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FORMULATION AND EVALUATION OF TRANSDERMAL FILMS OF DICLOFENAC SODIUM

Jadhav R.T.[1], Kasture P.V.[2], Gattani S.G.*[3], Surana S.J.[4]

[1]Senior R & D Manager ,M.J.Biopharma, Taloja, Mumbai,India.

[2]D.Y.Patil College of Pharmacy, Pune,India.

*[3]Dept. of Pharmaceutics, R.C.Patel College of Pharmacy, Shirpur,India.

[4]Principal, R.C.Patel College of Pharmacy, Shirpur,India.

**E-mail sggattani@rediffmail.com*

ABSTRACT: Transdermal films of Diclofenac Sodium were formulated by using natural polymer gelatin and plasticizer glycerin in different proportion. The objective of present investigation was to study the effect of varying proportion of plasticizers on gelatin film forming property and study the effect of varying concentration of gelatin on physical, mechanical and *in vitro* drug release profile. The placebo and medicated films were evaluated for physical and mechanical properties and also medicated films were evaluated for area variation, drug content and percent cumulative drug release. Optimized gelatin to glycerin ratio containing transdermal films shown effective physical and mechanical property along with *in vitro* drug release profile. The release rate found to follow first order rate and Higuchi model. Primary irritation study shows that the transdermal films are non-irritant.
Key words Gelatin, Glycerin, Transdermal films, Diclofenac sodium.

INTRODUCTION

Gelatin is widely used polymer in pharmaceutical products[1-3]. Recently, the use of gelatin as a polymer for the production of controlled release system has received much attention. In the past few years many studies have reported the use of gelatin in the formation of gels[1], particles[2] and microspheres[3] and bioadhesive[4]. Natural polymers are readily available and relatively inexpensive which could obviate toxicity or biodegradability problems that can be releated to the use of synthetic material[5]. The interest in gelatin arises mainly from the fact that this natural polymer allows the production of biocompatible and biodegradable drug delivery systems. Gelatin is the good candidate for the production of controlled release system being a good film forming material. In addition, gelatin is relatively cheap and is available in variety of medicinal agents. 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[6,7]

MATERIALS AND METHODS

Materials

Diclofenac Sodium (DS)-Gift sample from Rupam Chemicals Mumbai, Gelatin, Glycerin (Loba Chemie, Mumbai), 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. Weighed amount of gelatin was sprinkled on the surface of water and stirred well to avoid formation of lumps and kept aside for 15 minutes. Measured amount of glycerin was added and heated over a water bath, at 60° until gelatin dissolves. After cooling drug (2.027mg/cm^2) and sodium benzoate (0.2%) was dissolved in it. Polymeric solution was poured within a glass bangle

placed on glass mould and dried at room temperature. 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[8]. Physical and mechanical properties of blank and medicated transdermal films such as thickness uniformity, percent flatness, moisture uptake, tensile strength, percent elongation at break and modules of elasticity were studied [9,10]. 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* drug release of DS from 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 7.4) 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 percent drug cumulative release data for various polymeric films are shown in Table III and the percent cumulative amount of drug release Vs time profile is shown in Fig 1- 2 and Higuchi plots shown in Fig. 2-4.

Data Analysis

The percent cumulative amount of the drug permeated 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*[11].

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 gelatin (5,10,20 and 30%) along with the plasticizer glycerin (5,10,30 and 40%) 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. Comparative physical and mechanical study of placebo polymeric and medicated film was carried out to check the effect of addition of drug on the integrity of the transdermal films

Placebo Films: Gelatin films without glycerin were found to be very dry, rigid and break in to flakes on bending. This confirms the need of the plasticizer glycerin in the films. Physical evaluation study shows that there is increase in the thickness as the gelatin concentration increase. Almost all films showed 100% flatness except 5:20 and 20:5 films show 99 and 98% flatness respectively. Moisture uptake study shows that increase in the concentration of gelatin increase in moisture uptake and glycerin variable films decrease in moisture uptake as glycerin concentration is increased. Films stored at higher relative humidity's showed proportionate increase in the moisture uptake. The films with highest concentration of glycerin (40%) showed lowest tensile strength 2.28 x 10^6 and films with gelatin 5% showed a 2.8710^6 dynes/ cm^2 tensile

strength. Overall tensile strength obtained in the range of 2.28 x 10^6 to 11.15 x 10^6. As the gelatin concentration is increased there is increase in tensile strength while decrease in tensile strength as the glycerin concentration increased.

Medicated films: Optimized concentration of gelatin: glycerin combinations were selected for incorporation of drug. DS was incorporated in each film in the concentration 2.270mg/cm^2. Films shown shrinkage on drying so the drug content per cm^2 was slightly increased. Medicated films showed increased thickness than the placebo films. All the films shown good thickness uniformity. There was no considerable variation in weight, area and drug content. Moisture uptake was increased as compared with placebo films. Tensile strength of medicated film increased as compared with placebo films. Medicated films have better tensile strength than blank films.

In vitro drug release profile of medicated films shows that increase in the gelatin concentration decrease in the release rate and increasing the glycerin concentration increase in the release rate. Decrease in the drug release rate in case of gelatin variable films might be due to gelatin is hygroscopic[12] in nature on contact with diffusion media it gels and produces resistance to drug release and increase in the release rate of drug in case of glycerin variable film may be due to glycerin acts as humectant[12] and it maintain the moisture content of films and film does not produce resistance for drug release. Thus the release rate of gelatin variable films in following order 5:20> 10:20 >20:20> 30:20> 40:50. While glycerin variable films shows 20:40> 20:30> 20:10 >20:5. Permeation flux and permeability coefficient of formulated transdermal films shown in Table 1V.

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 0.957 to 0. 9917. This indicates that mechanism of drug release was diffusion type. Higuchi plots shown in Fig. 3 and 4.

Thus it was seen that by taking appropriate concentration one can control the desired release rate from the films.

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 natural polymer gelatin holds potential for transdermal drug delivery system. A slow and controlled release of drug release versus time is linear, these supporting the test products for transdermal films.

Table I: Evaluation of Blank Polymeric Films (Gelatin: Glycerin)

Formulation code	Mean thickness cm	% Flatness	Tensile strength dyne/cm^2	Modules of elasticity	% Elongation	Moisture uptake (58% RH)		
						58	79	98
DS F1	0.0966(0.0011)	99	2.87X10^6	1.50X10^6	10.1	13.72	25.50	35.34
DS F2	0.102(0.00645)	100	2.30X10^6	1.90X10^6	121.66	16.51	30.36	39.15
DS F3	0.110(0.01)	100	5.34X10^6	3.44 X10^6	155.60	18.08	35.81	43.69
DS F4	0.124(0.00578)	100	11.15X10^6	11.95X10^6	93.33	20.05	38.62	51.07
DS F5	0.140(0.00005)	100	11.20X10^6	18.95 X10^6	59.16	21.09	39.72	53.35
DS F6	0.113(0.00943)	100	10.40 X10^6	14.52 X10^6	71.66	26.52	48.16	58.71
DS F7	0.116(0.00476)	100	8.44 X10^6	12.41 X10^6	68.00	24.68	41.95	57.82
DS F8	0.118(0.00576)	98	6.64 X10^6	5.04 X10^6	131.66	15.46	30.04	36.11
DS F9	0.120(0.00168)	100	2.28 X10^6	2.51 X10^6	90.50	11.57	25.84	33.73

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

Table II: Evaluation of Medicated 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	0.0986(0.00101)	100	2.98X10^5	5.96X10^8	7.5	20.289	25.759	40.840
DS F2	0.105(0.0064)	100	7.66X10^6	8.24X10^8	91.66	24.658	29.764	53.22
DS F3	0.115(0.0057)	100	13.46X10^6	11.70 X10^8	110	32.61	35.14	58.13
DS F4	0.125(0.0068)	100	14.11X10^6	14.62X10^8	96.33	35.98	41.64	60.00
DS F5	0.144(0.0005)	100	17.19X10^6	27.51 X10^8	63.33	40.96	45.64	67.73
DS F6	0.115(0.0083)	98	16.31 X10^6	14.49 X10^6	69	45.81	55.04	71.10
DS F7	0.118(0.0073)	99	14.94 X10^6	12.45 X10^6	120	39.52	47.05	67.81
DS F8	0.119(0.0079)	100	7.41 X10^6	7.17 X10^6	103	27.17	32.55	48.37
DS F9	0.129(0.0069)	100	4.55 X10^6	4.09 X10^6	110	24.48	29.47	42.24

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

Table III: Formulation Composition And Evaluation of Medicated Transdermal films

Formulation Code	Polymer %w/v	Plasticizer % w/w	Thickness	Area	Drug Content	% Cumulative Release	
	Gelatin	Glycerin					
DS F1	5	20	0.5644(0.00754)	4.9284(0.0342)	13.53(0.03)	77.92	
DS F2	10	20	0.6897(0.00036)	4.9153(0.00666)	13.91(0.0387)	75.95	
DS F3	20	20	0.9596(0.0005)	4.9274(0.0277)	15.79(0.01)	61.01	
DS F4	30	20	0.9883(0.0006)	4.912(0.0057)	16.03(0.0578)	55.52	
DS F5	40	20	0.9326(0.0381)	4.9185(0.01697)	14.22(0.0254)	44.98	
DS F6	20	5	0.5272(0.00035)	4.9118(0.00542)	14.36(0.01)	55.72	
DS F7	20	10	0.6572(0.00032)	4.9217(0.0147)	16.13(0.0331)	58.62	
DS F8	20	30	1.1094(0.00802)	4.9152(0.0112)	16.71(0.0324)	63.59	
DS F9	20	40	1.115(0.000608)	4.9185(0.0099)	14.80(0.00707)	71.19	

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

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

Formulation code	Permeation flux(µg/cm^2/hr)	Permeability coefficient(Kp)
DS F1	2.98	0.2202
DS F2	3.2181	0.2313
DS F3	2.7646	0.1755
DS F4	2.4827	0.1548
DS F5	2.047	0.1439
DS F6	2.386	0.1661
DS F7	2.4960	0.1547
DS F8	2.6673	0.1596
DS F9	3.0246	0.2043

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

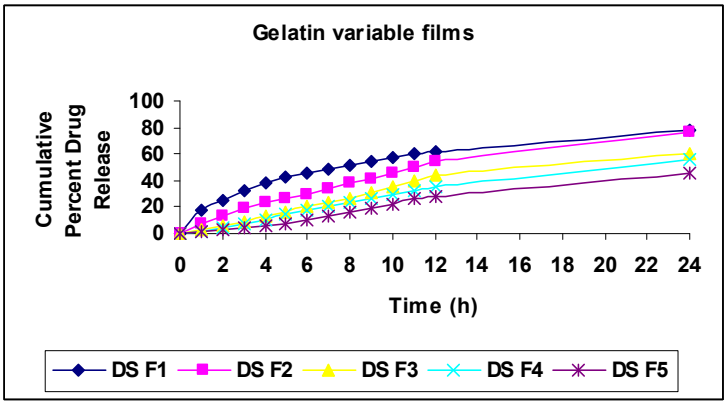

Fig.1: Plots of Cumulative Percent Drug Release Verses Time (h) For Gelatin Variable Films

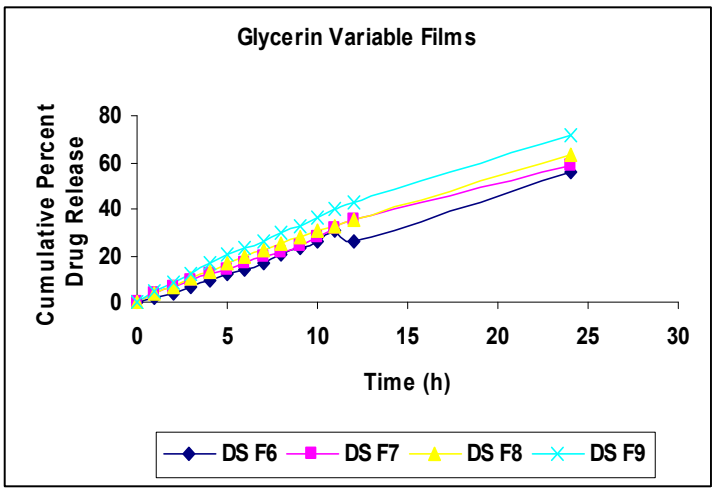

Fig.2: Plots of Cumulative Percent Drug Release Verses Time (h) For Glycerin Variable Films

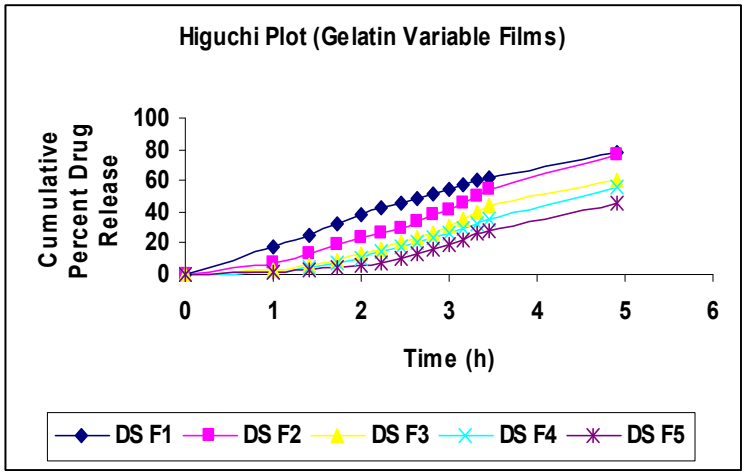

Fig.3:Higuchi Plots For Gelatin Variable Films

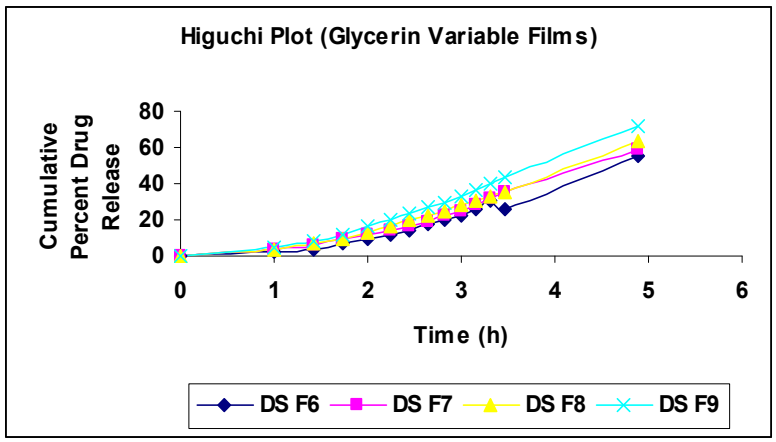

Fig.4:Higuchi Plots For Gelatin Variable Films

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