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Research Article

FORMULATION AND EVALUATION OF CREAMS CONTAINING CELECOXIB INCLUSIONS FOR TREATING PSORIATIC ARTHRITIS

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ABSTRACT

Objective: The main objective of the present work was to prepare and evaluate 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 creams. Cocoa butter, triethanolamine, stearic acid, methylparaben, gum acacia, and coconut oil were used in cream preparation. Fourier transform infrared and differential scanning calorimetry studies were carried out for pure celecoxib and inclusions. Viscosity, pH, homogeneity, and type of emulsion under dye test were evaluation parameters done for creams.

Results: All the results obtained were within the limits and confirmed 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, Creams, Celecoxib, Inclusions.

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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]. PsA is a seronegative inflammatory arthropathy that occurs in 5–7% of people with psoriasis [3,4]. It is thought that environmental triggers which are infectious in nature, triggers 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 ultraviolet A (PUVA) [6]. Available drugs are corticosteroids, tacrolimus, tumor necrosis factor inhibitors, methotrexate, and sulfasalazine [7]. The disadvantages of these drugs are the radiation can dry out the skin and cause itching and redness, burning, blistering of the skin, etc. [8]. Celecoxib is a cyclooxygenase-2 (COX-2)-specific inhibiting agent that inhibits the conversion of arachidonic acid to the prostaglandins that mediate pain and inflammation [9]. In theory, a drug such as celecoxib that selectively inhibits COX-2 might block inflammation, pain, and fever [10]. Creams refer to disperse systems, in which one insoluble phase is dispersed as droplets in a second liquid phase. Creams are often preferred over other topical preparations because they are less irritating and easy to apply [11]. β-cyclodextrins are widely used in the pharmaceutical field for their ability of improving the solubility and the stability of drugs by complex formation at the solid state [12]. The use of cyclodextrins and their derivatives can encapsulate the bioactive compounds and protect the compounds from environmental conditions and improves the aqueous solubility and increases their capacity to function [13]. In the present study, an attempt has been made to develop inclusions (complexes) of celecoxib using β-CD. These inclusions are prepared to increase the solubility of the drug which is poorly water soluble. Prepared inclusions are incorporated into creams to obtain formulations for which further evaluation studies have been conducted.

METHODS

Celecoxib is a gift sample obtained from Wexford Laboratories Pvt., Ltd., Bengaluru. β-cyclodextrin was obtained from HiMedia, India. Cocoa butter was procured Rolex Chem Industries, India. Stearic acid and methylparaben were obtained from Qualikems Fine Chemicals Pvt. Ltd., Vadodara. Gum acacia was obtained from SD Fine-Chem Limited, Mumbai, triethanolamine from Pallav Chemicals and Solvents Pvt., Ltd., Boisar, India, and coconut oil from Herbs Nutri Products Pvt., Ltd., Mumbai.

Methodology

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±0.5°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 μg/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 μg/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

FT-IR 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/cm^2 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 were taken in nitrogen atmosphere at the heating rate of 10°C min^{-1}. The energy was measured as J/Kcal. It was performed for pure celecoxib drug and F2 formulation.

Preparation of celecoxib cream
Oil-in-water (O/W) emulsion-based cream (semisolid formulation) was formulated. The emulsifier (stearic acid) and other oil-soluble components (cocoa butter, acetyl alcohol, and coconut oil) were dissolved in the oil phase (Part A) and heated to 75°C. The preservatives and other water-soluble components (methylparaben, triethanolamine, propylene glycol, and drug celecoxib inclusions) were dissolved in the aqueous phase (Part B) and heated to 75°C. After heating, the aqueous phase was added in portions to the oil phase with continuous stirring and perfume was added [14]. The formulations of different creams prepared are given in Table 1.

Evaluation of creams
Type of emulsion under dye test
The scarlet red dye is mixed with the cream. A drop of the cream was placed on a microscopic slide and then it was covered with a cover slip and examined under a microscope. If the disperse globules appear red and the ground is colorless, the cream is O/W type. The reverse condition occurs in W/O type cream, i.e., the disperse globules appear colorless in the red ground [15].

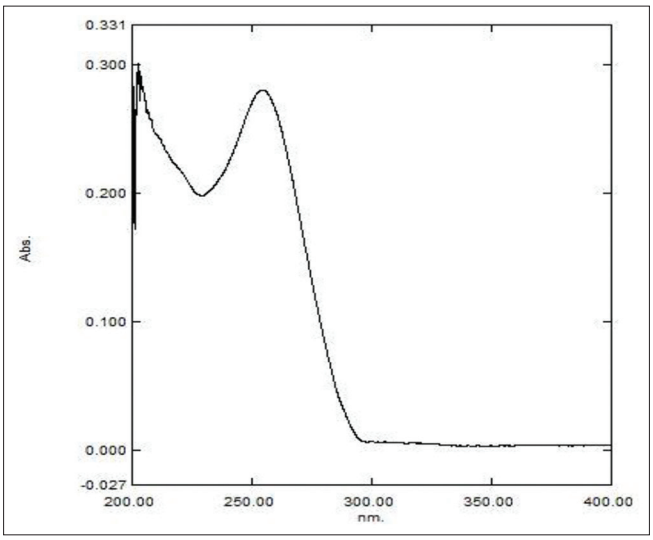

Fig. 1: Ultraviolet spectra of celecoxib in pH 7.4 phosphate buffer

Table 1: Formulation chart of creams (F1-F3)

S. No.	Ingredients	F1	F2	F3
1.	Celecoxib inclusions (mg)	50	50	50
2.	Cocoa butter (g)	1	2	3
3.	Stearic acid (g)	1	2	3
4.	Gum Acacia (%)	0.5	1	1.5
5.	Coconut oil (ml)	2	2	2
6.	Methylparaben (%)	1	1	1
7.	TEA (ml)	0.5	0.5	0.5

Appearance
The appearance of the cream was judged by its color, opalescence, and roughness and graded [15].

Homogeneity
The formulations were tested for the homogeneity by visual appearance and by touch [15].

pH
The pH meter was calibrated using standard buffer solution. About 0.5 g of the cream was weighed and dissolved in 50.0 ml of distilled water and its pH was measured [15].

Viscosity
Viscosity of the formulation was determined by Brookfield Viscometer at 100 rpm, using spindle no. 7 [15].

In vitro drug diffusion studies
The F2 cream was permeated through a dialysis bag. A 0.5 g of cream was taken in the bag and is placed in a beaker containing phosphate buffer of pH 7.4 and constantly stirred with a small magnetic bead. During the experiment, temperature was maintained at 37±0.5°C to simulate the human skin condition. A 5 ml of samples were withdrawn at 0.5, 1, 2, 6, and 12 h and replaced with fresh receptor solution. The samples withdrawn were analyzed spectrophotometrically at 235 nm. The amount of drug released was calculated and the percentage drug released was plotted against time.

Similarly, it was done for pure drug.

Statistical analysis (Analysis of variance [ANOVA])
Both the study and control groups were compared. ANOVA is performed for cream F2 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. The results are given in Table 2.

Evaluation studies
Type of emulsion
Prepared cream was found to be O/W emulsion. It shows that the cream has good spreadability and penetration on applying on the skin. Furthermore, it can be washed of easily.

Appearance
Prepared creams were light cream in color, opaque.

Homogeneity
Prepared creams are homogenous. No aggregates are present in the formulation.

pH
pH of the prepared creams was in the range of 6–7. It shows that obtained pH is near to skin pH and it does not cause any skin irritation.

Table 2: Solubility studies for celecoxib

Concentration of celecoxib in water (µg/ml)	Concentration of celecoxib in pH 7.4 (µg/ml)
6.87 (0.01)	13.55±0.0057

*n=3 [16]

Viscosity

It was carried out by Brookfield Viscometer. Obtained viscosity was in the range of 2020–2060. It shows that F3 has higher viscosity (2060) and F1 has lowest (2020).

All the obtained results are given in Table 3.

From the above results, it was found that F2 cream has high viscosity. Hence, it is considered for further studies such as FTIR and DSC. F2 cream formulation is shown in Fig. 2.

FT-IR studies

The characteristic peaks of pure celecoxib and F2 formulation are shown in Fig. 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 displaced peak of drug.

Fig. 2: Prepared cream formulation (F2)

***In vitro* drug release studies**

In vitro drug release studies were carried out for both F2 formulation and pure drug. Pure drug has shown drug release for 8 h and after that no release was noticed, whereas F2 formulation has shown release till 24 h (Max 91.78%). In case of F2 formulation, drug release occurred in prolonged manner. In the beginning, drug which is not encapsulated in the inclusions got released. This is the reason for increased % drug release during initial hours. 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 F2 formulation and pure drug is given in Table 4 and Fig. 7.

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.

Table 3: Evaluation results of creams

S. No.	Evaluation studies	F1	F2	F3
1.	Appearance	Light cream	Light cream	Light cream
2.	Homogeneity	No aggregates	No aggregates	No aggregates
3.	Viscosity	2020	2040	2060
4.	pH	6	7	7

Table 4: *In vitro* % drug release

S. No.	Time	F5	Pure drug
1.	0	0.00	0.00
2.	0.5	89.72	14.23
3.	1	76.98	28.45
4.	2	63.42	41.67
5.	4	59.43	54.82
6.	8	71.12	67.75
7.	12	82.43	-
8.	24	91.78	-

Table 5: Statistical analysis (ANOVA)

Newman–Keuls multiple comparison test	Mean difference	q	Significant ($p<0.05$)
F2 versus pure drug	−20.16	37.42	Yes

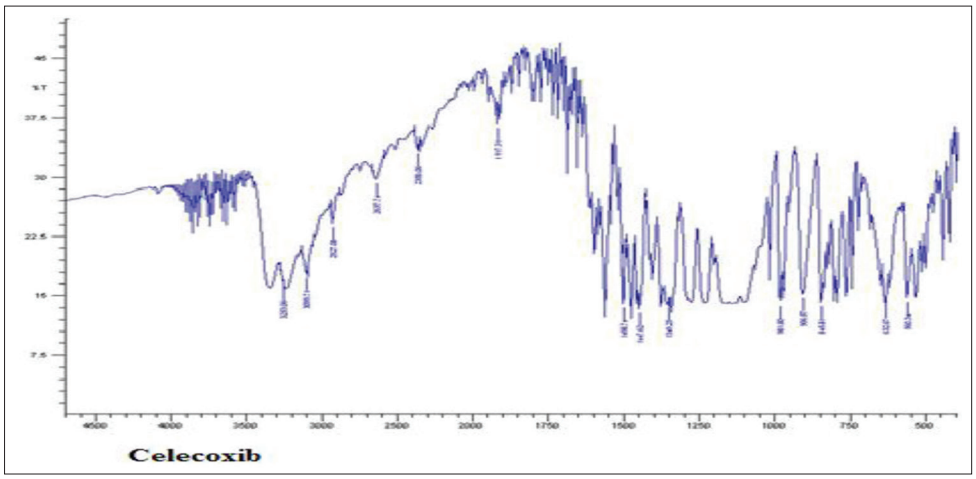

Fig. 3: Fourier transform infrared spectral data of pure celecoxib

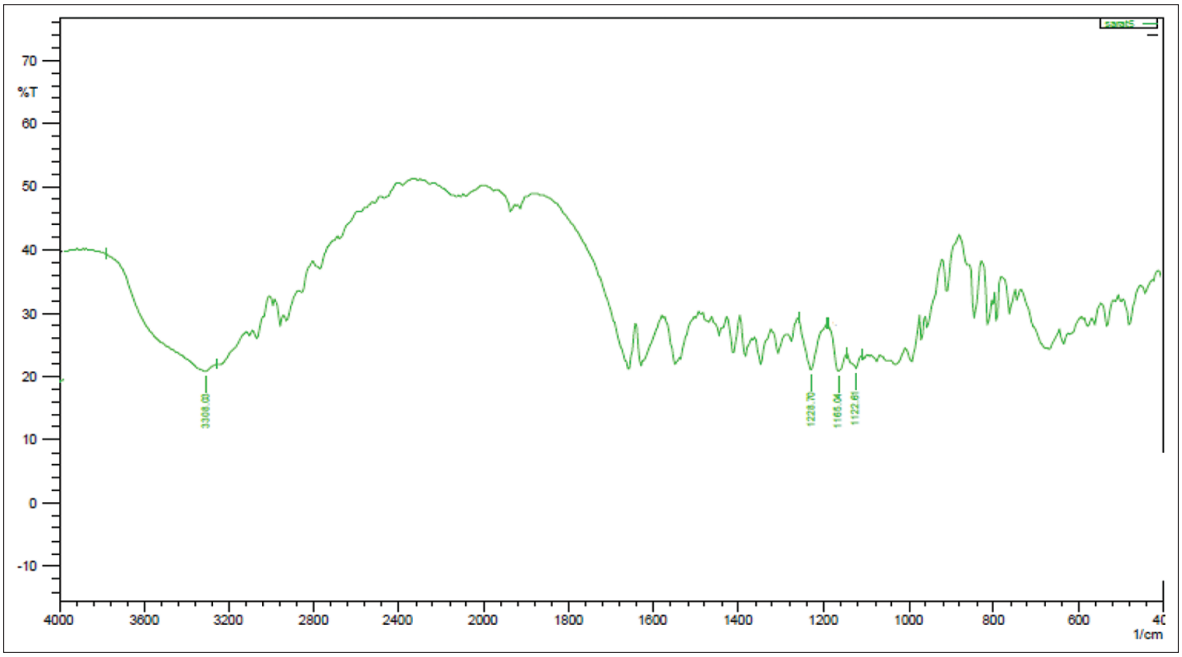

Fig. 4: Fourier transform infrared spectra of F2 formulation

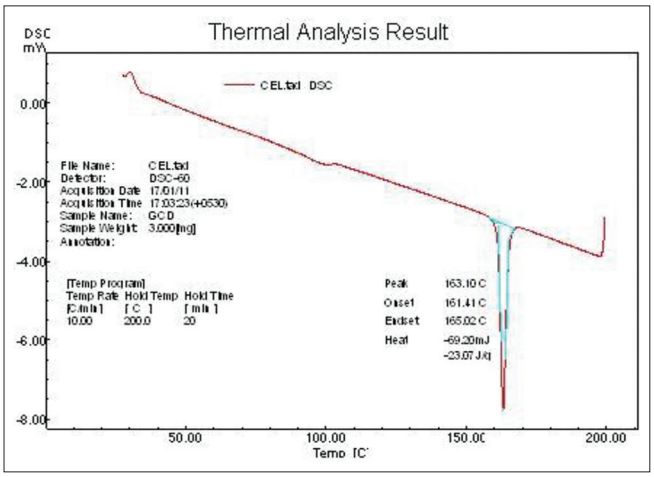

Fig. 5: Differential scanning calorimetry thermogram of pure celecoxib

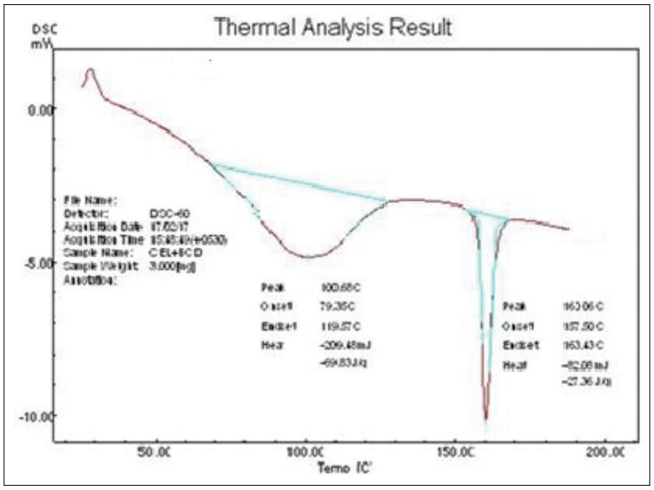

Fig. 6: Differential scanning calorimetry thermogram of F2 formulation

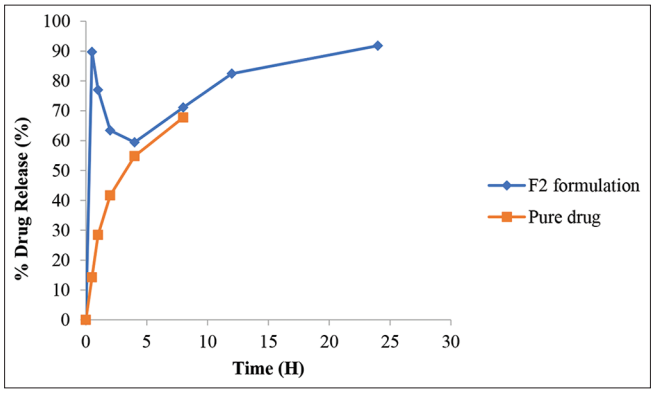

Fig. 7: Comparison of drug release between F2 formulation and pure drug

CONCLUSION

Solubility of celecoxib drug was increased by forming inclusions using β-CD as polymer. This further leads to increased bioavailability. From FT-IR 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 prepared creams were having good spreadability and no skin irritation on 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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