# DEVELOPMENT OF TRANSDERMAL DRUG DOSAGE FORMULATION FOR THE ANTI-RHEUMATIC AYURVEDIC MEDICINAL PLANTS

Manisha Verma, Pankaj Kumar Gupta*, Varsha B. Pokharkar, A. P. Purohit**

*Presenting author

**Corresponding author along with address:

Prof. A. P. Purohit,

Head, Deptt. of Pharmacognosy,

Bharati Vidyapeeth Deemed University,

Poona College of Pharmacy,

Erandwane, Pune-411 038,

Maharashtra, India.

E-mail: aparnajit@rediffmail.com

Tel: 91-20-5437237

**Abstract:**

The present investigation was aimed to formulate transdermal films incorporating herbal drug components. The allopathic system of medicine includes two conventional lines of treatment for rheumatoid arthritis, which come along with certain side effects. Hence, turning to safe, effective and time-tested Ayurvedic herbal drug formulation would be a preferable option. With this view transdermal films incorporating herbal drug components such as boswellic acid (*Boswellia serrata) a*nd curcumin (*Curcuma longa)* was envisaged. The drugs were selected on the basis that they produce synergistic action in suppressing inflammation and are proved time tested and safe drug.

The polymeric films were evaluated for their physical properties like percentage flatness, thickness uniformity, and drug content and diffusion studies across hairless mouse skin. The average per cent release of curcumin was found to be 50.70% and 69.84% for boswellic acid (peak 1) and 64.84% for boswellic acid (peak 2) in the hydroalcoholic diffusion medium at the end of 9 hrs. The graphs obtained for the average per cent release through transdermal film indicate drug release occurred at a constant rate.

The skin irritation study done on albino rabbit skin showed that the formulation does not produce irritation to the skin.

Overall, it was observed that the well-known ayurvedic drugs have been found to be effective through modern pharmaceutical formulation techniques.

**Keywords:**

Curcumin, Boswellic acid, Transdermal Film

**Introduction:**

Rheumatic diseases have affected mankind since ages and are one of the commonest inflammatory conditions in developing countries. Rheumatoid arthritis (RA) forms a major prototype of rheumatic diseases and is a common cause of disability[1,2].

RA is both an extravascular immune complex disease and a disorder of cell-mediated immunity leads to chronic inflammation, granuloma formation and joint destruction. The etiopathogenesis of RA involves diverse and complex factors such as genetic background, rheumatic factor (circulating antibodies), immune complexes, compliment activation, lymphocytes, arachidonic acid metabolites, free oxygen radicals etc[1,3].

Currently synthetic drugs form a major line of treatment in the management of arthritis. The conventional drug treatment of RA consists of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and cortico-steroids[1]. These agents act at various sites in the schema of pathogenic mechanisms. An important problem in the drug therapy in the elderly RA patients is the lack of compliance. They have other illnesses for which they may be taking medicines[4]. Transdermal delivery thus offers a better route of delivery, reported to have better patient compliance.

Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin[5].

Transdermal drug delivery system (TDDS) can deliver certain medication to systemic circulation in a more convenient and effective way than is possible with conventional dosage form. The potential of skin as a path of drug administration has been amply demonstrated by the acceptability of marketed therapeutic systems[6]. TDDS can minimize first-pass metabolism associated with gastro-intestinal administration of drugs. The TDDS can maintain constant drug level in blood. It is possible to enhance the transdermal permeation of drug using penetration enhancers[7]. The present investigation was aimed to formulate transdermal films incorporating boswellic acid and curcumin.

Boswellic acid, a constituent of *Boswellia serrata* (Family- Burseraceae) showed anti-inflammatory and anti-rheumatic activities along with anti-pyretic effect with no ulcerogenic effect and well tolerated in as high a dose as 2 gm/kg (p.o) in mice. It improves blood supply to joints and restores integrity of vessels obliterated by spasm of internal damage. *B. serrata*

(Sallai guggul) shows its superiority over conventional drugs as it is a plant product being used since ages and is absolutely free from any toxic and side effects[8].

Curcumin, a constituent of *Curcuma longa* (Family-Zingiberaceae), chemically known as diferuloylmethane has been shown to be an effective anti-inflammatory agent and lacks analgesic and anti-pyretic activity. It is well tolerated in as high a dose as 2 gm/kg (p.o) in mice[9]. It has been reported to inhibit both lipoxygenase & cyclooxygenase and a potent scavenger of oxygen free radicals[10]. It undergoes extensive first-pass metabolism and hence is a suitable candidate for transdermal patch formulation.

The drugs (boswellic acid and curcumin) were selected on the basis that they produce synergistic action in suppressing inflammation and are time tested and proven safe[11,12].

**Material and methods:**

**Chemicals:**

Ethyl cellulose, Polyethylene glycol (PEG) 6000, Dibutylphthalate, Menthol, Chloroform, Methanol, Ethanol

**Preparation of medicated polymeric film**:

Curcumin (20 mg) and boswellic acid (200 mg) were dissolved in chloroform (5 ml) along with dibutylphthalate (0.3 ml) and menthol {0.1 ml (5% w/v in ethanol)}. This solution was then added to polymer base, prepared by dissolving ethyl cellulose (900 mg) & PEG 6000 (90 mg) in chloroform (10 ml) and stirred continuously to get uniform solution. The final volume was made to 22 ml with chloroform. Definite volume (5.5 ml) of the above solution was then poured into siliconized glass mould and dried at room temperature for 30 min to obtain films. These films were then subjected to further evaluation.

**Evaluation of polymeric film:**

The films were evaluated for the following parameters:

**Thickness:** The thickness of film was measured by using electronic vernier calipers, with a least count of 0.01mm. Thickness was measured at five different points on the film and average of five readings was taken[7].

**Percentage flatness:** Film was cut into strips, two from either end and one from the center. The length of these strips was measured to the nearest centimeter without applying any additional pressure. The percent flatness of the strips was selected as the average percent of length calculated from the 7cm strips.

**Drug content:** Drug content was found out by dissolving four patches each of 2 cm x 2 cm in 10 ml of Ethanol. 0.1ml of this solution was diluted to 10 ml with hydroalcoholic medium. The absorbance of these solutions were found out at 254 nm for Boswellic acid and 425 nm for Curcumin and the drug content determined using the standard calibration curves[6].

***In vitro* diffusion study:**

Herbal transdermal film measuring 3.14 $cm^2$ were subjected to *in vitro* diffusion testing using Keshary-Chien diffusion cell. Suitably prepared hairless mouse skin was clamped between the donor and receptor compartments and the film was placed over the skin. The receptor compartment contained distilled water / ethanol (9:1) at $37^o$ C ± $1^o$C. The medium was magnetically stirred and the amount of drugs diffusing into the receptor compartment across the skin were determined by withdrawing 2 ml samples over the duration of experiment and an equivalent amount of diffusion medium was added to the receptor compartment to maintain a constant volume[6]. The samples for analysis were prepared by diluting 0.1 ml. of the solution to 1 ml with ethanol. These samples were analyzed by using HPTLC (CAMAG) method. 20µl of samples were applied on precoated silica gel $F_{254}$ plate (10 X 10 cm) as bands (Linomat IV). The plate was developed in petroleum ether : acetone (7:3) as mobile phase and peak height & area was determined. Drug content was determined using standard calibration curve. The cumulative amount of drug permeating through the skin was then calculated and average per cent release and flux values were determined.

**Primary Skin Irritation Study:**

Three albino rabbits of either sex weighing 2-2.5 kg were used for the test. The intact skin was used. The skin from the back of each rabbit was depilated 24 hours prior to application of the patch. Two areas of the back of each rabbit, approximately 10 cm apart were designated for the position of the patches. One area was used for application of plain polymeric patch and the other was used for drug patch. The animals were immobilized using rabbit holder during 24 hours exposure. Upon removal of the patches, the resulting reaction was evaluated using weighed scores. Reading was also made after 72 hours and the final scores represent an average of the 24 and 72-hour reading[13].

**Anti-inflammatory studies:**

**UV-light induced erythema in guinea pigs:**

The erythema was induced by UV irradiation to male albino guinea pigs and scored at 1, 2 and 4 hours after application of formulation, using score system '0' as absence of any erythema, '1' as definite redness and '2' as intense erythema and the percent inhibition of erythema was determined[14].

**Results and discussion:**

Curcumin and Boswellic acid are lipid soluble so dissolved in chloroform and dispersed uniformly throughout the film. The films were formed within a short period of time and easy to prepare. The film of curcumin and boswellic acid showed a satisfactory flatness (Table 1). Average thickness of films was found to be 0.0085 cm (Table 1). Average content of curcumin and boswellic acid in films was found to be 82.74% and 88.72% respectively.

For easy penetration of drugs through skin penetration enhancer as menthol (5% w/v in ethanol) had been selected.

The calibration curve of curcumin and boswellic acid was prepared in hydroalcoholic medium using HPTLC and the peak area versus concentration graphs were plotted. The peak of curcumin was found to be at 0.22 $R_f$ value and two peaks for boswellic acid were found to be at 0.37 $R_f$ and 0.44 $R_f$ values respectively for peak 1 and peak 2 (Fig. 1). The precoated silica gel $F_{254}$ plates were developed in petroleum ether : acetone (7: 3) as mobile phase.

The *in vitro* diffusion profile of films of curcumin and boswellic acid was found to be better in hydroalcoholic medium than either buffer medium and surfactant solution (sodium lauryl sulphate) so hydroalcoholic diffusion medium was taken for study. The release of drugs from transdermal patch was found to be linear for the first 4 hours and attained a steady level upto 9 hours (Fig. 2). The average per cent release for curcumin was found to be 50.70% and for boswellic acid (peak 1) 69.84% & for boswellic acid (peak 2) 64.84% in the diffusion medium (Fig. 3). The graphs obtained for the average per cent release through transdermal film indicate that the drugs are released from the film at a constant rate and follows nearly zero order release kinetics. The flux of drugs from transdermal patch (Fig. 4) shows that flux of curcumin and boswellic acid is not steady during the study period.

The skin irritation study done on albino rabbit skin showed that the formulation does not produce irritation to the skin (Table 2) and hence supposed to be safe for human use also.

In the acute study, UV light induced erythema, the patch showed 55.56% inhibition while the standard patch (ketoprofen) showed 77.78% inhibition (Fig. 5). This indicates that the activity of the patch is comparable to the standard patch and with further optimization of the formulation the activity can be further enhanced.

**Conclusion:**

Ayurvedic system of medicine has described specific methods and natural drugs. Through the present experimentation, it has found that the drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms. This experimentation is one of the first few attempts to utilize ayurvedic drugs through TDDS. Use of turmeric in TDDS can be also considered as a new version of ayurvedic turmeric *poultice* or *lepa*.

**Fig 1: HPTLC ANALYSIS OF SAMPLE :**

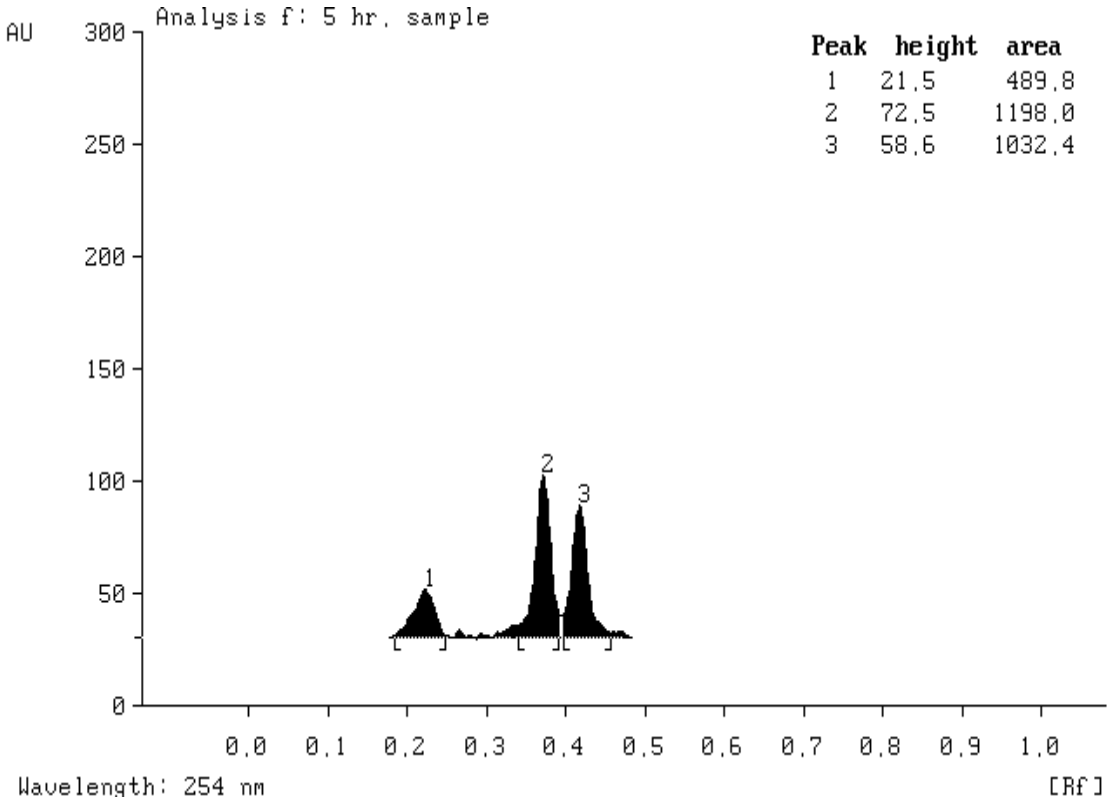


**Fig 2: IN VITRO RELEASE FROM TRANSDERMAL PATCH**

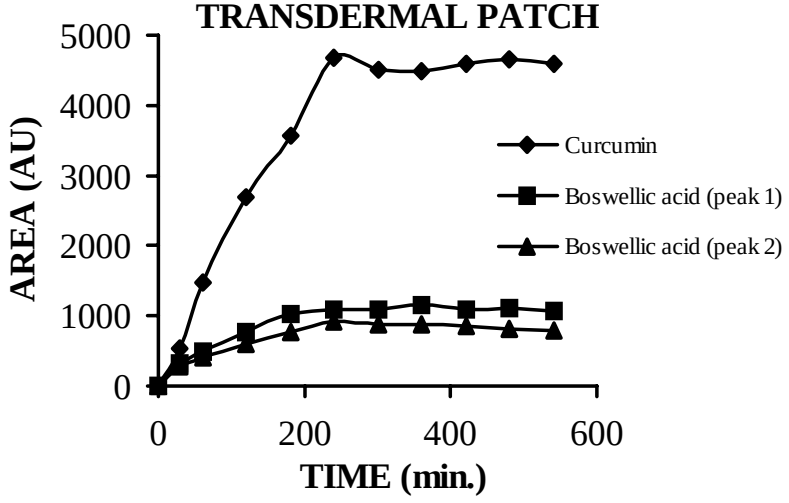

**Fig 3: IN VITRO AVERAGE % RELEASE FROM TRANSDERMAL PATCH**

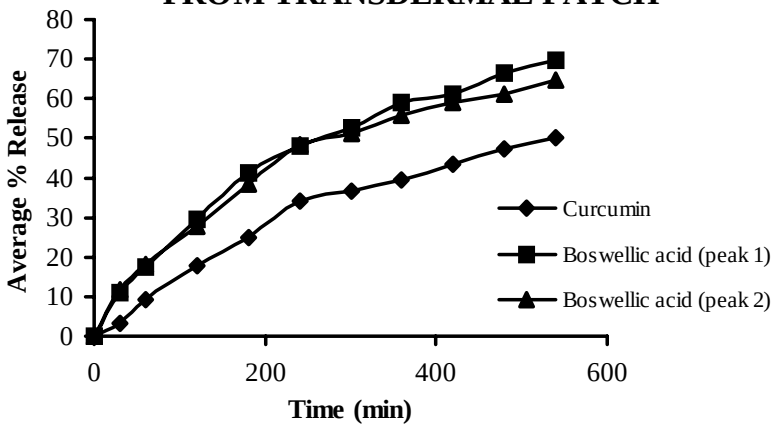


**Fig 4:FLUX THROUGH SKIN**

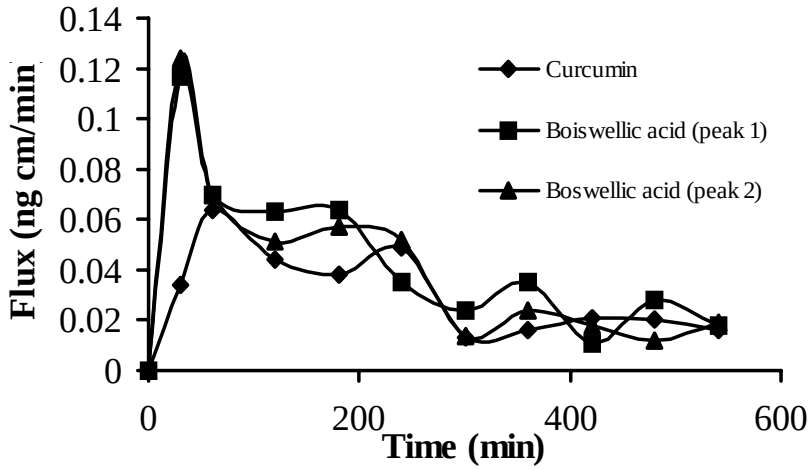


**Fig 5: % INHIBITION OF UV LIGHT INDUCED ERYTHEMA**

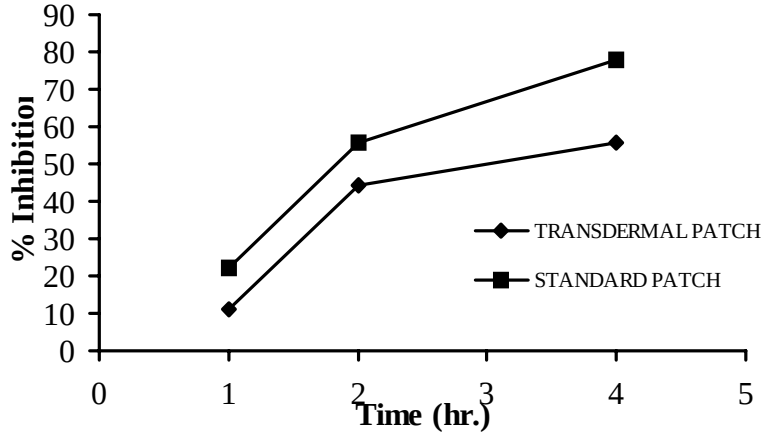

**Table 1: Percentage flatness and thickness uniformity of film.**

| S. No. | % Flatness | Thickness (cm) |
|---|---|---|
| 1 | 99.87 | 0.009 |
| 2 | 99.99 | 0.008 |
| 3 | 99.97 | 0.009 |
| 4 | 99.87 | 0.008 |
| 5 | 99.88 | 0.009 |
| 6 | 99.97 | 0.008 |
| MEAN | 99.925 | 0.0085 |
| S.D. | 0.052202 | 0.000548 |

**Table 2: Evaluation of skin reactions.**

| Skin reaction | Score |
|---|---|
| A) Erythema and Eschar formation: | |
| Very slight erythema | 1 |
| Well defined erythema | 2 |
| Moderate to severe erythema | 3 |
| Severe erythema | 4 |
| Total possible erythema score | 4 |
| B) Edema formation | |
| Very slight edema | 1 |
| Slight edema | 2 |
| Moderate edema | 3 |
| Severe edema | 4 |
| Total possible edema score | 4 |
| Total possible score for primary irritation | 8 |

**References:**


1. Raut, A.A., Joshi, A.D., Antarkar, D.S., Joshi, V.R., Vaidya, A.B., 1991. Antirheumatic formulation from Ayurveda. Ancient Science of Life XI (1,2), 66-69.
2. Rang, H.P., Dale, M.M., and Ritter, J.M., 1999: Pharmacology. Churchill Livingstone, London, pp. 293-295.
3. Nuki, G., Ralston, S.H., and Lugmani, R., 1999. Diseases of the Connective Tissues, Joints and Bones. In: C. Haslett, R.E. Chilvers, A.A.J. Hunter, and A.N. Boon (Eds.), Davidson's Principles and Practice of Medicine, Churchill Livingstone, London, pp. 802-837.
4. Francis, C.M., 1991. Rheumatoid Arthritis and Rational Drug Therapy. Health Action, 25-35.
5. Misra, A.N., 1997. Controlled and Novel Drug Delivery. In: N.K. Jain(Eds.), Transdermal Drug Delivery, CBS Publishers, New Delhi, pp. 100-101.
6. Bhalla, H.L., Bhate, A.S., 1994. Feasibility Studies on Transdermal Films of Ephedrine. Indian Drugs 31(7), 328-332.
7. Lalla, J.K., Seethalakshmi, K.R. Dattani, K.K., 1988. Nitroglycerin Controlled Release Transdermal Patch. Indian Drugs 26(6), 284-295.
8. Gupta, V.N., Yadav, D.S., Jain, M., Atal, C.K., 1986. Chemistry and Pharmacology of Gum Resin of Boswellia serrata. Indian Drugs 24(5), 227-229.
9. Srimol, R.C., Dhawan, B.N., 1973. Pharmacology of Diferuloyl Methane (Curcumin), A Non-steroidal Anti-inflammatory Agent. J. Pharm. Pharmacol. 25, 447-452.
10. Anto, R.J., Kuttan, G., Babu, K.V.D., Rajasekharan, K.N., Kuttan, R. 1998. Anti-inflammatory Activity of Natural and Synthetic Curcuminoids. Pharm. Pharmacol. Commun. 4, 103-106.
11. Kulkarni, R.R., and Patki, V.P., 1991. Treatment of Osteoarthritis with Herbomineral Formulation: A Double - Blind, Placebo - Controlled, Cross Over Study. Journal of Ethnopharmacology 33, 91-95.
12. Deodhar, S.D., Sethi, R., and Srimal, R.C., 1980. Preliminary Studies on Antirheumatic Activity of Curcumin (Diferuloyl Methane). Indian Journal of Medical Research 71, 632-634.
13. Draize, J.H., Woodward, G.S., and Calvery, H.O. 1994. J. Pharmacol. Expt. Therap. 82, 377-390.
14. Thompson, E.B., 1990. Drug Bioscreening, Drug Evaluation Techniques in Pharmacology. VCH Publishers, New York, p. 251.