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Research Article

TRANSDERMAL DELIVERY OF CALCIUM CHANNEL BLOCKER: DEVELOPMENT AND CHARACTERIZATION

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ABSTRACT

Objective: Felodipine, a BCS class II calcium channel blocker, is used in the management of hypertension and angina pectoris. Due to the poor solubility and low bioavailability of the drug, there is a necessity to design an alternative route to achieve a constant plasma concentration of felodipine for its maximum therapeutic utility and can be achieved by transdermal route.

Methods: In this study, matrix type transdermal patches were prepared using different combinations of hydrophilic polymer, namely, polyvinylpyrrolidone (PVP) and hydrophobic polymer, namely, ethyl cellulose (EC) by solvent evaporation technique and were subjected for characterization.

Results: The Fourier transform infrared studies confirmed the compatibility between drug and polymers. Hydrophilic nature of the polymers greatly influenced physical characteristics and dissolution rate. Equal percentage of PVP and EC yielded patches with good folding endurance. The concentration of plasticizer present in the patches gave them desired folding endurance, and it increased with the presence of hydrophilic polymer. The formulation with highest PVP concentration, F3, exhibited a maximum drug release of 96.23% for 24 hrs. While the formulation with highest EC concentration, F5, exhibited only 74.45% drug release for 24 hrs.

Conclusion: From the data, formulation F2 (PVP/EC, 2:1) can be concluded as best formulation due to its desired physical characteristics, good initial drug release, sustained release behavior, and good *in vitro* permeation. This formulation can be further studied in a clinical scenario.

Keywords: Calcium channel blocker, Felodipine, Transdermal, Permeation.

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INTRODUCTION

Sustained release preparations were developed intended to provide prolonged drug release than the conventional dosage forms. In prolonged treatment of hypertension (high blood pressure), they are highly recommended and commercially available mostly in the form of conventional tablets [1]. An approach to sustained delivery of a therapeutically active agent is transdermal drug delivery system [2]. They provide relatively constant plasma drug concentrations, avoiding the peaks and valleys associated with conventional dosage forms. They also offer advantages such as decrease in frequency of administration, avoiding first-pass metabolism, reducing gastrointestinal side effects, and improving patient compliance [3]. Skin is the most magnanimous and readily accessible organ of human body and is used as an administration site of drug for both local and systemic actions; the highly organized structure of stratum corneum forms an effective barrier to the permeation of poorly penetrating drugs [4-6].

Felodipine, BCS class II drug, a calcium channel blocker is primarily used to treat hypertension and also used in the treatment of angina, arrhythmia, and coronary vasospasm [7]. It acts by inhibiting the influx of calcium in smooth muscle cells and prevents calcium-dependent myocyte contraction and vasoconstriction. Due to its low bioavailability and short half-life, it needs to be frequently administered creating patient incompliance [8]. It possesses ideal characteristics for being formulated as transdermal patch, such as low molecular weight (384.25), low dose (5 mg), and low solubility and bioavailability (15%), and undergoes extensive first-pass metabolism [9].

The objective of the present study is to fabricate a novel transdermal delivery system for treating hypertension, which achieves a prolonged drug release and effective management of hypertension, while at the same time by reducing the frequency and dose of administration. The objective includes designing more patient friendly delivery system of felodipine for sustained release using a combination of hydrophilic and hydrophobic polymers.

MATERIALS AND METHODS

Materials

Felodipine was obtained from Orchid Chemicals and Pharmaceuticals Ltd. as a gift sample. Ethyl cellulose (EC), polyvinylpyrrolidone (PVP), and polyvinyl alcohol (PVA) were procured from Sigma Aldrich, Mumbai, India, and all other chemicals and reagents used were of analytical grade.

Determination of partition coefficient

Shake-flask method was employed to determine the partition coefficient of the drug using n-octanol and phosphate buffer pH 7.4 as oil and water phases, respectively. Equal quantities of two phases were taken in a separating funnel. A known quantity of felodipine was added and shaken for 10 minutes and allowed to stand for an hour. Aqueous and oil phases were separated and filtered through Whatman filter paper. The samples were analyzed for drug content in each phase. The partition coefficient $k_{o/w}$ was calculated using the formula. Triplicate reading was taken, and average was calculated [10,11].

$$K_{o/W} = \frac{\text{Drug concentration in octanol}}{\text{Drug cencentration in phosphate buffer 7.4}}$$

Infrared spectral analysis

Compatibility studies of felodipine and the polymers were carried out using Fourier transform infrared (FTIR) spectroscopy. Spectroscopy of

the samples was obtained in the range of 4000/cm to 400/cm using a PerkinElmer-FTIR 8201 PC spectrophotometer by the KBr disc method [12].

Preparation of transdermal patches

Different ratios (Table 1) of PVP and EC were taken in the open-ended cylindrical glass molds to prepare the matrix type transdermal patches of felodipine. Backing membrane was cast by pouring 4% w/v of PVA solution in the molds previously wrapped with aluminum foil. It was allowed to dry at 60°C in hot air oven for 6 hrs. The two polymers were taken in requisite ratio and dissolved in chloroform. Di-n-butyl phthalate was taken in 30% w/w of polymer composition and used as plasticizer. Drug was added, 20% w/w of polymer composition, to form homogenous dispersion with plasticizer and polymers. Three milliliters of dispersion were cast on previously prepared PVA backing membrane and dried at 40°C for 6 hrs. The prepared patches were kept in desiccators until used [13].

Thickness

Thickness of both the backing membrane and patch was measured using digital calipers. The average thicknesses of the backing membrane and the whole patch were determined [14,15]. The average thickness of the adhesive matrix containing the drug was determined using the following equation:

Thickness of adhesive matrix=Thickness of whole patch−Thickness of backing membrane

Moisture content

The prepared patches were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hrs. The individual films were weighed again until it showed a constant weight [16]. The percentage of moisture content was calculated as:

$$\%\text{Moisture content} = \frac{\text{Intail wt of the film - Final wt of the film}}{\text{Initial wt of the film}} \times 100$$

Moisture uptake

The patches were weighed and kept in a desiccator at normal room temperature for 24 hrs. This patch was taken out and exposed to 84% RH (saturated solution of potassium chloride) in a desiccator. After 3 days, the patches were taken out and weighed [17]. The percentage of moisture uptake was calculated as:

$$\%\text{Moisture uptake} = \frac{\text{Final wt of the film} - \text{Initial wt of the film}}{\text{Initial wt of the film}} \times 100$$

***In vitro* drug release study**

In vitro drug release study was performed using US Pharmacopeia Type V dissolution apparatus (Paddle over disc). The patches were placed in between the stainless steel discs (of which one side is mesh and one side is plate stainless steel disc, meant for transdermal study). To the stainless steel plate, the backing membrane was attached with a double-sided adhesive tape so that drug releases from one side only. The drug release study was performed at 37±0.5°C and 50 in dissolution jar holding 900 ml of 20% v/v polyethylene glycol (PEG) 400 in normal saline as dissolution medium. A 5 ml of sample was withdrawn at regular time intervals and replaced with 5 ml of 20%v/v PEG400 in normal saline. The samples were analyzed to calculate the quantity of drug released. The mean cumulative amount of drug released of patch was plotted against time [18].

***Ex vivo* permeation**

Franz diffusion cell was used to study the permeation of transdermal patch. Full thickness of rat abdominal epidermis was mounted onto a Franz diffusion cell. Place the patch in such a way that stratum corneum side of rat skin was in contact with transdermal patch in the donor compartment and the dermis side was in constant contact with the receptor solution. The receptor compartment was filled with 20% v/v PEG 400 in normal saline and stirred magnetically. A 1 ml of sample was withdrawn at different time intervals and analyzed for drug content and replaced with an equal volume of 20% v/v PEG 400 in normal saline at each time interval. The cumulative amount of drug permeated was calculated for 12 hrs and plotted against time [19].

Statistical analysis

All data were represented as the mean ± standard deviation. The graphs and error bars were depicted using GraphPad Prism 5 software (GraphPad Software, Inc., San Diego, CA).

RESULTS AND DISCUSSION

To determine the drug partition coefficient between skin and *in vitro* study fluid, octanol and phosphate buffer pH 7.4 were considered to be a standard system. The studies were conducted in triplicate. The mean value of all these experiments was considered as partition coefficient. The log P of felodipine was found to be 4.46. The log P clearly indicates that felodipine possesses optimum lipophilic nature to be formulated into a transdermal delivery system.

The spectrum of pure drug shows absorption band at 3389/cm due to the stretching N-H group of dihydropyridine moiety. The band between 2946/cm and 3070/cm was due to stretching aromatic and aliphatic C-H bond. The absorption band at 1694/cm can be attributed to carbonyl group present on the side chain of dihydropyridine moiety. The band at 1495/cm was due to aromatic C=C bond. The bands present at 1204/cm indicate C=O stretching. The spectrum of the mixture showed that they were in good agreement with the spectra of felodipine. Thus, from the spectra in Fig. 1, it was understood that there was no significant interaction between felodipine and polymers used in the preparation of transdermal patches.

PVP and EC combination was also preferred in preparation of transdermal patches for sustaining the release of diclofenac [20]. The transdermal patches for felodipine were analyzed for various physical characterizations such as moisture content, moisture uptake, thickness, and folding endurance. The summary of the characterization parameters was given in Table 2. The moisture content and moisture uptake studies on patches revealed that an increase in the concentration of PVP resulted in high moisture content and high moisture uptake ability (Fig. 2).

On the other hand, the formulations exhibited, increasing the EC proportion resulted in patches with low moisture uptake ability. This can be attributed to the hydrophilic nature of PVP and hydrophobic

Table 1: Formulation of transdermal patches

Formulation code	Ratio of PVP:EC	Total weight of PVP and EC (mg)	Chloroform (ml)	Di-n-butyl phthalate (ml)	Felodipine (mg)
F1	1:1	250	10	30% w/w of polymers	20% w/w of polymers
F2	2:1	250	10	30% w/w of polymers	20% w/w of polymers
F3	5:1	250	10	30% w/w of polymers	20% w/w of polymers
F4	1:2	250	10	30% w/w of polymers	20% w/w of polymers
F5	1:5	250	10	30% w/w of polymers	20% w/w of polymers

PVP: Polyvinylpyrrolidone, EC: Ethyl cellulose

Table 2: Physical characterization of transdermal patches

Formulation code	Folding endurance*	Thickness* (mm)	Percentage moisture content* (%)	Percentage moisture uptake* (%)
F1	177±12	0.189±0.25	5.90±0.10	11.28±0.01
F2	189±31	0.201±0.98	7.36±0.12	12.33±0.12
F3	223±15	0.240±0.23	8.01±0.05	16.91±0.05
F4	171±18	0.199±0.73	3.46±0.29	6.38±0.26
F5	169±09	0.233±0.59	1.28±0.06	4.79±0.21

*Data were presented as mean±standard deviation (n=6)

Table 3: *In vitro* dissolution profile of transdermal patches

Time (hrs)	Cumulative drug release (%)				
	F1	F2	F3	F4	F5
0.5	6.02±1.13	12.21±1.51	15.60±1.09	4.25±1.83	4.28±1.52
1	12.08±2.26	23.02±1.62	24.21±1.50	11.56±1.12	8.65±1.93
2	29.23±1.39	37.29±1.43	34.23±1.46	19.24±1.72	13.47±1.27
4	36.89±1.42	41.35±2.30	53.24±1.77	32.29±2.38	26.02±2.48
8	50.35±2.16	54.24±1.19	68.03±3.33	48.89±1.55	43.09±1.61
12	62.64±2.96	76.21±1.25	79.56±2.17	53.32±1.42	48.32±1.17
24	80.24±1.48	92.37±2.19	96.23±2.28	60.65±1.50	55.45±2.58

Data were presented as mean±standard deviation (n=6)

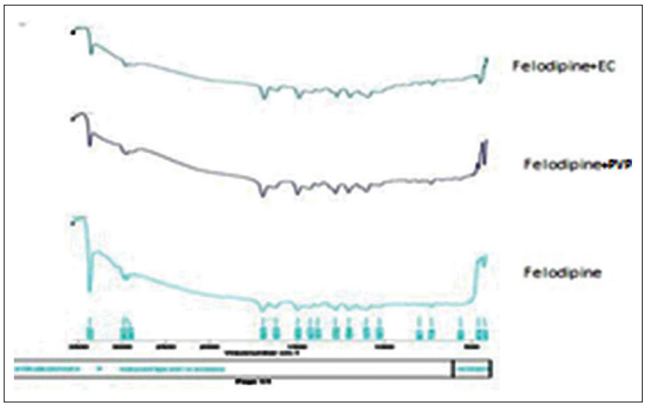

Fig. 1: Fourier transform infrared spectra of felodipine and physical mixtures

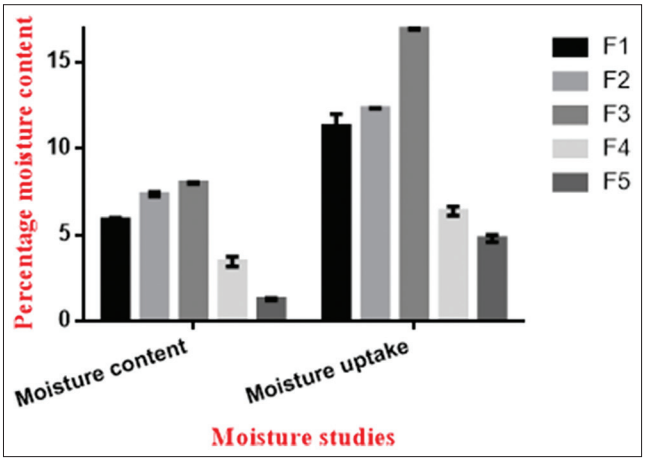

Fig. 2: Moisture studies on transdermal patches. Data are presented as mean±standard deviation (n=6)

nature of EC. At the same time, the patches with more PVP percentage also seen to be thicker than that of patches with more EC percentage. Low moisture content in the formulations maintains the stability and protects the film from being completely dried. It also protects the patches from being susceptible to microbial contamination and also yields thin patches [21]. The patches with high moisture content were observed to be bulky and thicker. Thickness of the patch is an important criteria which gives more patient compliance [22]. Weight variation was observed to be negligible and helped to maintain the uniformity of dose. By increasing the percentage of PVP, a higher folding endurance was observed and it decreased with increasing the percentage of hydrophobic polymer (EC). Equal percentage of PVP and EC yielded patches with good folding endurance. The concentration of plasticizer present in the patches gave them desired folding endurance, and it increased with the presence of hydrophilic polymer.

Table 4: *Ex vivo* skin permeation studies

Formulation	Percentage cumulative drug permeated (%)
F1	60.83%±1.77
F2	67.37%±1.41
F3	76.83%±2.17
F4	50.27%±1.84
F5	43.35%±1.45

Data were presented as mean±standard deviation (n=6)

In vitro drug release is an important tool to predict the *in vivo* behavior of drug [23]. Table 3 shows the release profiles of patches carried out for 24 hrs. In the formulation F3, which had highest percentage of PVP, a maximum drug release of 96.23% was seen at the end of 24 hrs. In the formulations, F2 and F3, an initial burst release was observed. PVP reduced the crystalline nature of felodipine and resulted in increased drug release. The rate of release was decreased with decreasing proportion of PVP and increasing proportion of EC. The formulation F5 which contains maximum EC concentration exhibited lowest drug release of 74.45%, and their dissolution profile is depicted in Fig. 3. This clearly indicates the sustained release behavior of EC due to its hydrophobic nature. The patches containing equal amounts of PVP and EC exhibited a good drug release of 80.24% which can be helpful in maintain a stable plasma concentration.

Ex vivo permeation studies are a predictive assessment of *in vivo* performance of drug. The cumulative amount of drug permeated after 12 hrs was calculated and was given in Table 4. A maximum permeation of 76.83% was observed in the formulation F3, which had a maximum proportion of PVP. This result clearly indicates that an increase in hydrophilic polymer (PVP) in the patch increases the skin permeation of the drug. Increase in the concentration of hydrophobic polymer (EC) inhibited the drug permeation. This can be clearly noticed from the formulation containing maximum amount of EC, F5, allowed only 43.35% of drug to permeate after 12 hrs of study. About 60.83% of drug

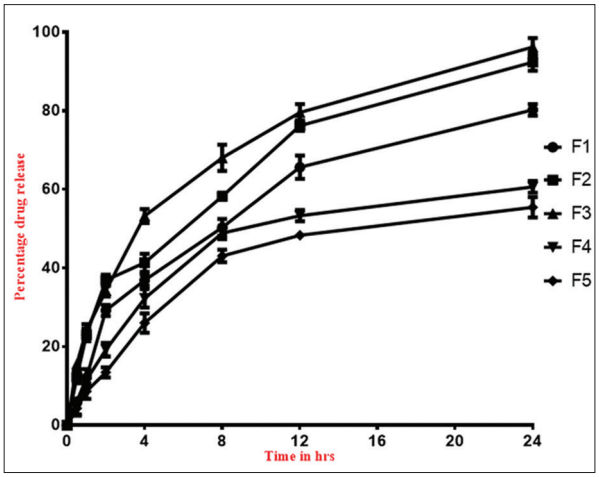

Fig. 3: Dissolution profile of transdermal patches. Data are presented as mean±standard deviation (n=6)

permeation was seen in the formulation F1, which had equal proportion of hydrophilic and hydrophobic polymers.

CONCLUSION

EC and PVP combination can be used to prepare the transdermal patches of felodipine or other calcium channel blockers. The prepared patches are capable of surmounting the low bioavailability factor associated with oral administration of felodipine. From the data, formulation F2 (PVP/EC, 2:1) can be concluded as best formulation due to its desired physical characteristics, sustained release behavior, and good *in vitro* permeation. This formulation can be further studied in a clinical scenario.

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