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Preparation, characterization, *in vitro* and *in vivo* evaluation of transdermal matrix films of celecoxib

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Abstract

The matrix type transdermal drug delivery system of celecoxib were prepared by the film casting method and characterised by physicochemical, *in vitro* by drug release studies, skin permeation studies and *in vivo* studies. Eight formulations were developed, which differed in the ratio of matrix forming polymers (PVA and HPMC) individually or in combination. All the eight formulations carried 2% m/m of celecoxib, eucalyptus oil or isopropyl alcohol as a permeation enhancer (10% v/v), plasticiser (20% w/w of polymer). Cumulative amounts of the drug released in 12 h from the eight formulations were ranged from 96.40±0.04 to 99.68±0.05 %. *In vitro* drug release was found to follow zero order kinetics and Higuchi kinetics. The cumulative amounts of the permeated drug for developed formulation ranged from 87.18±0.09 to 96.01±0.05 %. On the basis of *in vitro* drug release and skin permeation study, formulation F1 was found to be better than the other seven formulations and it was selected to *in vivo* studies. Paw edema study was done in wistar rat, Maximum percentage inhibition was observed for oral and transdermal application as 59.14% and 89.96%, respectively. An inhibition in paw edema volume of 31.95% and 39.30% was observed on oral and transdermal application of drug in adjuvant arthritis, chronic model in wistar rat, as well.

Keywords: transdermal drug delivery, matrix system, celecoxib, *in vitro* drug release, *in vivo* study

Introduction

Transdermal drug delivery is one of the most promising methods for drug application. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation *via* skin (Prausnitz et al. 2004). The success of Transdermal Therapeutic System has created much interest in the pharmaceutical industry and has activated research activities related to it. In the present decade, a good number of drugs have been reported for their transdermal applications: scopolamine, nitroglycerin, nicotine, estrogen, testosterone, fentanyl, buprenorphine, lignocaine, clonidine, oxybutynin and diclofenac (Brown et al. 2006). The transdermal route offers several advantages over conventional dosage forms e.g. avoidance of first-pass metabolism by the liver, minimization of pain, reduction of side effects, extended duration of activity, reduction in the fluctuations of drug concentrations in the blood, and sustained drug release (Li et al. 2007).Transdermal administration of drugs avoids many of the

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problems that arise with conventional oral route and with the more invasive methods of drug delivery. Transdermal delivery is best suited for drugs, which display high toxicity and/or narrow therapeutic windows (Hadgraft and Lane 2008). The present work is aimed at the development of matrix-type transdermal drug delivery system of celecoxib an anti-inflammatory drug. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs to reduce pain and inflammation. Celecoxib (CXB), a selective cyclo-oxygenase-2 (COX-2) inhibitor, has been recommended orally for the treatment of arthritis and osteoarthritis (Gaurel and Martel 1997). Long-term oral administration of CXB causes serious gastrointestinal side effects. Furthermore, poor aqueous solubility of CXB limits its formulation as topical dosage forms. Therefore, an improved CXB formulation with a high degree of permeation could be useful in the treatment of locally inflamed skin and inflammatory and painful states of the body (Baboota et al. 2007).

Materials and Methods

Materials

Celecoxib was gift sample form Aarti Drugs Ltd., India. Polymer PVA and HPMC were supplied by CDH Fine Chemicals, India. Eucalyptus oil and Isopropyl alcohol were supplied by Ranbaxy Fine Chemical, India. All the other chemicals were of analytical grade.

Preparation of transdermal films

Matrix type transdermal patches containing celecoxib were prepared using varying concentrations of HPMC and PVA individually or in combination keeping drug concentration constant (Table 1). The required amount of drug and polymer were dispersed in casting solvent and allowed to stir for 6 h. Glycerol was incorporated as plasticizer. Isopropyl alcohol or eucalyptus oil was used as penetration enhancers. The polymeric dispersion of drug was poured into a fabricated casting assembly. The polymeric drug solution allowed drying in an oven. Aluminium foil was used as backing membrane. Dried films were stored in presterilized aluminium foil papers in the suitable conditions. Formulations, F1, F2, F3, F4, F5, F6, F7, and F8 were prepared using alone or in different combinations of PVA, HPMC (Chandak and Verma 2008).

Table1. Composition of celecoxib transdermal films in different Formulations

Formulation	Celecoxib	Polymer	Permeation enhancer (10% v/v)	Plasticiser (20% w/w of polymer)	Buffer vol. upto 100ml
F1	2 %	PVA (3%)	Eucalyptus oil	Glycerol	PBS pH 7.4
F2	2 %	HPMC (3%)	Isopropyl alcohol	Glycerol	PBS pH 7.4
F3	2 %	HPMC(1%), PVA(2%)	Eucalyptus oil	Glycerol	PBS pH 7.4
F4	2 %	HPMC(3%)	Eucalyptus oil	Glycerol	PBS pH 7.4
F5	2 %	PVA(3%)	Isopropyl alcohol	Glycerol	PBS pH 7.4
F6	2 %	HPMC(2%), PVA(1%)	Isopropyl alcohol	Glycerol	PBS pH 7.4
F7	2 %	HPMC(2%), PVA(1%)	Eucalyptus oil	Glycerol	PBS pH 7.4
F8	2 %	HPMC(1%), PVA(2%)	Isopropyl alcohol	Glycerol	PBS pH 7.4

Evaluation of Transdermal Films

Thickness of Film

Thickness of the film was measured using digital vernier caliper. The procedure was repeated at different points and the mean value of thickness was calculated for all prepared films. Experiment was done on the randomly selected three films (Chandak and Verma 2008).

Folding Endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance was determined by repeatedly folding the film at the same place until it break. Three films were selected. The number of times the film could be folded at the same place without breaking was folding endurance value (Tanwar et al. 2007).

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip was cut from the centre and two from each side of patches. The length of each strip was measured and variation in length was measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = [(I_1 - I_2) / I_1)] \times 100$$

Where, I_1 = Initial length of each strip, I_2 = Final length of each strip (Chandak and Verma 2008).

Surface pH Determination

The films were kept in contact with 0.5 mL of distilled water for 1 h. The surface pH was measured by means of pH paper placed on the surface of the swollen patch. It was measured by pH meter also. The mean of three readings was recorded (Chandak and Verma 2008).

Tensile Strength

To determine tensile strength, polymeric films were sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights were added gradually to the pan attached with the hanging end of the thread. A pointer on the scale was used to measure the elongation of the film. The weight just sufficient to break the film was noted. Experiment was done on the randomly selected three films. The tensile strength was calculated using the following equation.

$$\text{Tensile strength} = F/a.b\ (1+L/l)$$

Where, F is the force required to break, a is width of film, b is thickness of film, L is length of film, l is elongation of film at break point (Gattani et al. 2006).

Uniformity of weight

Weight variation was studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight (Jamakandi et al. 2009).

Drug content determination

Assay of each of the ten randomly selected medicated patches was carried out to determine the drug content. The patch was dissolved in 5 ml of the casting solvent and the volume was adjusted to 100 ml with Phosphate buffer saline. The solution was filtered, suitably diluted, and content per film was estimated spectrophotometrically at 247 nm using standard curve (UV, Shimadzu 1601, Japan) (Jamakandi et al. 2009).

Moisture Uptake

Weighed films were kept in a desiccator at room temperature for 24 h. These were then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight was achieved. % moisture uptake was calculated as given below (Bhatt et al. 2008).

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

In vitro drug release study procedure

A modified paddle over disc USP dissolution apparatus was used in this study. A transdermal matrix film was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 ml of phosphate buffer saline of pH 7.4. The apparatus was equilibrated to 37±0.5°C and the stirrer paddle speed was set at 50 rpm. The samples were withdrawn at appropriate time intervals and analyzed at 247 nm using a spectrophotometer. The amount of drug released was calculated from the standard curve. All the experiments were carried out in triplicate. This procedure was done for each formulation separately (Bhatt et al. 2008)

In vitro skin permeation study procedure

Usually permeation studies were performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as Franz diffusion cell or Keshary-Chien diffusion cell. The transdermal system was applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophilic side in contact with receptor fluid. The receiver compartment was maintained at specific temperature (usually 32±5°C for skin) and was continuously stirred at a constant rate. The samples of 1 mL were withdrawn at predetermined time intervals and equal amount of buffer was replaced each time. The samples were diluted appropriately and absorbance was determined spectrophotometrically at 247 nm. Then the amount of drug permeated per centimeter square at each time interval was calculated. All experiments were carried out in triplicate (Aqil et al. 2003, Chandra and Kumar 2009).

In vivo study procedure (Paw edema study an acute model)

The anti-inflammatory efficacy was evaluated by carrageenan induced paw inflammation in Wistar rat. The protocol of the study in rats was approved by the institutional animal ethical committee, Gyan Vihar University, Jagatpura, Jaipur, India. All animals were housed at room temperature of 28±1°C. All animals were randomly assigned to different groups and a period of one month was allowed for adaptation before commencement of each experiment. The patch was securely adhered over the dorsal abdominal skin of the rat. The rat received intraplantar injection of 50 µg of 0.5% w/v carrageenan suspension into the left hind paw subcutaneously by inserting the needle into the central part of the paw. The paw volume was measured and compared to with that found in animals treated with carrageenan alone. The right hind paw which served as control was treated with physiological saline solution without carrageenan. The inflammatory response was determined by measuring the changes in paw volumes with a screw gauge at

0, 2, 4, 6, 8, 10 h after the carrageenan injection (Baboota et al. 2007, Chandra and Kumar 2009).

In vivo study procedure (Inhibition of adjuvant arthritis, chronic model)

Heat-killed *Mycobacterium tuberculosis* was used to prepare complete Freund's adjuvant. The prepared complete Freund's adjuvant (0.1 mL equivalent to 0.6 mg), was injected subcutaneously into the plantar site of the right hind paw of male Wistar albino rats under ether anaesthesia. After 14 day, animals with secondary inflammation (left hind foot, bilateral front foot and/or tail) were selected. On the 15th day, the test and standard preparations were applied once a day for 7 days. After 5 h, the paw was rinsed with warm water and edema was measured daily on the right hind paw for 7 days (Kesavanarayanan et al. 2007).

Results and Discussion

The thickness, folding endurance, flatness, surface pH, tensile strength, weight, drug content, moisture uptake values of the formulation made are shown in Table 2. Thickness of films varied from 0.090±0.001 to 0.185±0.001 mm. The folding endurance value for formulation F2 and F4 were less than 300, it may be due to low polymer elasticity, remaining all films show good folding endurance greater than 300 which is considered as good film properties (Tanwar et al. 2007).

Table 2. Evaluation of celecoxib matrix films

Formulation	Thickness* (mm)	Folding Endurance*	Flatness*	Surface pH*	Tensile strength* (g/mm^2)	Weight (mg)#	Drug content (mg)#	Moisture uptake %
F1	0.180 (0.001)	>300	100%	7.0	30.99 (0.01)	80.11 (0.21)	24.94 (0.01)	3.12 (0.06)
F2	0.090 (0.002)	<300	100%	7.0	20.18 (0.12)	51.22 (0.21)	24.24 (0.01)	1.21 (0.12)
F3	0.150 (0.001)	>300	100%	7.0	25.09 (0.01)	76.81 (0.32)	24.50 (0.01)	2.07 (0.21)
F4	0.090 (0.001)	<300	100%	7.0	19.16 (0.01)	56.76 (0.12)	24.14 (0.02)	1.51 (0.18)
F5	0.185 (0.001)	>300	100%	7.0	30.16 (0.02)	79.12 (0.01)	24.65 (0.01)	3.14 (0.01)
F6	0.120 (0.002)	>300	100%	7.0	23.12 (0.01)	71.54 (0.03)	24.10 (0.02)	2.58 (0.02)
F7	0.110 (0.002)	>300	100%	7.0	23.02 (0.09)	73.02 (0.15)	24.28 (0.01)	2.85 (0.20)
F8	0.12 (0.001)	>300	100%	7.0	26.81 (0.20)	77.21 (0.03)	24.28 (0.02)	3.09 (0.33)

* Data represent mean (S.D.) (n=3); # Data represent mean (S.D.) (n=10).

The results of flatness study showed that none of the formulation had the difference in the strip lengths before and after longitudinal cut, indicating 100 % flatness, and thus they could maintain a smooth surface when applied onto the skin. The surface pH of all formulations was about to 7.0, that comes to pH range of skin and hence no skin irritation was expected (Chandak and Verma 2008). The weight was found between 51.22±0.210 – 80.11±0.211 mg. The variation in weight uniformity of the prepared films was within acceptable limits. The drug content per patch was found within 24.10±0.01 to 24.94±0.02 mg per patch. The moisture present in the matrix films helps in maintaining suppleness thus preventing drying and brittleness. Low moisture

uptake protects the films from the microbial contamination as well as bulkiness of the transdermal patch. Moisture uptake % range was found 1.51 to 3.12 that was acceptable and within limit. Tensile strength shows the strength and elasticity of the films. Low tensile strength and high elongation at break shows soft and weak films characterization. High tensile strength and low Elongation at break shows hard and brittle films characterization. So films should have should have a relatively moderate tensile strength and elongation at break. Result shows tensile strength in the range of 19.16±0.001 to 30.99±0.015 g/mm^2, which shows moderate tensile strength values.

The dissolution studies were performed using the USP paddle over disc method. The objective was to estimate, characterize and rationalize the drug release from matrix films. The cumulative amount of drug released in 12 hours was found to be highest 99.68 ± 0.05 % from formulation F1 carrying PVA 3 % (Table 3).

Table 3. *In vitro* drug released and permeation of the developed transdermal drug delivery system of celecoxib

Parameters	Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
Cumulative amount of drug released in 12 h (%)	99.68 (±0.05)	96.48 (±0.04)	98.21 (±0.06)	96.48 (±0.01)	98.48 (±0.01)	96.40 (±0.04)	97.00 (±0.09)	97.80 (±0.02)
Cumulative amount of drug permeated in 12 h (%)	96.01 (±0.05)	89.82 (±0.08)	92.21 (±0.08)	89.77 (±0.08)	95.02 (±0.07)	87.18 (±0.09)	89.50 (±0.01)	93.11 (±0.02)
Flux(mg/cm^2/h)	0.2802 (±0.0002)	0.2534 (±0.0010)	0.2737 (±0.0009)	0.2517 (±0.0002)	0.2754 (±0.0011)	0.2412 (±0.0008)	0.2628 (±0.0009)	0.2691 (±0.0006)

Results are the mean (S.D.) of triplicate observations.

The *in vitro* dissolution profiles are often used as surrogates, indicating how a drug will behave in *in vivo*. In order to propose a release mechanism, celecoxib release data was fitted to zero order and the Higuchi empiric mathematical model. Drug release profiles did not fit into the first order kinetics (r^2=0.856-0.983). However, the drug release (Fig. 1) was found to follow zero order kinetics and Higuchian kinetics, as the correlation coefficient (r^2 value) was the highest for these models, for zero order ($r^2 = 0.962 - 0.993$)), for higuchi model ($r^2 = 0.962 - 0.993$) (Table 4).

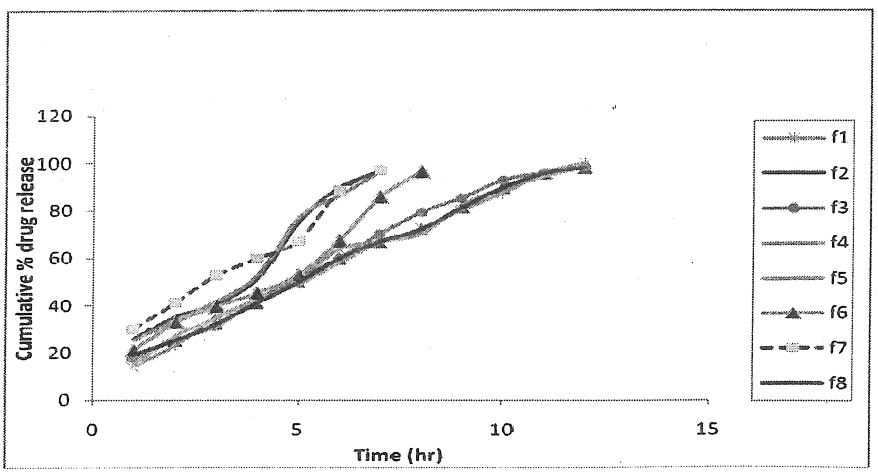

Figure 1. Drug release profiles of transdermal formulations F1-F8 containing drug celecoxib

In vitro permeation study was performed on the transdermal formulations code F1, F2, F3, F4, F5, F6, F7, F8 using modified Keshary-Chien diffusion cell, from study it was revealed that formulation F1 exhibited the satisfactory results. Cumulative % drug release in 12 h for formulation F1 were 96.01± 0.05 % (Table 3).

Table 4. Kinetics of *in vitro* release of celecoxib from transdermal patches

Formulation	Zero order		First order		Higuchi matrix	
	K_0(mg h^{-1})	r^2	K_1(h^{-1})	r^2	K($h^{-1/2}$)	r^2
F1	0.743	0.993	0.059	0.856	7.74	0.988
F2	1.32	0.962	0.102	0.771	13.01	0.962
F3	0.770	0.987	0.066	0.816	7.86	0.984
F4	1.26	0.974	0.104	0.983	12.66	0.974
F5	0.759	0.993	0.065	0.803	7.62	0.993
F6	1.04	0.963	0.095	0.979	10.50	0.969
F7	0.721	0.973	0.075	0.832	12.89	0.962
F8	0.777	0.967	0.091	0.840	11.85	0.978

Other formulations did not show satisfactory results. Formulation F1 showed good flux value that was 0.2802 mg/cm^2/h. formulations contaning eucalyptus oil showed good permeation or flux value than others. Cumulative amount of drug permeated through the skin (µg cm^{-2}) was plotted as a function of time for each formulation(Fig. 2).

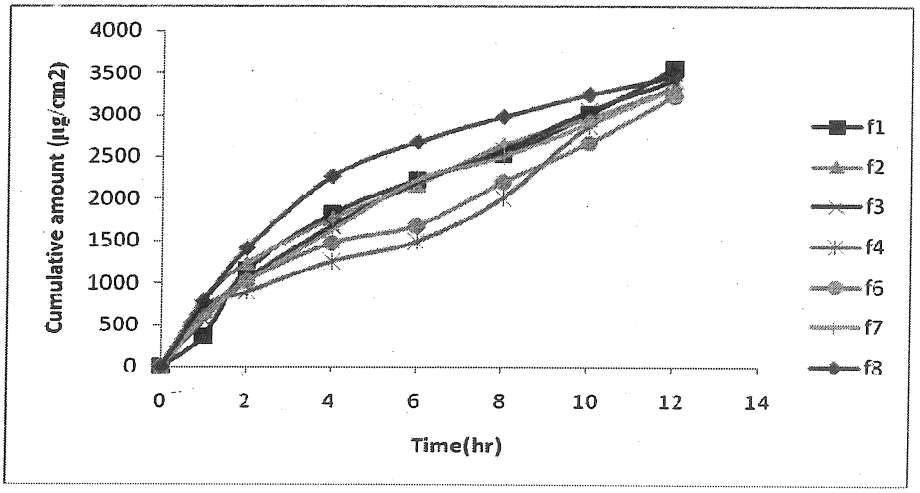

Figure 2. The permeation profile of transdermal formulations through diffusion cell

In paw edema inflammation study, the formulation showed a prominent increase in activity. Oral administration showed swelling of 56.12% while TDS formulation demonstrated 44.22% swelling. Maximum percentage inhibition was observed for oral and transdermal application of

59.14 and 89.96 %, respectively (Fig. 3). Celecoxib transdermal patch formulation demonstrated a significant anti-inflammatory potential (Table 5) as compared with the oral ($P<0.05$). The probable reason may be that transdermal delivery delivers the drug direct to blood circulation.

Table 5. Anti-inflammatory effects of TDDS and Oral drug delivery of drug celecoxib in carrageenan induced rat paw edema

Group	Formulation	N	Mean weight g ± SD	Time h	Mean % Edema ± SD	Inhibition %
I	Control (carrageenan only)	6	210 ± 13.5	0	0	
				2	30.16 ± 0.9	
				4	83.54 ± 0.8	
				6	80.07 ± 1.1	
				8	74.17 ± 1.1	
				10	63.98 ± 0.9	
II	TDDS	6	215 ± 15.2	0	0	
				2	24.77 ± 0.9	17.87
				4	44.22 ± 0.9	47.06
				6	31.00 ± 1.0	61.28
				8	13.57 ± 1.1	81.70
				10	6.42 ± 0.9	89.96
III	Oral	6	210 ± 18.5	0	0	
				2	28.88 ± 1.2	4.24
				4	56.12 ± 1.0	32.82
				6	44.60 ± 0.9	44.29
				8	30.53 ± 1.0	58.83
				10	26.14 ± 1.1	59.14

N=Number of rats in each groups.
P<0.05 Significant, TDDS was compared with oral % inhibition in paw volume.
P < 0.05 Significant, TDDS was compared with control mean edema in paw volume.

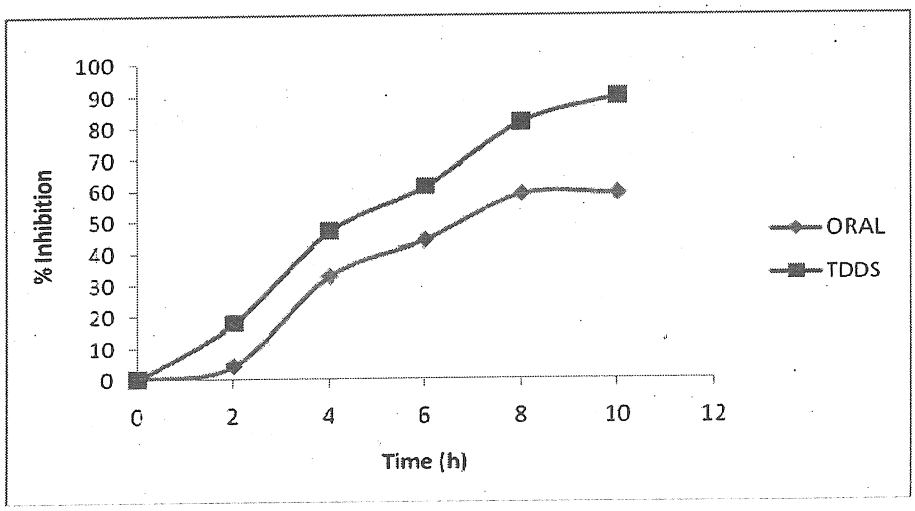

Figure 3. Anti-inflammatory effects of TDDS and oral drug delivery in wistar male rats

In chronic inflammation model, Maximum percentage inhibition was observed for oral and transdermal application of 31.95% and 39.30%, respectively (Table 6). Celecoxib transdermal

patch formulation demonstrated a significant anti-arthritis potential as compared with the oral ($P<0.05$).

Table 6. Anti-inflammatory effects of TDDS and Oral drug delivery of drug celecoxib in Freund's adjuvant induced rat arthritis

Group	Formulation	N	Mean weight g ± SD	Time day	Mean edema mm ± SD	Inhibition %
I	Control (Freund's adjuvant only)	6	210 ± 13.5	1	5.50 ± 0.02	
				15	7.08 ± 0.01	
				16	7.21 ± 0.05	
				17	7.63 ± 0.05	
				18	8.01 ± 0.07	
				19	8.47 ± 0.08	
				20	8.98 ± 0.08	
				21	8.98 ± 0.03	
II	TDDS	6	215 ± 15.2	1	5.45 ± 0.03	
				15	7.00 ± 0.08	01.12
				16	6.92 ± 0.03	04.02
				17	6.20 ± 0.06	18.74
				18	5.95 ± 0.06	25.70
				19	5.65 ± 0.06	33.29
				20	5.45 ± 0.03	39.30
				21	5.45 ± 0.09	39.30
III	Oral	6	210 ± 18.5	1	5.47 ± 0.08	
				15	7.02 ± 0.06	00.84
				16	6.95 ± 0.01	03.60
				17	6.80 ± 0.02	10.87
				18	6.55 ± 0.03	18.22
				19	6.40 ± 0.08	24.43
				20	6.15 ± 0.06	31.51
				21	6.11 ± 0.06	31.95

N=Number of rats in each groups.
P<0.05 significant, TDDS was compared with oral % inhibition in paw volume.
P <0.05 significant, TDDS was compared with control mean edema in paw volume.

Conclusion

The results of this study indicate that polymer PVA had excellent film forming ability. On the basis of the *in vitro* characterization it was concluded that celecoxib could be administered transdermally through the matrix type TDDS. On the basis of the *in vitro* and *in vivo* study, it could be concluded that celecoxib TDDS holds promise as a viable option for effective and controlled management of inflammation. Further work is needed to establish the therapeutic utility of these systems by pharmacokinetic and pharmacodynamic studies on human beings.

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