Research Article

Formulation and Evaluation of Transdermal Patch of Diclofenac Sodium as Ladies Bindi for Treatment of Rheumatoid Arthritis

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Received: 06-02-2018; **Revised:** 28-02-2018; **Accepted:** 14-03-2018.

ABSTRACT

Traditionally physicians prescribed Diclofenac tablet for the treatment of Rheumatoid Arthritis in geriatrics patients, The survey of Rheumatoid Arthritis states that the disease is common in females than in males. Diclofenac sodium used for topical applications and can be absorbed transdermaly. Rather than the Transdermal patch we are formulated a TDDS as ladies bindi to enhance the Patient compliance and patient does not feel like a patient and does not feel that she were taking a medicine by application of bindi, for females which meets the requirement of both e.g. Bindi and Medicine (Transdermal Patch) .The drug undergoes substantial hepatic first-pass metabolism and only about 50% of administered dose reaches systemic circulation. This originates the need of an alternative choice of route of administration for such drugs. The Diclofenac sodium also possesses the characteristics such as poor bioavailability, short biological half life and smaller dose etc., to be formulated in to a transdermal patch. The aim of the present study was to develop different transdermal matrix films with varied ratios of hydrophilic and hydrophilic – lipophilic combination containing the drug Diclofenac sodium and to perform the physicochemical and in vitro evaluation along with primary irritation study of the prepared films. The purpose was to provide the delivery of drug at a controlled rate across intact skin to achieve a therapeutically effective drug level for a longer duration of time from transdermal patch (Bindi).

Keywords: Diclofenac Sodium, Transdermal patch, Bindi, *In-vitro* study.

INTRODUCTION

Diclofenac is non-steroidal anti-inflammatory agent, widely used to reduce the pain and inflammation in arthritis, toothache, Trauma, Wound, burn etc. Transdermal films of Diclofenac Sodium were formulated by using different polymer combinations such as hydrophilic (Poly vinyl alcohol: Poly vinyl pyrolidone), and combination of hydrophilic - lipophilic polymers (Ethyl cellulose: Poly vinyl pyrolidone). To study the effect of plasticizers such as dibutyl phthalate and propylene glycol by using Franz diffusion cell. The placebo and medicated films were evaluated for physicochemical properties and also medicated films were evaluated for area variation, drug content and percent cumulative drug release. In vitro drug release study through cellophane membrane indicates that hydrophilic polymer showed higher release than the hydrophilic - lipophilic combinations. The release rate found to follow Zero order rate kinetic. Primary irritation study shows that the transdermal films are nonirritant. Transdermal patches offer added advantages such as maintenance of constant and prolonged drug level, reduced frequency of dosing, self administration and easy termination of medication leading to patient compliance.

MATERIALS AND METHODS

Table 1: List of Chemicals

Sr. No.	Name of the Ingredients	Category	Manufacturer / supplier
1	Diclofenac Sodium(DS)		Merck Ltd.
2	Polyvinyl alcohol(PVA)	Polymer	Fisher Chemicals
3	Polyvinyl pyrrolidone(PVP)	Polymer	Merck Ltd.
4	Ethyl cellulose(EC)	Polymer	Fisher Chemicals
5	Dibutyl phthalate (DBP)	Plasticizer	Merck Ltd.
6	Propylene glycol (PG)	Plasticizer	Merck Ltd.
7	Backing membrane	Bindi	ABR Shringar Mumbai

Preparation of Medicated Patch

Films were prepared by the film casting method of specially designed glass molds with the plastic transparent sheet. Different combination of polymers like PVA: PVP and EC: PVP were used for preparation of films. Varying proportion of polymers in each pair was dissolved in solvents such as water and chloroform respectively. The final concentration of mixture of polymers in each solution was 10%. Solutions were prepared at room temperature using plasticizers as 30% DBP for EC: PVP

combination and 30% Propylene glycol for PVA: PVP combination. Drug was incorporated in 10% polymer solution, obtained by stirring on magnetic stirrer. Polymeric solution was poured within a glass bangle placed on glass mould. The rate of evaporation of solvent was controlled by inverting cup funnel. After 24 hours the dried films were taken out and stored in desiccator.

Table 2: List of Instruments

Sr. No.	Name of the Instrument	Model/Manufacturer
1	Analytical weighing balance	Labline Analytical Balance ,Mumbai
2	UV spectrophotometer	Cary Win UV
3	Magnetic Stirrer	Remi Equipments, Mumbai.
4	Sonicator	Citizen.
5	Hot Air Oven	Thermolab, Mumbai.
6	USP Dissolution Apparatus	Lab India DS 8000
7	Digital PH meter	Hanna Instruments
8	Stability chamber	Thermolab, Mumbai.
9	Franz Diffusion Apparatus	Orchid

Evaluation of Medicated Patch

Weight of Patch

Transdermal patches were weighed on analytical balance and average weight was determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API.

Thicknesses of Patch

The thickness of the patch was measured by micrometer screw gauge at five different places; an average of three values was calculated**.** This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film.

Surface pH

Patches were kept in glass tubes containing 10 ml phosphate buffer (pH -7.4) and the pH of the surface measured after 1, 2, 3, 4, 5, 6, 7 and 8 hours by placing the tip of the glass microelectrode of a digital pH meter close to the surface of the patch and allowing it to equilibrate for 1 min prior to recording.

Folding Endurance

Folding endurance of the patch is essential to study the elasticity of the film during storage and handling. The folding endurance of the patch was determined by repeatedly folding one film at the same place till it break. This is considered to reveal good film properties. A film (2 X 2 cm) was cut evenly and repeatedly folded at the same place till it breaks. All determinations were performed in triplicate.

Swelling and Erosion

Swelling and erosion of patches were determined under conditions identical to those for dissolution tests. The degree of swelling (water uptake) and extent of erosion (mass loss) were determined according to the equations:

$$\text{Degree of swelling} = \frac{\text{Wet weight - Original dry weight}}{\text{Original dry weight}}$$

$$\% \text{ Erosion} = \frac{\text{Original weight – Remaining dry Weight} \times 100}{\text{Original weight}}$$

Assay of Patch

A complete patch from petriplate was cut in to2*2 pieces and crushed in mortar pestle and dissolved in phosphate buffer pH 7.4 with continuous agitation. Then contents were filtered through Whatman filter paper into volumetric flask. After appropriate dilution with

phosphate buffer pH 7.4, solutions were analysed by determination of absorbance at 226nm (UV 2450 spectrophotometer) against a solvent blank. Drug content was estimated from a calibration curve.

Content Uniformity

Drug content was determined by dissolving the film containing 2 mg of drug in 100 ml phosphate buffer pH 7.4 to get 20 µg/ml solutions. An aliquot of 1ml sample was withdrawn and diluted to 10 ml with water. Then solution was filtered through whatman filter paper and analyzed by UV-spectrophotometer at λ max of drug. Content uniformity studies were carried out in triplicates for each batch of the film.

In-Vitro Drug Release

Patches were firmly secured in beaker (250ml) placed on magnetic stirrer and 100 ml phosphate buffer saline (PBS pH 7.4) added as the dissolution medium. At specified times (1, 2, 3, 4, 5, 6, 7, 8 hours) 5ml aliquots were removed using a syringe and replaced with equal volumes of fresh PBS to maintain the total volume. Samples were filtered through whatman filter paper and concentration of Iodine determined by measuring absorbance at 226 nm.

In-vitro Permeability

The rate and extent of Transdermal permeation of Iodine through the mice skin was determined using Franz diffusion cell. Briefly, the receptor compartment (10 ml) was filled with PBS pH 7.4 at 37.0 ^{0}C and stirred at 50 RPM. The patch was sandwiched between the donar and acceptor compartment of the diffusion cell on Swiss albino mice skin the Aliquots (3 ml) of the receptor medium withdrawn at regular intervals(1, 2, 3, 4, 5, 6, 7 and 8 hours) and replaced immediately with equal volumes of PBS pH 7.4 The amount of Iodine released in to the receptor medium was determined by measurement of absorption at 226 nm against a blank.

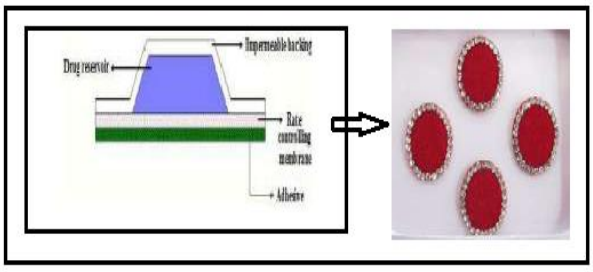


Fig: Patch to (Patch + Bindi transformation)

RESULTS AND DISCUSSION

In view of low permeability of DS, monolithic device of drug has been attempted. Placebo films were studied for flexibility, clarity, elasticity and ease of removal of films from the molds and also for thickness uniformity, percentage flatness, moisture uptake test, tensile strength, modulus of elasticity and percentage elongation at break.. Study shows that for PVA: PVP and EC: PVP along with the plasticizer 30% w/w PG and 30% w/w DBP respectively of polymer weight was suitable for good flexibility, clarity & elasticity. Medicated films were evaluated for physical and mechanical properties like thickness uniformity, percentage flatness, moisture uptake test, tensile strength, modulus of elasticity and percentage elongation at break. No amount of constriction in the placebo and medicated transdermal films ensured their 98-100 % flatness. Thus these formulations can maintain a smooth and uniform surface when applied on skin. Results are shown in Table I and III

Placebo Films: Films of EC: PVP and PVA: PVP subjected for evaluation of moisture uptake at different relative humidity. Results indicate that increases PVP proportion in the film increases the moisture uptake. Increase in the concentration of PVP decrease in the tensile strength and percent elongation at break. Results shown in Table I and III. Medicated Films: Medicated films of EC: PVP and PVA: PVP showed lower tensile strength value as compared to placebo film, but film with 7:3 and 6:4 showed better tensile strength than blank film. Medicated films shows increase in moisture uptake as compared to blank film. Medicated films were subjected to test for weight variation and drug content uniformity. The film does not shows significant deviation from average value.

PVA: PVP Medicated films with 10:0, 4:6 and 6:4 showed slightly increase in tensile strength and films with 2:8 and 8:2 showed a slightly decrease in tensile strength as compared to blank films. Almost all medicated films showed similar moisture uptake as compared to blank films. Results shown in Table I and III.

Formulation containing hydrophilic polymer showed better *in-vitro* drug release than the and lipophilic - hydrophilic polymer combination. Hydrophilic polymer (PVA: PVP) DS F5 gave 64.89 % cumulative release & flux 2.848µg/cm2/hr. Hydrophilic - lipophilic polymer combination (EC: PVP) DS F8, F9 and F10 showed 92, 93 and 94.5 % cumulative release and flux 2.48±0.25, 2.82±0.64 and 2.83±0.21µg/cm2/hr respectively. The increasing order of release of drug from formulation DSF10 > DSF9>

DSF8> DSF7 > DSF6 > DSF5 > DSF3> DSF4 > DSF2 > DSF1. Films of hydrophilic and lipophilic polymer with different concentrations (10:0>9:1>8:2>7:3>6:4) were studied. Combination 6:4 and 7:3 showed highest cumulative release due to increased proportion of PVP. Results are shown in Table III and Fig. 1 and 3. Films of hydrophilic polymer PVA: PVP with different concentrations (10:0, 8:2, 6:4, 4:6, 2:8) were studied. Combination 2:8 , 4:6 and 6:4 showed highest cumulative drug release. Increasing the proportion of PVP concentration increases the cumulative amount release; this increased release rate may be due to highly hydrophilic nature of PVP and which has very less interactions with drug. Due to its high hydrophilicity it absorbs water and swells resulting in the more release of drug from the film. Release rate of DS from the PVA: PVP film was in following order 2:8 > 4:6 >

6:4 > 8:2 > 10:0. Results are shown in Table III and Fig.2 and 4. Permeation flux and permeability coefficient of formulated Transdermal patches shown in Table IV. In order to understand mechanism of drug release, *in vitro* release data were treated to kinetic models and linearity was observed with respect to Higuchi equation. The correlation coefficient obtained from Higuchi plot was found to be in the range of 0.907 to 0. 9917. This indicates that mechanism of drug release was diffusion type. Higuchi plots shown in Fig. 3 and 4. Decrease in drug release rate from films containing lipophilic-hydrophilic polymer combination (EC: PVP) in comparison to films containing hydrophilic polymer (PVA: PVP) may be attributed to the relatively hydrophobic nature of polymer which have less affinity for water, this result in decrease in thermodynamic activity of the drug in the film and decreased drug release. The films containing hydrophilic polymer showed higher drug release rate. More permeability of these films may be due to hydrophilic nature increase the thermodynamic activity of the drug[11]. No erythema or edema was noticed on the skin of human volunteer, except patch containing lipophilic polymer evoked mild response after the application of the films for 24hrs. From above studies it can be concluded that the polymeric matrix-type transdermal films of D prepared with different grades and ratios of polymers holds potential for transdermal delivery. A slow and controlled release of drug release versus time is linear, these supporting the test products for transdermal films. Developed formulation has the best effective combination of polymer but slight modification required to achieve therapeutic plasma concentration.

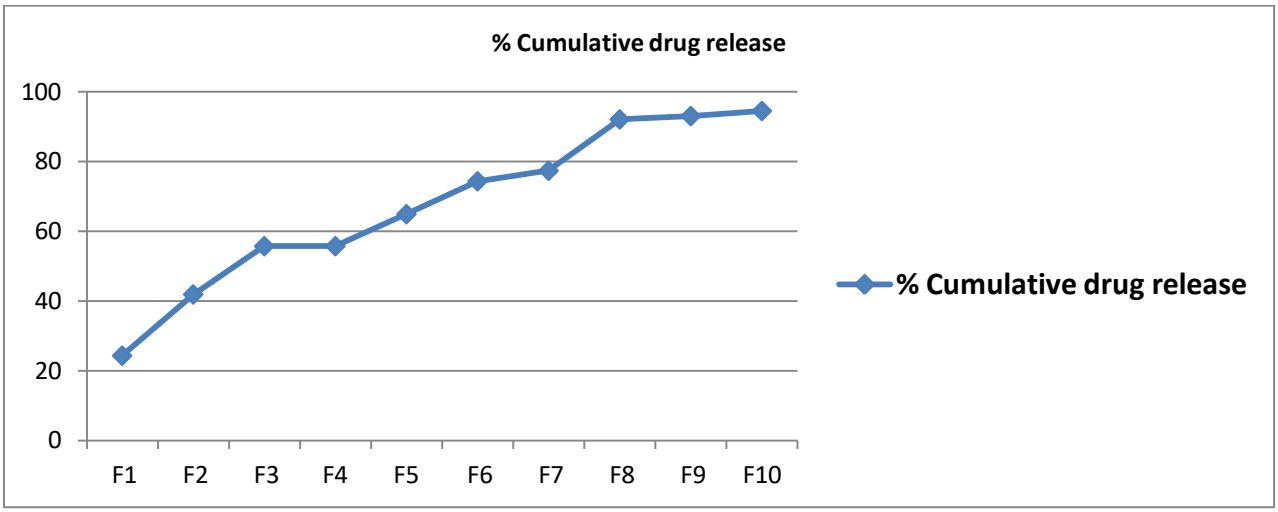
Table 2: Evaluation of Placebo Polymeric Films

Formulation code	Mean thickness (cm)	Tensile strength dyne/cm^2	% Elongation	Moisture uptake (58% RH)		
				58	79	98
F1	0.031(0.0006)	49X10^6	7.16	1.13	1.13	**4.20**
F2	0.030(0.0005)	25X10^6	9.00	1.53	1.53	**9.69**
F3	0.028(0.0001)	21X10^6	5.00	5.96	5.96	**16.07**
F4	0.027(0.0006)	11X10^6	3.00	8.65	8.65	**20.52**
F5	0.026(0.0003)	4.4X10^6	4.66	10.22	10.22	**30.28**
F6	0.022(0.0014)	65 X10^6	40	15.87	15.87	**44.17**
F8	0.022(0.0012)	63 X10^6	76	23.58	23.55	**53.12**
F9	0.019(0.0016)	69 X10^6	111	24.01	24.01	**55.24**
F10	**0.019(0.0025)**	**20 X10^6**	**49**	**28.53**	**28.55**	**56.55**

Table 3: Formulation Composition and Evaluation of Medicated Transdermal films

Formulation Code	Polymer %w/v	Plasticizer % w/w	Thickness	Drug Content	% Cumulative Release
	EC: PVP	DBP			
F1	10:0	30	0.21(0.01)	11.16(0.05)	24.30
F2	9:1	30	0.19(0.0006)	10.84(0.02)	41.88
F3	8:2	30	0.19(0.0004)	11.15(0.05)	55.71
F4	7:3	30	0.21(0.001)	10.65(0.04)	55.71
F5	6:4	30	0.2(0.0002)	11.60(0.04)	64.89
	PVA:PVP	PG			
F6	10:0	30	0.14(0.004)	12.41(0.03)	74.33
F7	8:2	30	0.14(0.0002)	12.24(0.09)	77.36
F8	6:4	30	0.13(0.001)		92.08
F9	4:6	30	0.15(0.007)	11.53(0.05)	93.03
F10	2:8	30	0.15(0.0004)	11.73(0.03)	94.50

Values in Parenthesis are expressed as ± S.D (n =3)



Graph 1: Plots of Cumulative Percent Drug Release

Table 4: Permeability flux and permeability coefficient of patch

Formulation code	Permeation flux(µg/cm^2/hr)	Permeability coefficient(Kp)
F1	0.88	0.0788
F2	1.6	0.15
F3	2.4	0.21
F4	2.3	0.22
F5	2.8	0.20
F6	2.5	0.22
F7	2.2	0.20
F8	2.4	0.16
F9	2.8	0.24
F10	2.8	0.23

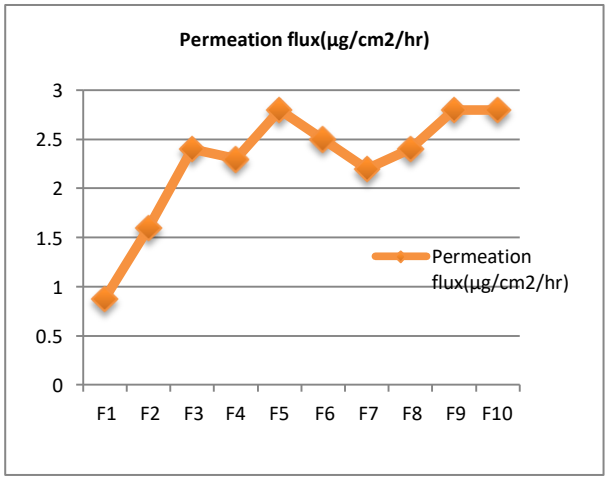


Figure 2: Permeation Flux of Different Batches

Acknowledgement: The author's thanks to Dr.Anil Jadhav principal of SIPS College Nashik, Dr.G.Chhabra and Dr.Milind Wagh for providing all the support and encouragements to do this work. The author's also thanks to Ramhari Sagar, Prashant Salunke and Teaching Staff of S.G.R.S. College of Pharmacy Saswad for Inspiring me all the times etc.

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Source of Support: Nil, **Conflict of Interest:** None.