Transdermal drug delivery systems can be designed to deliver drugs at appropriate rates to maintain suitable plasma–drug levels for therapeutic efficiency. Ultimately the success of all Dual Transdermal systems depends on the ability of the drug to permeate skin in sufficient quantities to achieve its desirable therapeutic effects.

Rheumatoid arthritis is a chronic, autoimmune, inflammatory joint disease of unknown cause affecting approximately 1% of the population worldwide. Without early disease-modifying treatment, progressive and irreversible joint damage can occur that results in lifelong functional impairment. (Saag KG *et al*., 2008) RA is a chronic disease, mainly characterized by inflammation of the lining, or synovium, of the joints. It can lead to long-term joint damage, resulting in chronic pain, loss of function and disability. Diclo-para dual release transdermal patch was desired to apply in the condition of Rheumatoid arthritis as anti-inflammatory and analgesic effect for treating chronic pain. It is also used in post-operative condition in ICU patients (Rennie *et al*., 2003)

## MATERIALS AND METHODS

### Material

Diclo-para samples were collected from Milton laboratory, Pondicherry, India. Ethyl cellulose, HPMC, PEG, Chloroform, Propylene glycol, DMSO was received from Medrich, Bangalore. All the other solvents and chemicals were of analytical grade.

### Preparation of Matrix Type Dual Transdermal patch

Dual Transdermal patches of Diclo-para were prepared by solvent evaporation technique by incorporating different concentration of polymer HPMC and EC along with suitable solvent. The polymers are dissolved in the solvent to get polymer solution; Diclo-para in the ratio of 1:1 was added to the above solution and stirred continuously until both the drugs soluble in the polymer solution. Then add poly ethylene glycol (PEG) as plasticizer to increase the plasticity of the transdermal patch. DMSO was added as a permeation enhancer. The optimized formulations of dual transdermal patches of Diclo-para were shown in Table 1. The polymer solutions were prepared by dissolving appropriate polymers, plasticizer in suitable vehicle using a magnetic stirrer. Both the drugs was added slowly to the solution and dissolved by continuous stirring for 30 min to get a clear solution. Glass petridish with a partition made by aluminium foil at the center equal half was taken and lubricated. Then the solution was spread separately uniformly in this petridish, so that two solution separated by the aluminium foil partition .The mould was kept for one day. The rate of evaporation was controlled by inverting a funnel over the mould. After 24 h, the dried patches were then detached from the petridish and patches were cut to generate dual transdermal patch of 2.0 cm in diameter. The formulated patches were stored in desiccators. (Mutalik S and Udupa N, 2005)

## EVALUATION OF DUAL TRANSDERMAL PATCH

### Interaction studies

Interaction studies were conducted on the medicated TDDS formulations by comparing them with the pure drug and placebo formulations on the basis of assay, UV, IR. The TDDS was dissolved in isopropanol and the drug content was determined by UV spectrophotometry. UV Analysis: – The isopropanol solutions of the pure drug, medicated and placebo formulations were filtered through Whatman filter paper no. 42 and scanned spectrophotometrically between 200–400 nm. IR analysis. – The IR absorption spectra of the pure, medicated and placebo formulations were taken in the range of 400–4000 $cm^{-1}$ using the potassium bromide disc method (Lab India IR spectrophotometer, OPUS software). (Mohamed Aqil *et al*., 2003)

### Physical characterization

The physicochemical parameters such as thickness, uniformity of weight, tensile strength, content uniformity test, moisture content, moisture uptake, drug content uniformity and folding endurance of various patch were determined and shown in Table 2.

### Thickness

The thickness of the patch was determined by measuring the thickness at random sites on the formulated patch using micrometer screw gauge and the average thickness was determined. (Amnuaikit C *et al*., 2005).

### Uniformity of weight

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average

weight. The individual weight should not deviate significantly from the average weight.

**Tensile strength**

A small film strip (40 x 15 mm) was used. One end of the strip was fixed between adhesive tapes to give support to the film when placed in the film holder. Another end of the film was fixed between the adhesive tapes with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached to the other end to the hold the weights. A small pointer was attached to the thread, which travels over the graph paper affixed on the base plate. To determine the tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The weight required to break the film was noted as break force (Kulkarni R *et al*., 2000).

**Percentage Moisture content**

The prepared patch are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The patch is weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula. (Kusum DV *et al*., 2003).

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

**Moisture uptake**

Initial weight of the patch was taken and noted, then weighed patch are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. Final weight of the patch was calculated and percentage moisture uptake is calculated as given below. (Kusum DV *et al*., 2003).

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

**Folding endurance**

The folding endurance was measured manually for the prepared patches. Folding endurance of the film was determined by repeatedly folding a small strip of film (2cm x 2cm) at the same place till it breaks. The number of times, the film could be folded at the same place either to break the film or to develop visible cracks, gave the value of folding endurance (Devi VK *et al.*, 2003).

**Drug content uniformity**

The uniformity of drug content of the dual transdermal film was determined, based on dry weight of drug and polymer used by means of a UV/VIS spectrophotometer method. The formulated patch was cut into pieces and dissolved in 10 ml of ethanol. The resulting solution was quantitatively transferred to volumetric flasks, and appropriate dilutions were made with phosphate buffer pH 7.4 and filtered through 0.22 µ filter and analyzed for Diclofenac content at 254 nm and Paracetamol content at 249 nm by using UV/VIS spectrophotometer. (Ubaidulla U *et al*., 2007). 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then dual transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the dual transdermal patches pass the test (Mutalik S *et al*., 2005).

***Invitro* permeation study**

The *invitro* permeation study of fabricated dual transdermal patches of Diclo-para was carried out by using excised mice abdominal skin and Franz diffusion cell. The skin was sandwiched between donor and receptor compartments of the diffusion cell. A 2.2 cm diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 12ml of normal saline. The cell contents were stirred with a magnetic stirrer and a temperature of 37 ± 5 º C was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24h, simultaneously replacing equal volume by phosphate buffer pH 7.4 after each withdrawal. The samples were analyzed spectrophotometrically at 254nm for Diclofenac & 249 nm for Paracetamol. (Chein YW, 1988)

**Primary skin irritation Study**

The patches were tested for their potential to cause skin irritation in mice. Placebo patches were applied to the 8 healthy volunteer and observed for any sign of

redness, itching, erythema and edema for a period of 24 hr (Dey S *et al*., 2010).

***Invitro* drug release kinetics**

In order to study the exact mechanism of drug release from Microspheres, drug release data was analyzed according to Zero Order , First Order , Higuchi square root, Hixson Crowell, Korsermeyer Peppas model. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test. Data obtained from *invitro* release study were fitted to various kinetic equations. The kinetic models used are,

Zero order equation : ($Q=k_0t$)
First order equation : {ln (100 – Q) = ln Q – k1t}
Higuchi equation : (Q= kt 1/2)
Korsmeyer and Peppas equation :($Q = kpt^n$).

Further, to find out the mechanism of drug release, first 60% drug release was fitted in the above equation .Where, Q is the percent of the drug release at time t and $k_0$ and kt are the coefficients of the equations and n is the release exponent. The n value is used to characterize different release mechanism as follows. If $n < 0.5$, the polymer relaxation does not affect the molecular transport, hence diffusion is Fickian. If $0.5<n<1.0$, the solid transport will be non – Fickian and will be relaxation controlled (Koresmeyer RW *et al*., 1983).

**RESULT AND DISCUSSION**

**Physicochemical Evaluation**

The formulated Dual Trans of Diclo-para was evaluated for weight variation, thickness, tensile strength, moisture content, moisture uptake, folding endurance and content uniformity, which was shown in Table 2. An interaction study shows good compatibility between the drug and polymers. Thickness of dual transdermal patch was measured by micrometer screw gauge. The thickness of the patch varies from 0.074 ±0.008 mm to 0.104 ±0.006 mm. The F1 dual transdermal patch film was found to be of least thickness as compared to all. All the patches showed satisfactory folding endurance properties, and it is found to be within 80 to 120 folds. The drug content uniformity was determined using UV spectrophotometric method for all the five formulations and the results of the drug content of prepared patches of Diclo-Para Dual Trans varies between 84.04± 3.80% and 92.22±4.04% for Diclofenac and between 82.36±3.68% and 89.54±4.62% for Paracetamol. It concludes that the drug content is uniform throughout the all patches. All the polymers used for the fabrication of the transdermal system showed good film forming properties. Especially formulation F1 of 1:1 Drugs and HPMC patch is found to be most elegant, thin, flexible, smooth, and transparent patch. The drug content was nearly the same as the dose of the drug in all the patches. The moisture content is found to be satisfactory and it is within the specific limit. All the formulations are found to be permeable to the water vapor. All the formulations are selected for stability studies at room temperature for 6 months and observed for changes in color, appearance, flexibility, and drug content. The mean (n = 3) cumulative amounts of drug diffuse through the sliced mice skin (*invitro* skin permeation) are also performed for 24 hours, analyzed and their results are shown Fig 1 and 2. Among this five formulation F1 shows better release pattern as desired i.e., 48.85±4.45 to 52.33±3.20 for 24 hrs, this shows that F1 Dual Trans will release the drugs cumulatively for twice a day without accumulation of dose with the dose of next drug administration. Diffusion Studies revealed that HPMC dual transdermal film (i.e., formulation F1 of 1:1 Drugs and polymer) gave the desired controlled release. The *Invitro* release kinetics studies confirms that all the formulation F1-F5 shows Zero order release kinetics and Non-fickian diffusion mechanism, which was calculated and their values are shown in Table 3 i.e., if n value lies within 0.5 and 1, the solid transport will be Non-fickian and will be relaxation controlled system. Primary skin irritation studies revealed that after 24 hrs there is no stain, inflammation or rashes in the mice skin.

**Table 1. Formula for Dual transdermal patches containing Diclofenac –Paracetamol**

| Ingredients | Formulation code | | | | |
|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** |
| Diclofenac potassium | 20 | 20 | 20 | 20 | 20 |
| Paracetamol | 100 | 100 | 100 | 100 | 100 |
| HPMC | 120 | - | 240 | - | 120 |
| EC | - | 120 | - | 240 | 120 |
| PEG(plasticizer) | 36% | - | 36% | - | 18% |
| Poly propylene glycol | - | 36% | - | 36% | 18% |
| DMSO (permeation enhancer) | 12% | 12% | 12% | 12% | 12% |
| Chloroform | q.s | q.s | q.s | q.s | q.s |

**Table 2. Physical Evaluation Parameters of Dual Transdermal patch**

| Formulation Code | Weight Variation (mg/2cm$^2$) | Thickness (mm) | Folding Endurance | Moisture Content in % | Drug Content in % | |
|---|---|---|---|---|---|---|
| | | | | | Diclofenac | Paracetamol |
| F1 | 0.090±0.002 | 0.090 ±0.002 | > 120 | 0.98±0.12 | 91.44±3.24 | 89.54±4.62 |
| F2 | 0.072±0.002 | 0.074 ±0.008 | > 120 | 0.74±0.18 | 85.32±3.40 | 82.36±3.68 |
| F3 | 0.052±0.002 | 0.110 ±0.010 | > 120 | 0.84±0.08 | 92.22±4.04 | 87.34±3.04 |
| F4 | 0.064±0.002 | 0.104 ±0.006 | > 120 | 0.88±0.10 | 88.42±2.42 | 86.24±3.86 |
| F5 | 0.074±0.002 | 0.084 ±0.010 | > 80 | 0.82±0.06 | 84.04±3.80 | 88.90±3.34 |

All values are expressed as Mean±SD

**Table 3. *Invitro* release kinetics studies by fitting the release profile of Diclofenac and Paracetamol from dual transdermal patches F1-F5 in four different models (r values)**

| Formula code | Drug release kinetics for Diclofenac | | | | | | Drug release kinetics for Paracetamol | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Zero order | First order | Peppa's | | Hixon Crowell | | Zero order | First order | Peppa's | | Hixon Crowell | |
| | r | r | r | n | r | n | r | r | r | n | r | n |
| F1 | 0.9710 | 0.9197 | 0.9717 | 0.7140 | 0.8234 | 0.0712 | 0.9880 | 0.9594 | 0.9769 | 0.6246 | 0.8003 | 0.0675 |
| F2 | 0.9609 | 0.8877 | 0.939 | 0.7182 | 0.7513 | 0.0641 | 0.9900 | 0.9447 | 0.9736 | 0.6009 | 0.8044 | 0.0623 |
| F3 | 0.9601 | 0.9028 | 0.9367 | 0.8242 | 0.7239 | 0.0674 | 0.9586 | 0.8851 | 0.9199 | 0.6408 | 0.7211 | 0.0571 |
| F4 | 0.9747 | 0.9155 | 0.9470 | 0.7775 | 0.7980 | 0.0700 | 0.8893 | 0.7868 | 0.8369 | 0.5197 | 0.6235 | 0.0447 |
| F5 | 0.9800 | 0.9174 | 0.9356 | 0.6480 | 0.7355 | 0.0698 | 0.9760 | 0.9629 | 0.9760 | 0.6059 | 0.8233 | 0.0698 |

**Fig 1. Comparative *Invitro* Diclofenac release profile for F1-F5**

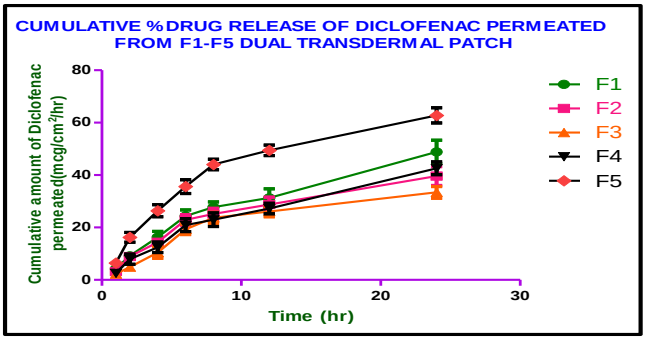



**Fig 2. Comparative *Invitro* Paracetamol release profile for F1-F5**

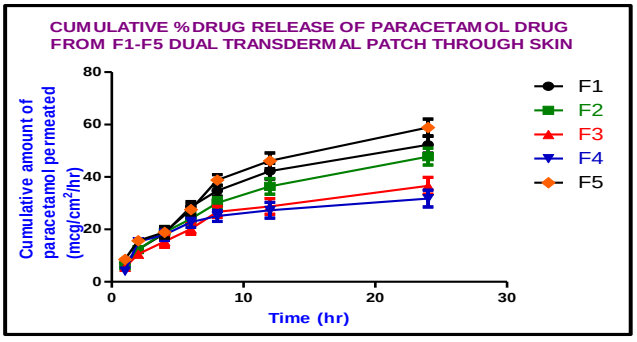



**Fig 3. Dual Transdermal Patches (Dual Trans)** Showing two portions of uniformly distributed drugs (Diclofenac & Paracetamol) which having partition at the centre

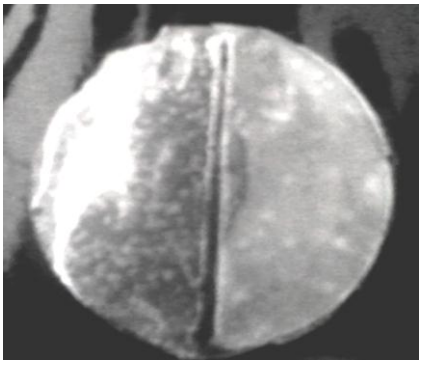
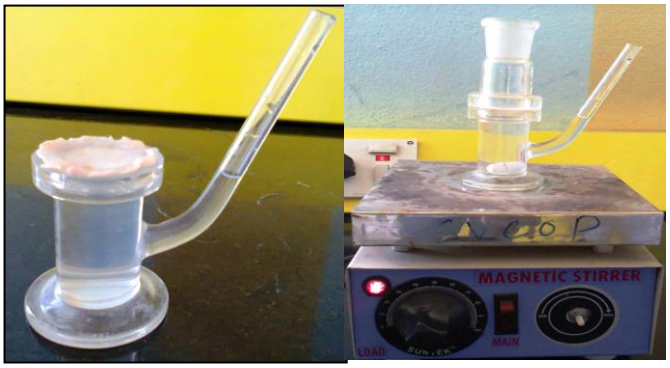


**Fig 4. Franz Diffusion set up for drug release (with mice skin and dual patch)**



## CONCLUSION

The preliminary study confirms the suitability of ethyl cellulose and HPMC for formulating dual transdermal drug delivery system of Diclo-Para. The Permeation of Diclo-Para from different polymeric membranes was found more with HPMC than EC. The *invitro* permeation and *invitro* release kinetics studies confirm reproducible release pattern of Diclo-para from the dual transdermal patch. Hence we conclude that dual transdermal patch containing Diclo-Para will maintain the plasma drug concentration required to treat pain associated with chronic disorders like rheumatoid arthritis and for post operative pain.

Our innovative design pattern of dual transdermal patch with along the sides of two different drugs shows added advantage as in this design any best combinations of drugs with physical incompatibility can be formulated as a dual trans patch, whereas with older dual transdermal patches in which drugs are in different layers i.e. one over the another may leads to incompatibility. Similarly our design pattern can be extended by trying with 3 or more drugs in a single transdermal patch along the sides.

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