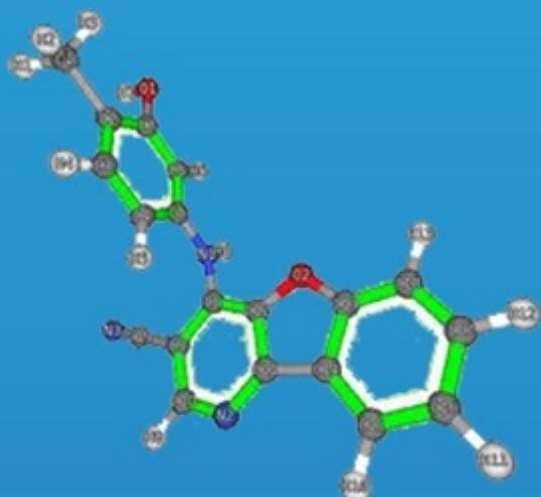
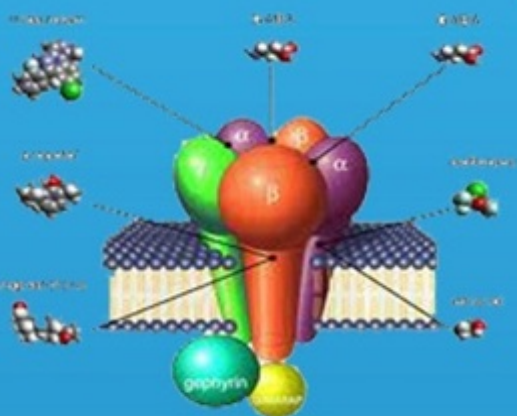


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PREPARATION AND EVALUATION OF IBUPROFEN TRANSDERMAL PATCH

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Abstract:

Ibuprofen is a NSAID used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea acts mainly by inhibition of COX-1 and COX-2. The main aim of this work is to prepare and characterize the transdermal patch of Ibuprofen and to increase the therapeutic effectiveness of ibuprofen by increasing its transdermal permeation. Three formulations of ibuprofen were prepared using different drug: polymer ratio i.e. 1:1, 2:3 and 3:2 for PVP and ethyl cellulose using solvent casting method. Prepared patches were evaluated for weight, thickness, swelling index, drug content uniformity, folding endurance and in vitro release. Patches exhibited controlled release over more than 5 h in vitro release studies. It was concluded that the patches containing 250 g of ibuprofen in PVP and ethyl cellulose (2:3 ratio) showed good swelling and a promising controlled drug release, thus can be selected for a development of transdermal patches for effective therapeutic uses.

Key words: transdermal patches, ibuprofen, invitro studies.

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Introduction:

Ibuprofen[2-(4-isobutylphenyl)propionic acid], a potent nonsteroidal anti-inflammatory (NSAID) drug that is often used for the treatment of acute and chronic arthritic conditions, has pH dependent solubility and permeability.¹ Although ibuprofen is highly permeable through the stomach, its poor water solubility (log P value 3.6) limits its entry into systemic circulation before gastric emptying (30 min to 2 hr) occurs.² During gastric emptying, ibuprofen enters the small intestine, where it cannot permeate through the membrane despite being solubilised.³ Since dissolution is the rate-limiting step during drug absorption, the poor water solubility in oral forms of ibuprofen results in low bioavailability due to erratic or incomplete absorption from the gastrointestinal tract.^{4,5} Oral formulations with rapid absorption rates aid pain relief and enhance IB's analgesic properties.⁶ In addition to absorption difficulties, oral formulations of ibuprofen can cause gastric mucosal damage, which may result in ulceration and bleeding.⁷

Therefore, there is a need to develop topical dosage forms of ibuprofen to minimize the gastrointestinal side-effects of oral ibuprofen, and to provide relatively consistent drug levels at the

application site for prolonged periods. Transdermal and topical deliveries also provide an increased bioavailability by avoiding first pass metabolism by the liver and a consistent delivery for an extended period.^{8,9} Topical delivery vehicles (creams, gels) and transdermal delivery agents (dermal patches) can improve patient compliance due to decrease in the dosage frequency. The permeability problems at the skin surface may be obviated by the use of drug carriers and penetration enhancers.

The percutaneous absorption of drugs involves two consecutive processes: the release of the drug from the topical formulation, and its absorption into the skin at the site of application. Increasing the release rate of the drug from the dosage form might therefore improve percutaneous absorption. The release rates of drugs from topical preparations depend directly on the physicochemical properties of the carrier and the drug employed.¹⁰

Transdermal therapeutic systems are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation. Thus, it is anticipated that transdermal drug delivery system (TDDS) can be designed to maintain suitable

plasma drug levels for therapeutic efficacy by using skin as the port of entry of drugs.¹¹

Materials & Methods:

Ibuprofen, ethylcellulose, Poly Vinyl Pyrrolidine, alcohol, toluene, 2% propylene glycol.

Preparation of transdermal patches:

The transdermal patch of ibuprofen was prepared by solvent casting technique. The polymeric solution taken was ethylcellulose 5% in combination with PVP 5%. The polymeric solution was prepared by dissolving the combination in alcohol and toluene mixture (1:4 ratios) in the ratio 1:1, 2:3, 3:2 respectively using 2% propylene glycol as a plasticizer. Weighed amount of drug was dispersed in polymeric solution while stirring to ensure the uniform distribution of the drug. The measured volume of polymeric solution (10 ml) was poured into a petri dish and dried at room temperature (petri dish previously covered with aluminum foil and greased with paraffin wax). After ensuring the complete evaporation of solvent patches of 2.5cm diameter were cut with a borer and packed in aluminum foil and stored for evaluation study.¹²

Table 1: Composition of transdermal patch of ibuprofen:

Formulation	F1 (mg)	F2 (mg)	F3 (mg)
Ibuprofen	250	250	250
Ethyl cellulose	250	200	300
Polyvinylpyrrolidine	250	300	200
Propylene glycol	2%	2%	2%

Characterization of transdermal patch:

Thickness:

Three films of every formulation were weighed individually in a digital balance and the mean weights were calculated. The mean value of film thickness was calculated by measuring thickness of three films of each formulation at three different places using Micrometer Screw Gauge.

Folding endurance:

Folding endurance was determined by repeatedly folding a small strip of size (2X2 cm) of film at the same place till it broke. The mean value (three readings and standard deviation) of folding endurance (the number of times, the film could be folded at the same place without breaking) were shown in **[Table 2]**.

Drug content uniformity:

To determine the drug content uniformity, three film units of 1 cm² of each formulation were taken in separate

100 ml volumetric flasks, 100 ml of pH 7.4 phosphate buffer was added and continuously stirred. The solutions were filtered, diluted suitably and analyzed at 221 nm in a UV spectrophotometer. The average of drug contents of three films was taken as final reading.

Weight uniformity:

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. A specified area of patch was cut in different parts of the patch and weigh in digital balance. The individual weight should not deviate significantly from the average weight.

Percent moisture content:

The prepared films were weighed individually and to be kept in a desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.

$$\% \text{moisture content} = \frac{[(\text{initial weight} - \text{final weight}) / \text{final weight}] \times 100}{1}$$

Invitro studies:

For the *in vitro* permeation study Franz diffusion cell with 18 ml pH 7.4 phosphate buffer (dissolution medium)

Table2: Evaluation of Transdermal Patch of Ibuprofen:

Formulation	thickness(mm)	drug content	Folding endurance	weight uniformity	%Moisture content
F1	0.111±0.0089	3.953±0.03	152±1.4	0.029±1.30	1.72±0.053
F2	0.118±0.0068	4.097±0.09	175±1.8	0.028±1.43	1.85±0.031
F3	0.125±0.0043	4.335±0.05	166±1.2	0.030±1.23	1.28±0.042

was used. One film of each formulation was placed in intimate contact with the dialysis membrane. Teflon bead was placed in receptor compartment. During the release study the temperature and rotation speed of the apparatus was maintained at $37 \pm 0.5^{\circ}\text{C}$ and 50 rpm, respectively. The release study was carried out for 3 h. After every hour, samples were withdrawn, filtered, diluted suitably and then analyzed spectrophotometrically at 221 nm.¹³

Result & Discussion:

Transdermal patches of ibuprofen were prepared by solvent casting technique with the use of polymers such as PVP and EC. The prepared films were evaluated for different physicochemical tests such as weight variation, thickness, content uniformity and *in vitro* permeation studies.

All the films showed uniform thickness throughout. The film thickness was observed to be in the range of 0.111 to 0.125 mm and average thickness found was about 0.118 mm. The weights of different formulation were found to be in the range of 0.028 gm to 0.030 gm.

Folding endurance was measured manually by folding the film repeatedly at a point till they broke. Films did not show any cracks even after folding for more than

180 times. Hence it was taken as the end point. The folding endurance was found to be in the range of 175 to 152. The values were found to be optimum to reveal good film properties. The results of content uniformity indicated that the drug was uniformly dispersed; the content was in range of 3.953 to 4.335 mg/cm².

The weights ranged between 0.029 ± 1.30 to 0.030 ± 1.23 mg, which indicates that different batches patch weights, were relatively similar. Good uniformity of drug content among the batches was observed with all formulations. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability.

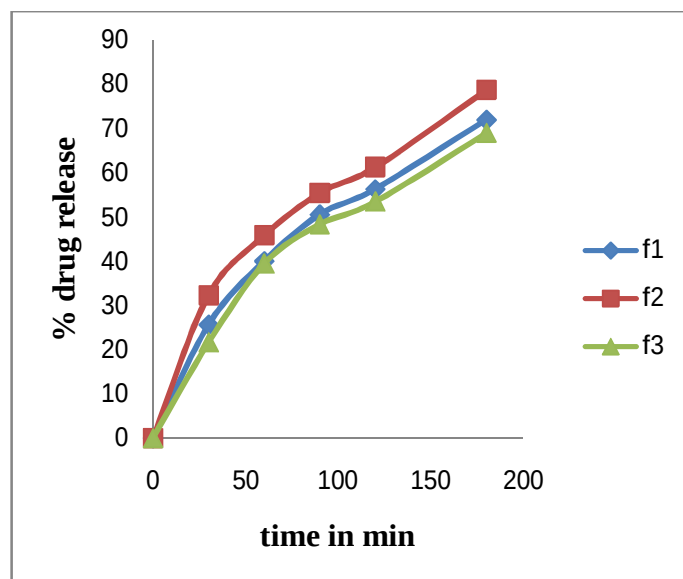
Moisture content studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content and moisture uptake of the patches. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage.

In vitro permeation studies of various formulations were performed using pH 7.4 phosphate buffer as

dissolution medium. The drug concentration was determined spectrophotometrically at 221 nm. Significant difference was observed in the release pattern of ibuprofen patches containing PVP and EC [Figure 1]. After three hours the release was found to be in the range of 69.12 to 78.8%. The rank order of drug release after 3 h was found to be 78.8>72.12>69.12 % for formulations F2>F1>F3, respectively.

Table 3: Percent drug release of ibuprofen patches in pH 7.4 phosphate buffer.

Time(min)	F1	F2	F3
0	0	0	0
30	25.67	32.34	21.67
60	40.12	45.87	39.54
90	50.65	55.54	48.43
120	56.43	61.34	53.56
180	72.12	78.8	69.12



[Figure 1: Percent drug release of ibuprofen patches in pH 7.4 phosphate buffer]

Conclusion:

It was also concluded that formulation F2 (containing EC and PVP 2:3) showed a promising drug release. The results of all the physical characterization of all formulations (F1-F3) were found to be satisfactory. The results of the study show that therapeutic levels of ibuprofen can be delivered transdermally. The present study concludes that these transdermal patches containing ibuprofen can be very promising for effective doses to systemic circulation. These may also provide an added advantage of circumventing the hepatic first pass metabolism. Patches exhibited controlled release over more than 3 h. It was concluded that the patches containing ibuprofen in ethyl cellulose and PVP (2:3

formulation F2), can be selected for the development transdermal patch for effective therapeutic uses. Further, the study may be extended for assessing the *in vivo* release and *in vitro-in vivo* correlation.

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