

FORMULATION AND EVALUATION OF TRANSDERMAL FILMS CONTAINING CELECOXIB INCLUSIONS FOR TREATING PSORIATIC ARTHRITIS

MANASA J, SAI KUMAR G, PADMINI IRIVENTI*

Department of Pharmaceutics, Dr. K.V. Subba Reddy Institute of Pharmacy, Kurnool, Andhra Pradesh, India. Email: paddhu.iriventi@gmail.com

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ABSTRACT

Objective: The main objective of the present work was to prepare and evaluate transdermal films and creams of celecoxib inclusions which are nonsteroidal anti-inflammatory drug to treat psoriatic arthritis.

Methods: Celecoxib inclusions were prepared using β -cyclodextrin to increase the solubility. These inclusions were incorporated in transdermal films. Hydroxy Propyl Methyl Cellulose (HPMC), dibutyl phthalate, propylene glycol, and glycerin were used to prepare the film. Fourier transform infrared and differential scanning calorimetry studies were carried out for pure celecoxib and inclusions. Morphological properties, weight variation, surface pH, percentage elongation, folding endurance, *in vitro* disintegration, and *in vitro* diffusion studies were carried out for films.

Results: All the results obtained were within the limits and confirmed the prolonged drug release and increased solubility of celecoxib inclusions.

Conclusion: From the results obtained, increase in solubility of celecoxib drug was confirmed by forming inclusions using β -CD as polymer.

Keywords: β -cyclodextrin, Psoriatic Arthritis, Transdermal films, Inclusions, Celecoxib.

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, systemic, and inflammatory disease that affects peripheral joints, connective tissues, and axial skeleton and is associated with psoriasis of skin and nails [1,2]. It is a seronegative inflammatory arthropathy that occurs in 5–7% of people with psoriasis [3,4]. Genetic factors have an important role in PsA. It is thought that environmental triggers which are infectious in nature trigger the disease in genetically susceptible individuals [5]. Currently available therapies for PsA are surgery, light therapy, narrowband ultraviolet (UV) B phototherapy, excimer laser, and Psoralen and Ultra Violet A (PUVA) [6]. Available drugs are corticosteroids, tacrolimus, tumor necrosis factor inhibitors, methotrexate, and sulfasalazine [7]. The disadvantages of these drugs are that the radiation can dry out the skin and cause itching and redness, burning, blistering of the skin, etc. [8]. Celecoxib is a cyclooxygenase (COX)-2-specific inhibiting agent that inhibits the conversion of arachidonic acid to the prostaglandins (PGs) that mediate pain and inflammation [9]. The mechanism of action of celecoxib is conversion of arachidonate to the PGs which is important in homeostatic function; COX-2 is present in immune cells, blood vessel endothelial cells, and synovial fibroblasts. Classic nonsteroidal anti-inflammatory drugs inhibit both COX isoenzymes by occupying the COX active site, preventing access by arachidonic acid. In theory, a drug such as celecoxib that selectively inhibits COX-2 might block inflammation, pain, and fever [10]. Transdermal patch generally refers to topical application and delivers agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. Transdermal patch offers many advantages over the conventional dosage forms or controlled release oral systems. Transdermal patch maintains constant blood levels, avoids first pass metabolism, increases patient compliance, and avoids dose dumping [11,12].

METHODS

Celecoxib is a gift sample obtained from Wexford Laboratories Pvt., Ltd., Bengaluru. β -cyclodextrin is a polymer obtained from HiMedia, Mumbai, India. HPMC is a polymer obtained from Rolex Chemical Industries Pvt., Ltd. Dibutyl phthalate is a plasticizer obtained from

Pallav Chemicals and Solvents Pvt. Ltd., Biosar, India. Propylene glycol is a solubilizer obtained from Qualikems Fine Chem Pvt., Ltd., Vadodara. Glycerine is a humectants obtained from Simson, Mumbai, India.

Solubility studies of celecoxib in water and in pH 7.4 buffer

Drug solubility was determined by adding excess amount of pure celecoxib in water and pH 7.4 phosphate buffer at $37 \pm 0.5^\circ\text{C}$ in vials, respectively. These vials were kept in orbital shaker for 24 h at 100 rpm. Final solution was filtered through membrane filter 0.45 μm . The concentration of the samples was measured using UV-visible spectrophotometer (UV 1800, Shimadzu, Japan). Each sample was analyzed in triplicate.

Analytical method for celecoxib

Calibration curve in pH 7.4 phosphate buffer

From the standard solution, a stock solution was prepared to give a concentration of 100 $\mu\text{g/ml}$ in 7.4 buffer. Aliquots of 0.5, 1.0, 1.5, 2.0, and 2.5 ml from the stock solution were pipetted out into 10 ml volumetric flasks. The volume was made up to the mark with 7.4 buffer. These dilutions gave 5, 10, 15, 20, and 25 $\mu\text{g/ml}$ concentration of celecoxib, respectively. The absorbance of prepared solutions of celecoxib in 7.4 buffer was measured at 252 nm spectrophotometrically against 7.4 buffer blank. Standard plot data of celecoxib in 7.4 pH buffer are reported in Fig. 1.

Fourier-transform infrared (FT-IR) spectroscopy analysis

Fourier transform infrared analysis was conducted to verify the interaction between drug and polymer. The sample powder was dispersed in KBr powder and pellets were made by applying 4 kg/cm² pressure. FT-IR spectra were obtained by powder diffuse reflectance on a FT-IR spectrophotometer type 8400S Shimadzu. It was performed for pure celecoxib drug and F2 formulation.

Differential scanning calorimetry (DSC)

DSC was performed on pure drug and its formulations using DSC-60 instrument. Calorimetric measurements were made with empty cell (high purity alpha alumina discs) as the reference. The dynamic scans

Table 1: Formulation chart of transdermal films (F1-F5)

Formulation	Drug complex (mg)	HPMC (mg)	Dibutyl phthalate (ml)	Propylene glycol (%)	Glycerine (ml)
F1	50	50	0.5	0.5	0.5
F2	50	75	0.5	0.5	0.5
F3	50	100	0.5	0.5	0.5
F4	50	125	0.5	0.5	0.5
F5	50	150	0.5	0.5	0.5

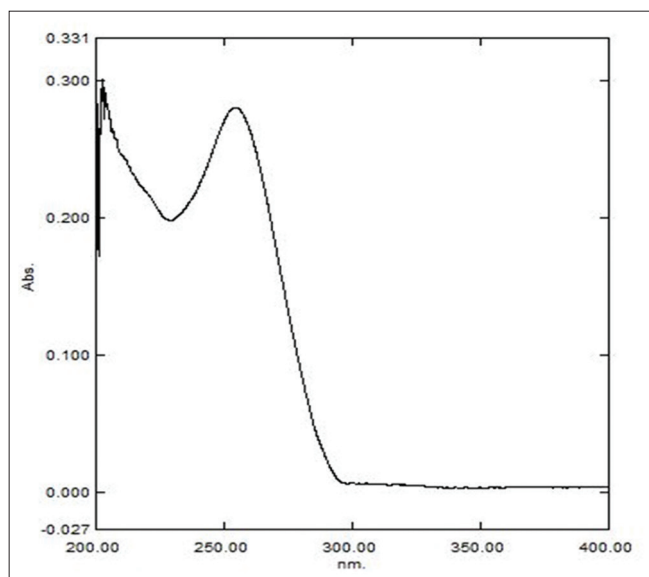


Fig. 1: Ultraviolet spectra of celecoxib in pH 7.4 phosphate buffer

were taken in nitrogen atmosphere at the heating rate of $10^{\circ}\text{C min}^{-1}$. The energy was measured as J/Kcal. It was performed for pure celecoxib drug and F2 formulation.

Procedure for preparation of transdermal films

The transdermal films of celecoxib were prepared by solvent casting method. HPMC polymer was soaked in distilled water for 1 h. Calculated amount of celecoxib was added to polymeric solution, followed by propylene glycol, dibutyl phthalate, and glycerin. The mixture was stirred well for uniformity. The resultant mixture was poured into a Petri plate and dried for 24 h. Obtained films were stored in dry conditions for further evaluation studies [13]. Formulation chart of prepared transdermal films (F1-F5) is given in Table 1.

Evaluation of celecoxib films [14]

Morphological properties

Homogeneity, color, and transparency of films were tested visually [14].

Weight variation

Weight of $2 \times 2 \text{ cm}^2$ film from different batches of the formulations was noted on electronic balance [14].

Surface pH study

A $2 \times 2 \text{ cm}^2$ prepared films were dissolved in a Petri plate, until the film dissolves and the pH of the solution was checked using pH stripes [14].

Percentage elongation (%E)

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement using the following formula [14].

$$\text{Percentage elongation} = [L - L_0] \times 100 / L_0$$

Where, L = Final length, L_0 = initial length

Table 2: Solubility studies for celecoxib

Concentration of celecoxib in water ($\mu\text{g/ml}$)	Concentration of celecoxib in pH 7.4 ($\mu\text{g/ml}$)
6.87 ± 0.01	13.54 ± 0.0057

*n=3 [15]

Folding endurance

Folding endurance indicates brittleness of the film and was determined by repeated folding of the film at the same place till the film breaks [14].

In vitro disintegration time

The film strip was placed in a glass Petri plate containing 25 ml of distilled water at 37°C with swirling at every 10 s. Disintegration time was recorded as the time at which the film starts to break or disintegrate [14].

In vitro drug release method

Beaker stirring method

These studies were conducted using 150 ml glass beaker with 125 ml of 7.4 pH buffer as dissolution medium. Film was placed on one side of the beaker using double-sided tape. Medium was stirred at a speed of 200 rpm using magnetic stirrer. A 5 ml samples were withdrawn at 0, 1, 2, 4, 8, 12, and 24 h time intervals and every time replaced with 5 ml of fresh medium solution. Samples were analyzed by UV at 252 nm [14].

Similar procedure was used for pure drug also. Drug release from prepared film (F5) was compared with pure drug. All the absorbance values at different time intervals are noted. From that, % drug release was calculated.

Statistical analysis (analysis of variance [ANOVA])

Both the study and control groups were compared. ANOVA is performed for film F5 and pure drug to determine the differences among the products tested.

RESULTS AND DISCUSSION

Solubility studies of celecoxib in water and in pH 7.4 buffer

From the results obtained, it was confirmed that solubility of celecoxib is more in pH 7.4 buffer. Hence, further studies were carried out using pH 7.4 buffer. Results are given in Table 2.

Evaluation parameters

Appearance

Prepared films were transparent. It shows that they were spread equally without any aggregates.

Weight variation

Weight variation of transdermal films of different formulations was between the limits of 0.03 and 0.07 mg.

Percentage elongation

It is carried out using the following equation:

$$\% \text{ elongation} = [L - L_0] \times 100 / L_0$$

Percentage elongation of different formulations was between 5% and 30%. As the percentage increases, the rate of drug release increases. The maximum percentage elongation was seen in F5 formulation.

In vitro disintegration time

The disintegration times for different formulations are between 10 and 65 s. It shows that the results are optimum.



Fig. 2: Prepared transdermal films

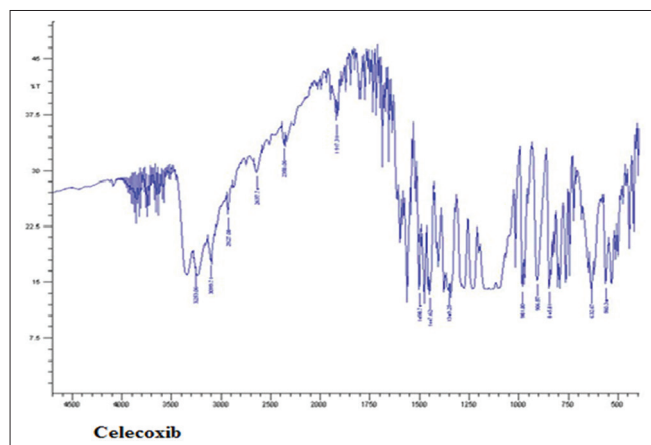


Fig. 3: Fourier transform infrared spectral data of pure celecoxib

Folding endurance

The folding endurance of different formulations was found between 59 and 65. It shows that all the films have optimum elasticity.

Surface pH

The pH of the prepared film was found to be between 6 and 7 which is nearer to the pH of the skin; hence, it does not show skin irritation.

All the obtained results are given in Table 3.

From the above results, it was found that F5 film has high folding endurance, good % elongation, and *in vitro* disintegration time. Hence, it is considered for further studies such as FT-IR, DSC, and *in vitro* drug release. F5 formulation film is shown in Fig. 2.

FT-IR studies

The characteristic peaks of pure celecoxib and F2 formulation are shown in Figs. 3 and 4. From the data, it was observed that characteristic peaks of drug appeared almost similar in F2 spectrum with disappearance of some peaks. Hence, it can be inferred that there is no chemical interaction between drug and polymer and it can be concluded that the characteristic bands of pure drug were not affected by β -cyclodextrin and method used for preparation.

DSC

Thermogram of pure drug has shown a sharp endothermic peak at 163.10°C, which corresponds to its melting point and is represented in Fig. 5. Formulation F2 has shown endothermic peak at 160.10°C which corresponds to the melting point of the drug and it is represented in Fig. 6. The DSC thermograms revealed that there was significant difference between the drug and the excipients. From the thermograms, it was evident that melting point of celecoxib was changed when it was formulated as complex. This was due to thermal transition behavior. Decrease in the melting point of the drug was due to decrease in the crystallinity of the compound and also might be due to displaced peak of drug.

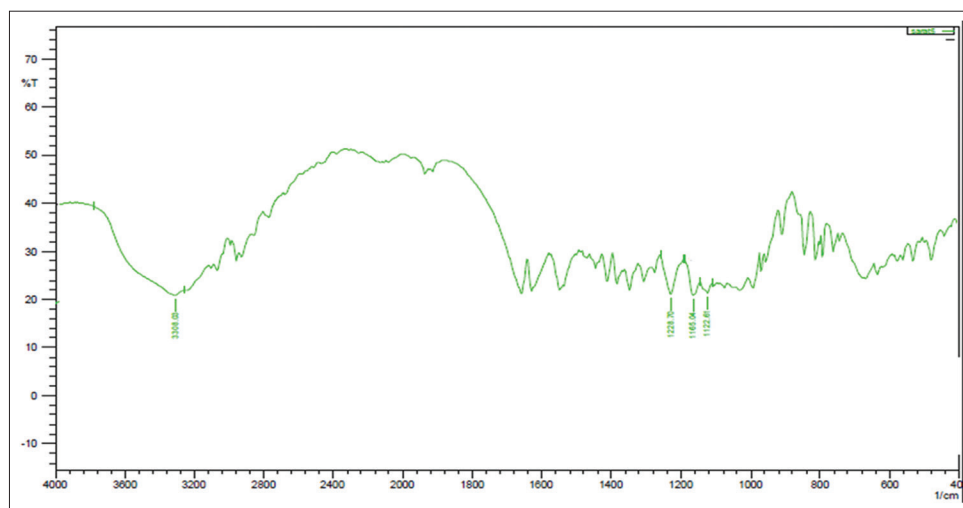


Fig. 4: Fourier transform infrared spectra of F2 formulation

Table 3: Evaluation results of transdermal films

S. No.	Evaluation parameter	F1	F2	F3	F4	F5
1.	Appearance	H and T*	H and T*	H and T*	H and T*	H and T*
2.	Weight variation (mg)	0.03	0.05	0.05	0.06	0.07
3.	Folding endurance	59	61	57	63	65
4.	<i>In vitro</i> disintegration time (s)	11	22	42	51	60
5.	% elongation	5	10	15	20	30
6.	pH	4	5	4.5	5	6

*H and T: Homogenous and transparent

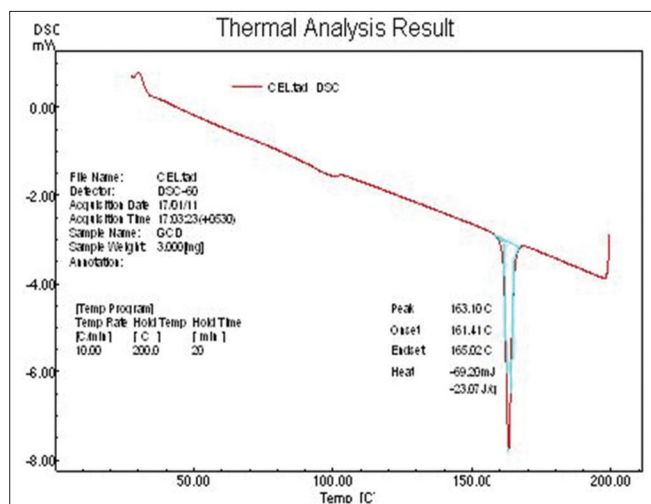


Fig. 5: Differential scanning calorimetry thermogram of pure celecoxib

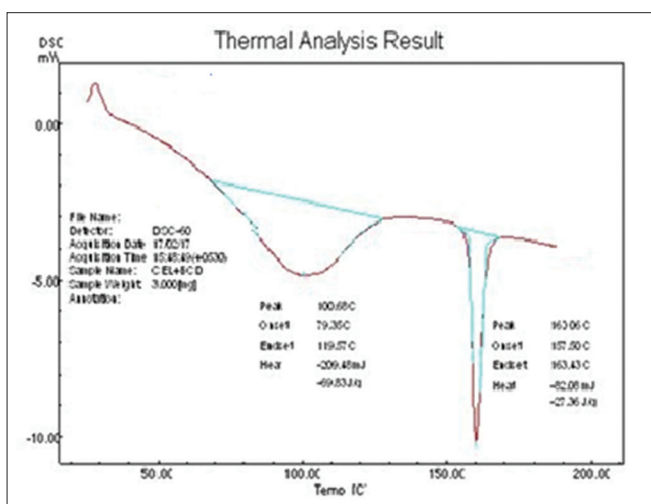


Fig. 6: Differential scanning calorimetry thermogram of F2 formulation

In vitro drug diffusion studies

In vitro drug diffusion studies were carried out for both F5 formulation and pure drug. Formulation containing pure drug has shown drug release for 8 h and after that, no release was noticed, whereas F5 formulation has shown release till 24 h (Max×93.05%). In case of F5 formulation, drug release occurred in prolonged manner. At the beginning, drug which is not encapsulated inside the inclusions released that has led to increased % release of drug. Then, after attaining saturation state, drug release from inclusions occurred. This was seen till 24 h. However, in case of pure drug, no encapsulation of drug is seen; hence, release occurred till 8 h and also since celecoxib is poorly water soluble, drug release was also less. Drug release of both F5 film formulation and pure drug is given in Table 4 and Fig. 7.

From the obtained diffusion studies, it was confirmed that drug which is not entrapped inside the cyclodextrin cup is released in the beginning 4 h and then release from cyclodextrin cup occurred. This release was prolonged till 24 h.

Statistical analysis (ANOVA)

ANOVA shows that in vitro results obtained by comparison between F5 and pure drug formulations have shown statistically significant differences (P < 0.05), as shown in Table 5.

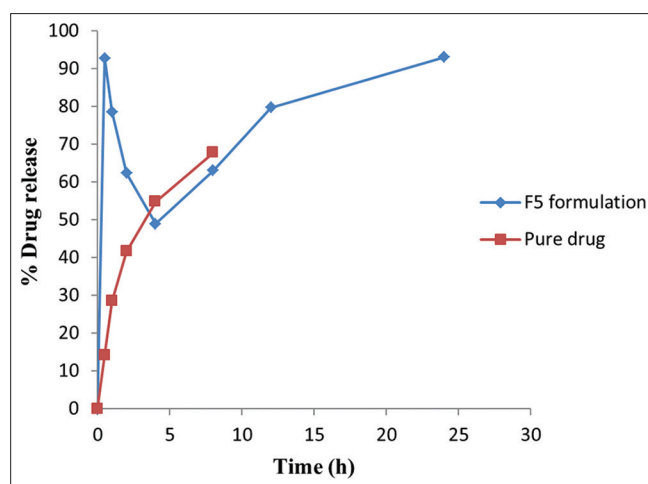


Fig. 7: Comparison of drug release between F5 formulation and pure drug

Table 4: In vitro % drug release

S. No.	Time	F5	Pure drug
1.	0	0.00	0.00
2.	0.5	92.81	14.23
3.	1	78.58	28.45
4.	2	62.34	41.67
5.	4	48.95	54.82
6.	8	63.02	67.75
7.	12	79.71	-
8.	24	93.05	-

Table 5: Statistical analysis (analysis of variance)

Newman-Keuls multiple comparison test	Mean difference	q	Significant (p<0.05)
F5 versus pure drug	-21.16	39.42	Yes

CONCLUSION

Solubility of celecoxib drug was increased by forming inclusions using β-CD as polymer. This further leads to increased bioavailability. From FTIR and DSC studies, compatibility between drug and polymer was confirmed. All the results obtained from evaluation parameters found to be within the limits and state that no skin irritation and prepared films were ideal for topical use. Prolonged release of celecoxib drug from 8 h to 24 h was achieved. This helps in decreasing the dose frequency of drug thus increases patient compliance.

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AUTHORS' CONTRIBUTIONS

All the authors contributed equally in preparation of manuscript.

CONFLICTS OF INTEREST

Authors have none to declare.

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REFERENCES

1. Boehncke WH, Menter A. Burden of diseases, Psoriasis and psoriatic arthritis. *Am J Clin Dermatol* 2013;14:377-88.
2. Gladman DD, Antonic, Mease P, Clegg DO, Nash P. Psoriatic arthritis: Epidemiology, clinical features, course, outcome. *Ann Rheum Dis* 2005;64:ii14-7.
3. Carol MP. Pathophysiology: Concepts of Altered Health States. 7th ed. Lippincott Williams and Wilkins; 2004. p. 1428-9.
4. Julsgaard M, Christensen LA, Gibson PR, Gearry RB, Fallingborg J, Hvas CL, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016;151:110-9.
5. Damini N, Aniruddha M, Bina KM, Sugato B. Metabolic syndrome associated complications. *Int J Pharm Pharm Sci* 2015;7(7):22-5.
6. Camilla F. Genetic Studies of Psoriasis and Psoriatic Arthritis. Department of Medical and Clinical Genetics, Institute of Biomedicine. Gothenburg, Sweden: The Sahlgrenska Academy at Goteborg University Sweden; 2007.
7. DoQuyen H, Arthur K. Psoriatic arthritis: Current therapy and future approaches. *Rheumatology* 2015;54:20-8.
8. Eun JK, Arthur K. Psoriatic arthritis: Latest treatments and their place in therapy. *Ther Adv Chronic Dis* 2015;16:194-203.
9. Jayashree V, Prakash R. Protective effect of COX inhibitors on lipopolysaccharide induced sickness behaviour or neuroinflammation and oxidative stress on male Wistar rats. *Int J Pharm Pharm Sci* 2015;7(6):240-45.
10. Baskar R, Joseph RS, Rajesh M, Subramanian I, Palanichamy A Thangathirupathi A. Formulation and evaluation of celecoxib loaded nanosized emulsion as transdermal drug delivery vehicle. *Int J Pharm Sci Res* 2010;1:41-9.
11. Goyal A, Kumar S, Nagpal M, Singh I, Arora S. Potential of novel drug delivery systems for herbal drugs. *Ind J Pharma Res Educ* 2011;45:225-35.
12. Archer HK, Pettit MS. Analgesic and Antiphlogistic Compositions and Therapeutic Wrap for Topical Delivery. United States Patent No. 5976547.
13. Ubaidulla U, Reddy MV, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on *in vitro* and *in vivo* characteristics. *AAPS Pharm Sci Tech* 2007;8:2.
14. Deodr SD, Sethi R, Srimal RC. Preliminary study on antirheumatic activity of curcumin (diferyloyl methane). *Indian J Med Res* 1980;71:632-40.
15. Shikha A, Nidhi S, Narendra KJ, Agarwal GP. Solubility enhancement of poorly water soluble celecoxib for parenteral formulations. *Int J Pharm Sci Res* 2012;3:2325-36.