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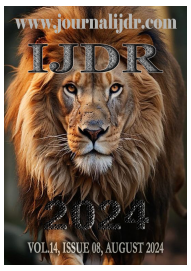

RESEARCH ARTICLE OPEN ACCESS

PREPARATION AND CHARACTERIZATION OF CELECOXIB MATRIX TRANSDERMAL PATCHES

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ABSTRACT

Transdermal Drug Delivery systems represent a category of topical, self-contained discrete dosage forms designed to deliver drugs at a controlled rate to the systemic circulation when applied to intact skin. This research reports the successful preparation of a Celecoxib transdermal patch using the solvent casting technique. Various plasticizers, including PEG, glycerol, and oleic acid, were employed in combination with different solvent ratios. The formulation incorporated polymers such as methylcellulose, guar gum, HPMC, and ERS 100. *In-vitro* release tests revealed distinct drug release rates for formulations F1, F2, F3, F4, F5, and F6 over a 6 h. Notably, formulations F3 and F6, utilizing a 30:20 ratio of Ethanol: Chloroform, demonstrated the highest solubility, efficient drug release, and no skin irritation. In contrast, formulations F1 and F2 exhibited slower drug release without causing skin irritation. Formulations F4 and F5, somewhat soluble, resulted in skin irritation. Remarkably, despite using different polymers, formulations F3 and F6, sharing the same solvent ratio and plasticizer, exhibited improved solvent characteristics, release behavior, and no skin irritation. The study concludes that adjusting the solvent type and plasticizer concentration offers a means to control the drug release rate in transdermal patches for Celecoxib, emphasizing the importance of tailored formulation parameters for therapeutic optimization.

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INTRODUCTION

Over the past decade, there has been a growing focus on controlled-release formulations, and significant advancements have been made in this technology (Begum M Y *et al*., 2011). The limitations of conventional drug delivery methods, such as toxicity, ineffectiveness, and the invasiveness of certain administration routes, have spurred increased interest in these alternative approaches. Controlled-release drug delivery systems are designed to offer predictable and reproducible drug release kinetics (Gandhi K *et al*., 2004). In response to challenges posed by traditional delivery systems, including issues related to toxicity and ineffectiveness, as well as the invasiveness of certain administration routes, controlled release formulations have garnered heightened attention and technological progress over the last decade (Gaur PK *et al*., 2009, Pandey S *et al*., 2013). Controlled-release drug delivery systems, characterized by their ability to provide consistent and predictable drug release kinetics, have emerged as a promising alternative. Transdermal drug delivery systems, in particular, have been proposed as an alternative route of administration to address the need for systemic absorption and ease of drug access (Begum MY *et al*., 2011, Moghimipour E *et al*., 2015).

Transdermal Drug Delivery systems(TDDS), represent a category of topical, self-contained discrete dosage forms designed to deliver drugs at a controlled rate to the systemic circulation when applied to intact skin (Gupta SP *et al*., 2006, SinghA *et al*., 2016). This method offers a non-invasive, convenient, and painless alternative, circumventing issues such as gastrointestinal toxicity and hepatic first-pass metabolism. The design of transdermal drug delivery systems aims to maintain therapeutic blood concentrations of the drug effectively (Begum MY *et al*., 2011, Ale I *et al*., 2009). Non-steroidal anti-inflammatory drugs (NSAIDs) constitute a pharmacological class primarily employed for pain and inflammation control in conditions like rheumatoid arthritis, exerting their effects through the inhibition of the cyclooxygenase (COX) enzyme (AjaySharma *et al*., 2012). This inhibitory action prevents the conversion of arachidonic acid to prostanoids (Ramesh Gannu *et al*., 2002). The COX enzyme exists in two subsets: COX-1, responsible for generating prostaglandins and thromboxane in most tissues, and cyclooxygenase-2 (COX-2), found in specific tissues such as the brain and blood vessels, with increased expression during inflammation or fever (Yadav V *et al*., 2012). Celecoxib specifically targets COX-2 and is administered orally for arthritis and osteoarthritis treatment, featuring a half-life of approximately 10 h and extensive binding (97%) to plasma proteins

(Yadav V *et al*., 2011, Vinod KR *et al*., 2012). The prolonged oral use of celecoxib is associated with significant gastrointestinal discomfort. In light of these considerations, an enhanced transdermal delivery system for celecoxib, characterized by heightened skin permeability, holds potential utility for treating skin inflammation locally and providing systemic treatment for inflammation in various organs (Begum MY *et al*., 2011, Moghimipour E *et al*., 2015).

MATERIALS AND METHODS

MATERIALS

Celecoxib was sourced from Prudence Pharma Chem, India, Eudrajet L 100 was obtained from Ozone chemie Pvt. Ltd, Hydroxypropyl methyl cellulose was procured from Loba chemie Pvt.Ltd, Guar gum was acquired from Loba chemie Pvt.Ltd, Methyl cellulose was sourced from Milton chemicals, Mumbai, Ethanol and chloroform were obtained from Changshu honsheng Fine Chennai Co.Ltd, Glycerol was sourced from Thermo Fisher Scientific India, Oleic acid was obtained from Nice Chemicals Pvt. Ltd, Polyethylene glycol was procured from Nice Chemicals Pvt. Ltd, Sodium chloride was sourced from Chem Ltd – Boisar India, and Potassium dihydrogen orthophosphate and hydrochloric acid were obtained from Nice Chemicals Pvt.Ltd.

Development of Patches: Transdermal patches containing Celecoxib were prepared using the solvent casting method, employing various polymers at different concentrations and different plasticizers at varying ratios (Table 1 and Table 2). Specifically, Methyl cellulose-guar gum and HPMC-E RS100 were chosen as polymers, while plasticizers such as PEG, Glycerol, and Oleic acid were incorporated (Prabhakar D *et al*., 2013). A solvent mixture, varied in ratio, was added to the polymer-plasticizer blend. Subsequently, the drug was introduced and stirred for 6 h using a mechanical stirrer (NidhiSharma, 2004, Bookya P *et al*., 2013). The resulting mixture was then poured into a glass dish and dried at a temperature range of 40°C to 42°C for 24 h. Following solvent evaporation, the patches were collected and subjected to further analysis for subsequent evaluation studies (Yasmin Begum M *et al*., 2011, Shingade GM *et al*., 2012).

Evaluation of Transdermal Patches: To address the potential impact of weight variation on drug content and in vitro behavior among the formulated patches, a study was conducted involving the weighing of 5 patches using an electronic balance (Mali AD, Bathe R, *et al*., 2015). The average weight of a patch, along with its standard deviation, was determined using the following formulas.

Table 1. Amount of ingredients used inselected patch formulations containing 0.2% Celecoxib

Formulations	Polymer	Plasticizer			Solvent
	MC: Guar gum	PEG	Glycerol	Oleicacid	Ethanol:chloroform
F1	0.3:0.5	1ml	-	-	20:30
F2	0.3:0.5	-	1ml	-	25:25
F3	0.3:0.5	-	-	1ml	30:20

Table 2. Amount of ingredients used in selected patch formulations containing 0.2% Celecoxib

Formulations	Polymer	Plasticizer			Solvent
	HPMC:ERs100	PEG	Glycerol	Oleicacid	Ethanol:chloroform
F4	0.3:0.5	1ml	-	-	20:30
F5	0.3:0.5	-	1ml	-	25:25
F6	0.3:0.5	-	-	1ml	30:20

METHODOLOGY

The prepared patches were evaluated for their physico-chemical parameters, *in-vitro* diffusion studies, skin irritation and, stability studies.

Physicochemical Parameters

Standard Calibration Curve: A standard stock solution of Celecoxib was prepared at a concentration of 100 µg/ml in methanol. From this stock solution, working standard solutions were further diluted to concentrations ranging from 2 to 20 µg/ml using methanol, distilled water containing 1% Sodium Lauryl Sulfate (SLS), and phosphate buffer at pH 7.4. The calibration curve for Celecoxib was constructed by plotting the absorbance against the concentration at 251 nm, using a PerkinElmer Lambda 25 UV/VIS Spectrometer. Regression analysis was then performed to determine the concentration of Celecoxib in the samples (Shaikh A *et al*., 2019).

Infra-red Spectroscopy Incompatibility Study: FTIR serves as a straightforward methodology for discerning variations in drug-polymer interactions, where the disappearance, reduction, or emergence of absorption peaks within the IR spectrum indicates the presence of such interactions between the Active Pharmaceutical Ingredient (API) and thepolymer (Ezhumalai K *et al*., 2011, GannuR *et al*., 2007). The solid-state IR spectrum of the drug was acquired using a potassium bromide dispersion method. The bands (cm-1) were assigned after the samples were meticulously ground and mixed with potassium bromide at a ratio of 1:100 (sample: KBr). Subsequently, KBr discs were prepared by compressing the powders under a force of 15 tons for 5 mins using a hydraulic press (Govil SK., 1988, Arunachalam A *et al*., 2013).

Average weight of each patch = total weight of 5 patches/5 (Arora P *et al*., 2002).

Standard deviation = $\sqrt{\sum(\boldsymbol{x}-\boldsymbol{X})\boldsymbol{2n}-\boldsymbol{1}}$

Where x = weight of individual patch
X = average weight
n = number of patches

Percentage of Moisture Content: Each film was individually weighed and placed in a desiccator with anhydrous calcium chloride at room temperature for 24 h. The individual films were subsequently weighed repeatedly until a constant weight was achieved. The percentage of moisture content was determined by calculating the difference between the initial and final weights, relative to the final weight (Peddapalli H *et al*., 2014, Amnuaikit C *et al*., 2005).

Drug Content: The film was segmented into small pieces, placed into a 100ml buffer solution with a pH of 7.4, and continuously shaken for 24 h. Subsequently, the solution underwent filtration, and the drug content was assessed at a wavelength of 251nm after the filtration process (Gupta R *et al.,* 2003, Kusum Devi V *et al*., 2003).

Film Thickness: The thickness of each of the five films was measured at five different locations using a dial caliper, and the mean value was calculated (Verma PR *et al.,* 2000, Pravin Gavial A *et al.,* 2010).

Folding Endurance: The assessment of folding endurance entails gauging the folding resilience of films exposed to frequent and rigorous folding conditions. It is determined by iteratively folding the film at a consistent location until it breaks. The folding endurance value is then derived from the count of how many times the films can

be folded at the same spot without breaking (Vamshi Vishnu Y *et al*., 2007).

In-vitro Permeation Studies: *Invitro* permeation studies were conducted using a Franz diffusion cell, which comprises a donor compartment and a receptor compartment. A cellulose membrane (45) was positioned between these compartments. The formulated patches were applied over the membrane, and the receptor compartment was filled with phosphate buffer at pH 7.4 (Trivedi D *et al.,* 2020). The entire assembly was affixed to a magnetic stirrer, where the solution in the receptor compartment was consistently stirred using a magnetic bead at 50 rpm, maintaining the temperature at 37 ± 1°C. Samples were withdrawn at various time intervals and analyzed for drug content. The receptor phase was replenished with an equal volume of phosphate buffer after each sample withdrawal. The cumulative amount of drug permeated per square centimeter of patches was plotted against time (Gandhi K *et al.,* 2012).

Skin irritation studies: Male Wistar rabbits (350–450 g) were used for skin irritation tests in this study. The animals, sourced from Nandha College of Pharmacy, Erode, were kept in controlled conditions with a temperature of 23±2°C, 50±5% humidity, and a 12-hour light-dark cycle. They were acclimatized for seven days before the study and randomized into experimental, normal, and control groups, housed individually in sanitized polypropylene cages with sterile paddy husk bedding. They had unrestricted access to standard pellets and drinking water. To minimize stress, the animals were habituated to laboratory conditions 48 hours before the experiment. The study was approved by the Institutional Animal Ethical Committee (IAEC) of Nandha College of Pharmacy (Approval No. NCP/IAEC/UG 2022-23/07). Testing for skin irritation and sensitization can be conducted on healthy rabbits with an average weight ranging from 1.2 to 1.5 kg. The dorsal surface (50 cm^2) of the rabbit is prepared by cleaning and removing hair through shaving. Subsequently, the surface is cleaned with rectified spirit, and the respective formulations are applied to the cleaned dorsal skin. After 24 h, the patch is removed, and the skin is observed, categorized into five grades based on the severity of any observed skin injury (Amnon C *et al.,* 2003).

RESULTS

Physicochemical parameters

Preparation of Standard Curve of Celecoxib: A standard curve (Figure 1) was established by plotting absorbance at 251 nm against various concentrations. The calibration curve exhibited linearity across different concentrations within the range of 10-50 µg/ml. The slope of the curve is 0.0129, and a high correlation coefficient of 0.996 was observed.

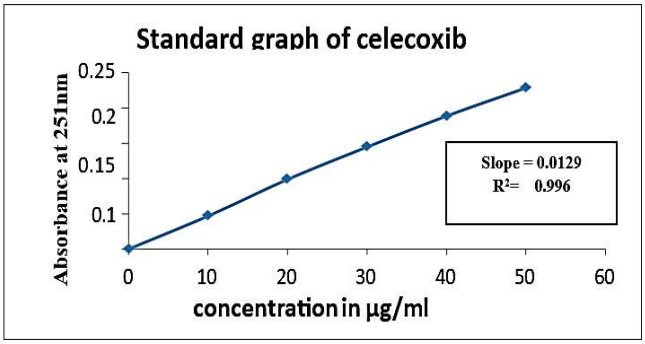

Figure 1. Standard graph of celecoxib

Infrared Spectroscopy: The presence of all characteristic peaks of Celecoxib, in IR spectra obtained with Celecoxib and the other excipients confirms the intactness of the drug in the polymer matrix (Table 3).

Table 3. IR spectra obtained with Celecoxib and the other excipients

Transition	Absorption wave number (cm^{-1})				
	Celecoxib	Eudragit	Methyl cellulose	HPMC	Guargum
C=Cstretching	1446.51	1456.16	1645.67	-	-
C-Fstretching	1164.92	-	-	-	-
C-H bending	1446.51	1456.16	1419.51	1456.16	1458.08
C-NStretching	2864.09	-	-	-	-
C=O Stretching	-	-	1747.39	1716.53	1747.39
C-H Stretching	2738.73	2952.81	2839.02	2846.74	2871.81
C-O Stretching	-	1064.63	1062.70	1020.07	1012.56

Evaluation of Transdermal Patches

Appearance of the Film: The overall appearance of transdermal patches (Figure 2) was found to be clear and transparency was good which shows that the drug was distributed uniformly.

Figure 2. Appearance of the film

Weight Variation: Six patches of the formulation (F3, F6) containing the same solvent ratio (ethanol: chloroform-30:20) were found to increase weight variation (Table 4) as per standard value, when compared to other solvent ratios.

Table 4. Weight Variation

Formulation	Weight variation (mg)
F1	0.498±0.0120
F2	0.398±0.0207
F3	0.145±0.0189
F4	0.354±0.0240
F5	0.402±0.0119
F6	0.201±0.0195

Mean±SD

Percentage Moisture Content: The percentage moisture content of all formulations (F1-F6), and formulations (F3,F6) containing the same solvent ratio was found to be decreased moisture content (Table 5) as per standard value when compared to other solvent ratios.

Table 5. Percentage Moisture Content

Formulation	%Lossofmoisture content
F1	0.56±0.060
F2	0.499±0.055
F3	0.245±0.020
F4	0.956±0.085
F5	0.796±0.080
F6	0.43±0.017

Mean±SD

Drug Content Determination: The amount of drug content determination for the formulation (F3, F6) containing the same plasticizer such as oleic acid showed increased drug content (Table 6) when compared to other formulations.

Table 6. Drug Content Determination

Formulation	Drugcontent determination
F1	65.12%
F2	72.70%
F3	83.54%
F4	67.12%
F5	73.18%
F6	77.12%

Film Thickness: The formulation (F3, F6) containing the same plasticizer such as oleic acid was found to increase the film thickness (Table 7) when compared to other formulations as per the standard value (230 – 830µm).

Table 7. Film Thickness

Formulation	Thicknessin (µm)
F1	170
F2	136
F3	339
F4	223
F5	110
F6	340

Folding Endurance: The formulation (F3,F6) containing the same plasticizer such as oleic acid was found to have increased folding endurance (Table 8) as per standard value when compared to other formulations.

Table 8. Folding Endurance

Formulation	Foldingendurance
F1	245
F2	238
F3	310
F4	250
F5	230
F6	312

***In-vitro* release study:** The findings from dissolution studies reveal that formulations F1, F2, F4, F5, and F6 release the drug at rates of 67.52%, 64.58%, 56.31%, 58.35%, and 88.35% in 6 h, respectively, Figure 3. Notably, our modified patch formulations, F3 and F6, demonstrated drug release percentages of 91.54% and 88.35%, respectively, within the same time frame. Consequently, the drug release for formulations F3 and F6 was extended compared to the other formulations.

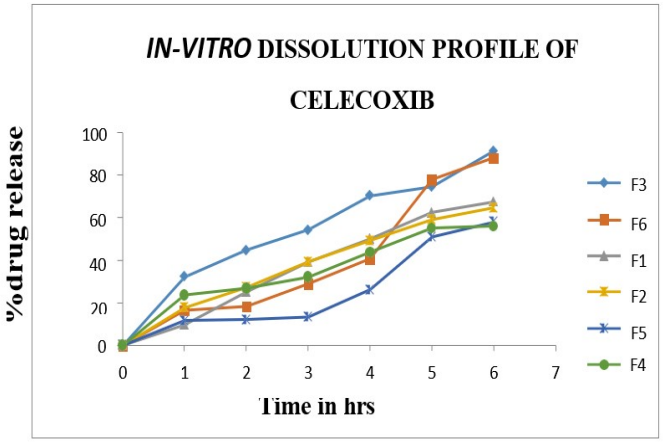

Figure 3. *In-vitro* Dissolution Profile of Celecoxib

Skinirritation Test: Skin irritation studies for the formulated patches (F1 to F6) were performed on the dorsal surface of the rabbit body. Formulations F1, F2, F3, and F6 do not produce skin irritation. Formulations F4 and F5 produce skin irritation (Figure 4).

DISCUSSION

The standard calibration curve of Celecoxib established in this study confirms the drug's adherence to Beer's law within the concentration range of 10-50 µg/ml in phosphate buffer at pH 6.8. This linear relationship is crucial for ensuring accurate and reproducible quantification of Celecoxib in various formulations. The high correlation coefficient (R^2=0.996) underscores the reliability of the method used for drug quantification. Similar studies often report calibration curves for Celecoxib with comparable linearity and correlation coefficients, indicating consistent methods for quantifying Celecoxib concentration in transdermal formulations. The FTIR analysis revealed no significant interactions between Celecoxib and the polymers used (Methylcellulose, HPMC, Guar gum, and Eudragit), as indicated by the presence of all characteristic peaks of Celecoxib in the IR spectra. This confirms the chemical stability of Celecoxib within the polymer matrix, which is essential for maintaining the drug's therapeutic efficacy in transdermal patches. Consistent with other studies, which typically show no significant chemical interactions, ensuring stability and compatibility of the drug within the polymer matrix.

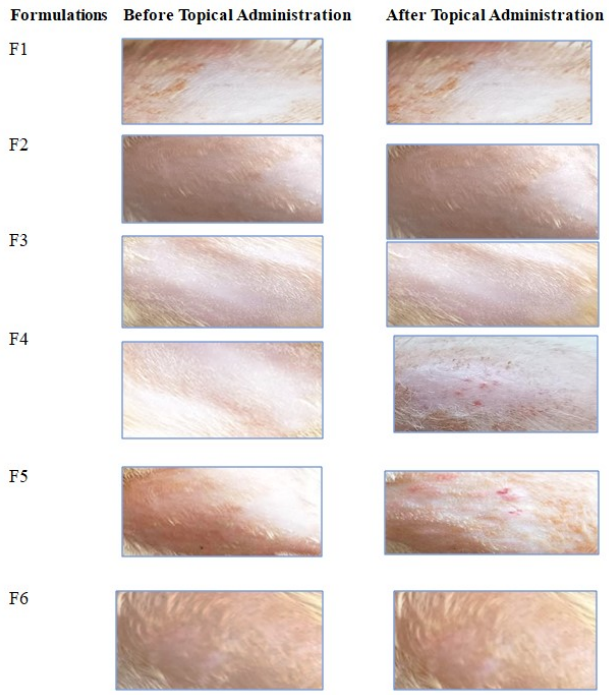

Figure 4. Skin Irritation Test

The solvent casting method used for preparing the transdermal patches of Celecoxib involved the use of various polymers and plasticizers. The selection of Methyl cellulose-guar gum and HPMC-E RS100 polymers, along with plasticizers like PEG, Glycerol, and Oleic acid, was aimed at optimizing the mechanical properties and drug release profile of the patches. The study found that the patches formulated with a solvent ratio of ethanol: chloroform (30:20) showed increased weight variation, indicating a need for further optimization to ensure uniform drug distribution and consistent dosing. Weight variation is a common issue in solvent-cast films, with other studies also reporting similar challenges and emphasizing the need for optimization to achieve uniform drug distribution. Formulations F3 and F6 exhibited decreased moisture content, which is desirable for maintaining the stability and shelf-life of the patches. Low moisture content is generally desired and reported in many studies to improve the stability and shelf-life of transdermal patches. The drug content was highest in formulations F3 (83.54%) and F6(77.12%), both containing Oleic acid as a plasticizer. This indicates that Oleic acid may enhance drug incorporation into the polymer matrix, ensuring adequate drug loading in the patches. Formulations F3 and F6, which included Oleic acid, had increased film thickness. This suggests that Oleic acid contributes to the formation of thicker films, which can affect the drug release rate and mechanical strength of the patches. Consistent with the literature were formulations with plasticizers like Oleic acid exhibit high mechanical strength and flexibility. The folding endurance was also highest for formulations F3 and F6, indicating good mechanical strength and flexibility. High folding endurance is critical for ensuring the patches remain intact during handling and application. Formulations F1, F2, F3, and F6 did not produce any skin irritation, demonstrating their safety for topical application. However, formulations F4 and F5 caused skin irritation, highlighting the importance of excipient selection in transdermal patch formulation. The *in-vitro* permeation studies using a Franz

diffusion cell revealed that formulations F3 and F6 exhibited the highest drug release rates (91.54% and 88.35% in 6 h, respectively). The enhanced drug release observed with these formulations can be attributed to the presence of Oleic acid, which likely acts as a penetration enhancer, facilitating greater drug permeation through the skin.

CONCLUSION

The study successfully developed and evaluated transdermal patches of Celecoxib, highlighting the critical role of formulation components in determining the physicochemical properties, drug content, mechanical strength, and in-vitro drug release profile of the patches. Formulations F3 and F6, which incorporated Oleic acid, demonstrated superior performance in terms of drug content, film thickness, folding endurance, and in-vitro drug release, making them promising candidates for further development. The absence of skin irritation in these formulations further supports their potential for safe and effective transdermal delivery of Celecoxib. Future studies should focus on optimizing the formulation to minimize weight variation and exploring *in-vivo* efficacy and pharmacokinetics to confirm the therapeutic benefits observed *in-vitro*.

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Conflict of Interest: The authors declare no conflicts of interest relevant to this article.

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