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FORMULATION AND EVALUATION OF TRANSDERMAL FILMS OF DICLOFENAC SODIUM

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ABSTRACT: 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 Keshary-Chein 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 first order rate kinetic. Primary irritation study shows that the transdermal films are non-irritant.
Key words : Transdermal film, Diclofenac Sodium, In-*vitro* study

INTRODUCTION

Diclofenac is nonsteroidal anti-inflammatory agent, widely used in musculoskeletal disorders, arthritis, toothache, etc., for symptomatic relief of pain and inflammation[1]. Diclofenac sodium is reportedly used for topical applications[2]. The drug undergoes substantial hepatic first-pass metabolism and only about 50% of administered dose reaches systemic circulation[3, 4]. This originates the need of an alternative choice of route of administration for such drugs. The Diclofenac sodium also possesses the ideal characteristics such as poor bioavailability, short biological half life and smaller dose etc., to be formulated in to a transdermal patch. 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[5,6].

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 films.

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MATERIALS AND METHODS

Materials

Diclofenac Sodium (DS)-Gift sample from Rupam Chemicals, Polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Ethyl cellulose (EC) (Loba Chemie), Dibutyl phthalate (DBP) (Qualingenes fine chemie), Propylene glycol (PG) (Loba Chemie) Backing membrane gift sample from 3 M Co.USA.

Preparation of Medicated Monolithic Films

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.

Evaluation of Medicated Films

The composition and concentration of the transdermal films has a considerable influence on the physical, mechanical properties as well as the permeability of the drugs[7]. Physical and mechanical properties of blank and medicated transdermal films such as thickness uniformity, percent flatness, moisture uptake, tensile strength and percent elongation at break and modules of elasticity were studied [8,9]. Also medicated films were evaluated for area, drug content and *in-vitro* drug release

***In vitro* drug permeation study**

In the present study, *in-vitro* release of DS from various matrix systems was studied using Keshery-Chien type diffusion cell using cellophane membrane. The cell consists of two chambers, the donor and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The receptor compartment was surrounded by a water jacket for maintaining the temperature at 37 ±1º and it was provided with sampling port. Diffusion media in the receptor compartment was stirred with magnetic needle. The diffusion medium was used phosphate buffer (pH 6) solution. The drug containing film with a support of a backing membrane was kept in the donor compartment and it was separated from the receptor compartment by standard membrane. The donor and receptor compartment hold together using clips of strong grip. The receptor compartment containing dissolution medium was maintained at 37 ±1º by circulating the water in outer jacket from organ bath. The diffusion medium was stirred with magnetic needle 2 mm in diameter and 6mm in length operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the standard membrane.

At each sampling time the solution in the receptor compartment was completely withdrawn and replaced with fresh phosphate buffer solution. The concentration of the drug was determined by UV-spectrophotometrically at 276nm for the drug content

In vitro cumulative percent drug release data for various polymeric films are given in Table III and graphically shown in Fig 1- 4.

Data Analysis

The cumulative amount of the drug permeated per unit skin surface area was plotted against time and the slope of the linear portion of the plot was estimated as the steady state flux (Jss) and permeability coefficient calculated by using equation

Kp = Jss / DC

DC- Donor concentration

Primary Skin Irritation Study

The patches were tested for their potential to cause skin irritation/ sensitization in healthy human volunteer. Each site of film application was rated with regard to the presence of severity of erythema and edema. Human volunteers were observed for any sign of erythema and edema for a period of 24h and scored as reported by *Draize et al*[10].

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/cm^2/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/cm^2/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 DS 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 I: Evaluation of Placebo Polymeric Films

Formulation code	Mean thickness cm	% Flatness	Tensile strength dyne/cm^2	Modules of elasticity	% Elongation	Moisture uptake (58% RH)		
						58	79	98
DS F1	0.0314(0.00061)	100	49.93X10^6	6.97X10^6	7.16	1.135	1.135	4.208
DS F2	0.0307(0.00054)	98	25.53X10^6	2.83X10^6	9.00	1.539	1.539	9.693
DS F3	0.0280(0.00013)	100	21.00X10^6	4.2 X10^7	5.00	5.960	5.960	16.076
DS F4	0.0278(0.00068)	99	11.28X10^6	3.76X10^7	3.00	8.658	8.658	20.522
DS F5	0.0267(0.00039)	100	4.40X10^6	0.95 X10^8	4.66	10.228	10.228	30.286
DS F6	0.0225(0.00148)	99	65 X10^6	70 X10^8	40	15.870	15.870	44.170
DS F7	0.0200(0.00037)	99	78 X10^6	70 X10^8	111.33	18.985	18.985	52.479
DS F8	0.0228(0.00129)	99	63 X10^6	81 X10^8	76	23.558	23.558	53.127
DS F9	0.0197(0.00168)	100	69 X10^6	71 X10^8	111	24.012	24.012	55.248
DS F10	0.0197(0.00256)	100	20 X10^6	30 X10^8	49	28.553	28.553	56.553

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

Table II: Formulation Composition And Evaluation of Medicated Transdermal films

Formulation Code	Polymer %w/v	Plasticizer % w/w	Thickness	Area	Drug Content	% Cumulative Release	
	EC: PVP	DBP					
DS F1	10:0	30	0.2119(0.0102)	5.1744(0.1167)	11.16(0.0583)	24.30	
DS F2	9:1	30	0.1907(0.00064)	4.9784(0.0942)	10.84(0.0282)	41.88	
DS F3	8:2	30	0.1924(0.0004)	5.0444(0.06789)	11.15(0.05)	55.71	
DS F4	7:3	30	0.2180(0.0017)	4.9253(0.0288)	10.65(0.047)	55.71	
DS F5	6:4	30	0.1820(0.00023)	4.8605(0.1290)	11.60(0.0452)	64.89	
	PVA:PVP	PG					
DS F6	10:0	30	0.1456(0.004)	4.9253(0.02886)	12.41(0.0324)	74.33	
DS F7	8:2	30	0.1422(0.00026)	4.9287(0.03475)	12.24(0.09)	77.36	
DS F8	6:4	30	0.1351(0.001)	4.9353(0.0461)		92.08	
DS F9	4:6	30	0.1559(0.0079)	4.94(0.0421)	11.53(0.0578)	93.03	
DS F10	2:8	30	0.1510(0.00049)	4.8439(0.1122)	11.73(0.03535)	94.50	

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

Table III: Permeation flux And Permeability coefficient of Drug Through Transdermal films

Formulation code	Permeation flux(µg/cm^2/hr)	Permeability coefficient(Kp)
DS F1	0.88	0.0788
DS F2	1.669	0.1539
DS F3	2.418	0.2168
DS F4	2.3933	0.2270
DS F5	2.848	0.2063
DS F6	2.56	0.2294
DS F7	2.28	0.2091
DS F8	2.48	0.1686
DS F9	2.824	0.2449
DS F10	2.813	0.2398

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

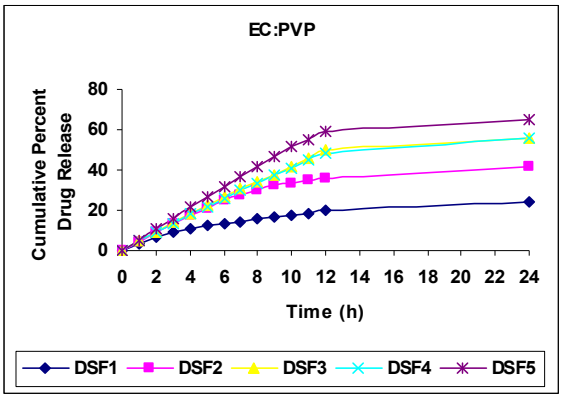

Fig.1: Plots of Cumulative Percent Drug Release Verses Time (h) For EC:PVP.

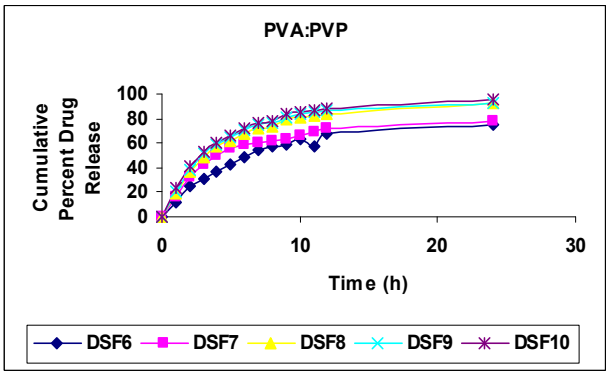

Fig.2: Plots of Cumulative Percent Drug Release Verses Time (h) For PVA: PVP.

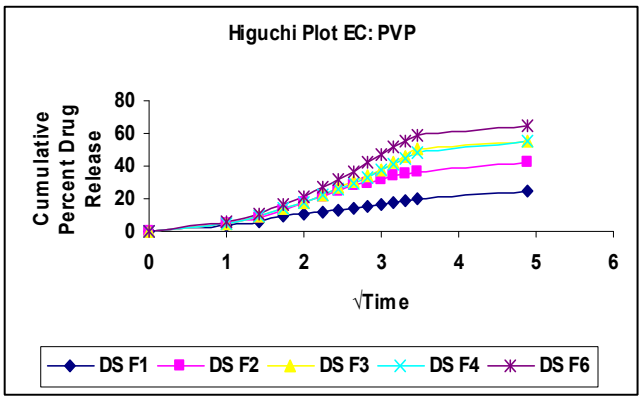

Fig.3: Plots of Cumulative Percent Drug Release Verses Time (h) For PVA: PVP.

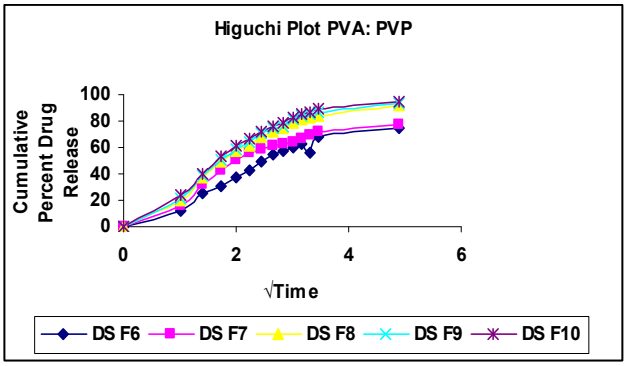

Fig4: Plots of Cumulative Percent Drug Release Verses Time (h) For PVA: PVP.

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