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Research Article

FORMULATION AND *IN VITRO* EVALUATION OF TRANSDERMAL MATRIX PATCHES OF DOXOFYLLINE

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ABSTRACT

Objective: The main objective of formulating the doxofylline transdermal system was to prolong the drug release time, reduce the frequency of administration, and to improve patient compliance.

Methods: Drug-excipient interactions play a key role with respect to release of drug from the formulation among others. ATR and DSC were carried out to assess these types of interactions. For this assay, a sample of pure doxofylline and physical mixture of doxofylline, HPMC E-50, and PVP were characterized by the ATR and DSC.

Results: The results show that patches of doxofylline obtained by the solvent evaporation method had acceptable physicochemical characteristics and satisfactory percentage drug release.

Conclusion: All the prepared patches were physically assessed for their appearance, thickness, weight variation, and percentage moisture loss, percentage moisture absorption, folding endurance, flatness, and drug content. In vitro drug release studies were carried using Franz diffusion cell. All prepared formulations indicated good physical stability. Formulation prepared with HPMC E-50 lone exhibited foremost in vitro release via dialysis membrane as compared to all other formulations.

Keywords: Matrix transdermal patch, Doxofylline, Hydroxy propyl methyl cellulose E-50, Poly vinyl pyrrolidone, Dimethyl sulfoxide, Polyethylene glycol 400.

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INTRODUCTION

Transdermal drug delivery systems (TDDS) can be defined as self-contained discrete dosage forms which, when applied to the intact skin, delivers the drug(s) through the skin at a controlled rate to the systemic circulation. For transdermal products, the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin. TDDS imparts a leading edge beyond injectables and oral routes by elevating patient compliance, minimize dosing frequency, painless, cost-effective, and bypassing first pass metabolism. Controlled drug release can be achieved by TDDS, which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period [1]. Transdermal patches are classified into three main categories: (i) Matrix type, (ii) reservoir type, and (iii) adhesive type. The only difference in these types is incorporation methodology of the drug in the system. In matrix type, the drug is uniformly dispersed in the polymeric matrix that has hydrophilic or hydrophobic identity [2].

Doxofylline, a new methylxanthine derivative, is extensively used as a remedy for asthma and chronic obstructive pulmonary disease. Doxofylline is chemically designated as 7-(1,3-Dioxolan-2-ylmethyl)-1,3-dimethylpurine-2,6-dione. Existence of a dioxolane group distinguishes it from theophylline.

The objective of the present study was to fabricate matrix type transdermal patch with the varied proportion of hydrophilic hydroxy propyl methyl cellulose E-50 (HPMC E-50) and (poly vinyl pyrrolidone [PVP]) combination incorporating the drug doxofylline and to execute the physicochemical and *in vitro* assessment. The motive was to provide the delivery of doxofylline at a controlled rate across the intact skin to attain a therapeutically effective drug level for a longer time span from transdermal matrix patch.

METHODS

Materials

Doxofylline was procured as a gift sample from Key Pharmaceuticals Limited, Ambala India. Polymers, i.e., HPMC E-50 and PVP were acquired from Otto Chemika Biochemika reagents and Loba Chemie Pvt. Ltd., Mumbai, India, respectively, and other chemical reagents, *viz*., Polyethylene glycol 400 (PEG-400) and dimethyl sulfoxide (DMSO) were obtained from Thomas Baker (Chemicals) Pvt. Ltd., Mumbai, India. Dialysis membrane-70 (LA 393) was purchased from Himedia Laboratories Pvt. Ltd., Mumbai, India. All other chemicals and solvents used were of analytical grade. Double distilled water was used throughout the study.

Instrumentation

Shimadzu UV 1800 double beam spectrophotometer, HPLC (Agilent Technologies), Sonicator (digital ultrasonic cleaner LMUC-2.5 L), weighing balance (Mettler Toledo ME 204), Oven (Universal Tanco An ISO 9001 2008 Certified Co. PLT-125 A), pH meter (Oakton Eco Tester pH-2 waterproof pH tester) were used throughout the experimental work.

Preformulation studies

Partition coefficient

Partition coefficient of doxofylline was determined using octanol as oily phase and water as aqueous phase system. 10 mg of doxofylline was added to 20 mL of water-octanol mixture in a separating funnel. The two phases were separated before use by manually shaking for 15 minutes. The two phases were separately scrutinized for doxofylline spectrophotometrically [3].

$K_{o/w}$ = Concentration in octanol × volume of aqueous phase/ concentration in aqueous phase × volume of organic phase.

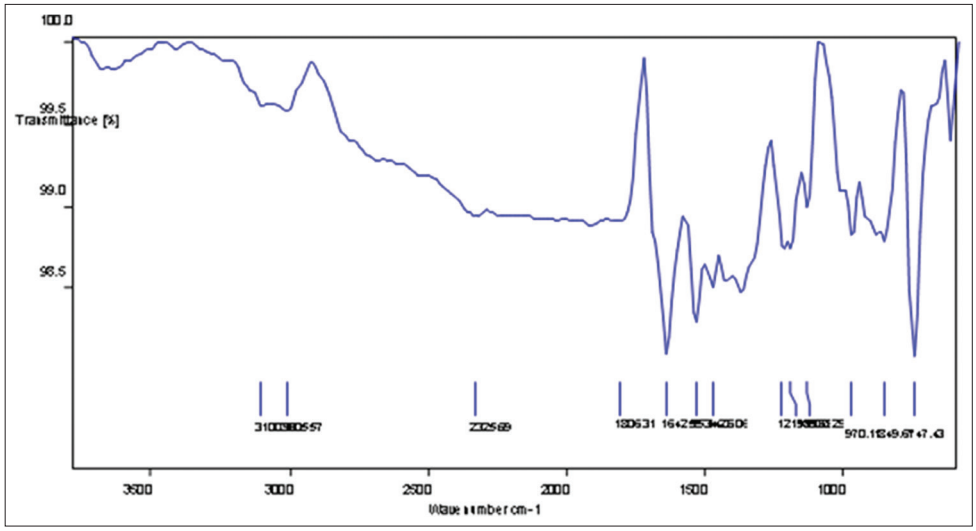

Fig. 1: Attenuated total reflection (ATR) spectra of doxofylline

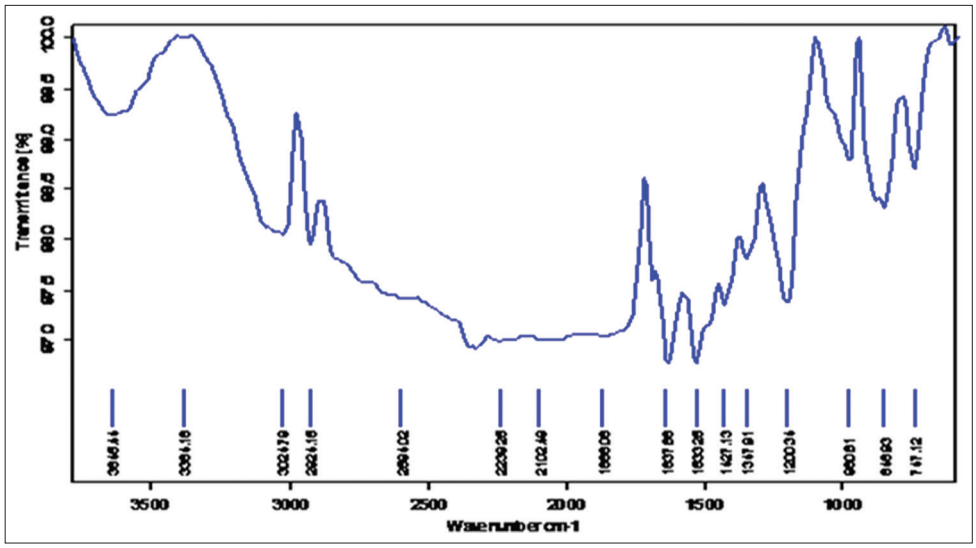

Fig. 2: ATR of doxofylline in physical mixture with hydroxy propyl methyl cellulose E-50 and poly vinyl pyrrolidone

Physicochemical compatibility of drug and polymer

To scrutinize the possible interaction between drug and selected polymers, attenuated total reflection (ATR) spectroscopy and differential scanning calorimeter (DSC) studies were carried out. ATR spectra and DSC thermogram of pure drug, i.e., doxophylline and physical mixture of hydroxy propyl methyl cellulose E-50 and poly vinyl pyrrolidone the drug with polymers are shown in Figs. 1 and 2, respectively [4].

Method of preparation

A 5% (w/v) solution of polyvinyl alcohol was prepared in double distilled water with continuous stirring and heating for 1 hr. Then, 3 mL of the solution was poured in both side open glass ring, one side of which is formerly covered by aluminum foil. Afterward, it was placed in dryer at 60°C±2°C for drying over a period of 24 hrs.

Different matrix type transdermal patches composed of different ratios of HPMC E-50 and PVP with the drug were prepared by solvent evaporation technique as shown in Table 1. The polymers were dissolved in methanol: Water (7:3) solvent system. A fixed volume (3 mL) of polymeric solution was withdrawn. Drug (5 mg), PEG-400 (36% of polymer weight), and DMSO (12% of polymer weight) were dispersed uniformly in the viscous polymeric solution with uninterrupted stirring for 1 hr using magnetic stirrer. The mixture was cast on the prepared backing membrane, and an inverted funnel was placed on the glass ring (area 32.18 cm^2) to facilitate the evaporation of the solvent at a controlled rate over the drying period of 24 hrs at 40° in a hot air oven.

Table 1: Composition of transdermal patch

Formulation code	HPMC E-50 (mg)	PVP (mg)
F1	300	-
F2	300	50
F3	300	100
F4	300	200
F5	250	150
F6	200	200

PVP: Poly vinyl pyrrolidone, HPMC E-50: Hydroxy propyl methyl cellulose E-50

Evaluation of transdermal patches

Physical appearance

All the developed transdermal patches were visually examined considering color, clarity, flexibility, and smoothness.

Thickness measurement

Thickness of each transdermal patch was determined via utilizing a micrometer screw gauge placed at six distinct positions. The average thickness and standard deviation values of six readings were calculated for each batch of drug loaded patch [5].

Folding endurance

It was determined by frequently folding a small strip of patch at the same position until it broke. The number of times, the patch could be folded at the same position without breaking gave the value of folding endurance.

Weight variation

For the assessment of patch weight, three patches of each formulation were taken and weighed separately on digital balance.

Percentage moisture lost

The patches were weighed precisely and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and reweighed. The moisture loss was enumerated using the formula

Percentage moisture loss = Initial weight - Final weight/initialweight ×100.

Percentage moisture uptake

The precisely weighed patches were kept in desiccators at ambient temperature for 24 hrs containing saturated solution of potassium chloride to maintain 84% relative humidity. After 24 hrs, the patches were reweighed, and the percentage moisture uptake by the patches was enumerated using the formula mentioned below.

Percentage moisture uptake = Final weight - initial weight/initial weight ×100.

Drug content determination

The prepared transdermal patches of doxofylline were dissolved in 100 mL of pH 7.4 phosphate buffer and forcibly agitated for 24 hrs and afterward sonicated for 15 minutes. Filter the drug contained polymeric solution via Whatman filter paper, then 1 mL of the filtrate was taken in a test tube and attenuate it for 10 times by the same solvent [6]. Double beam UV-visible spectrophotometer was utilized to resolved drug content on wavelength 272 nm. Respected placebo patch was taken as a blank solution. The test was done for three patches of each formulation, and the results were expressed as mean±standard deviation.

***In vitro* drug release studies using Franz diffusion cell**

The *in vitro* skin permeation from the prepared transdermal patches was studied across the dialysis membrane. The dialysis membrane submerged overnight into phosphate buffer possessing pH 7.4 before use for their activation. Franz diffusion cell using in the experiment consist of two compartments, namely, donor compartment and receptor compartment. After the activation of the dialysis membrane, it was fixed attentively to the receptor compartment of the diffusion cell which was filled with 50 mL phosphate buffer pH 7.4 as diffusion medium so that it exactly touches the receptor fluid surface [7]. The transdermal patch to be studied was placed over the dialysis membrane fixed to the donor compartment. The receptor medium was magnetically stirred using a magnetic bead for homogeneous drug distribution and was maintained at 32±10°C. After assembling the described set up, samples of 5 mL were taken periodically through the sampling port from the receptor compartment at predetermined time intervals (0.25, 0.5, 7.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 52, 54, and 56 hrs). The samples were analyzed by the UV-visible spectrophotometer at 272 nm to resolve the extent of drug liberated, taking phosphate buffer 7.4 as a blank. The volumes withdrawn at each interval were recovered by an identical volume of fresh, pre-warmed buffer solution [8].

RESULTS AND DISCUSSION

Drug-excipient interactions play a key role with respect to release of drug from the formulation among others. ATR and DSC were carried out to assess these types of interactions. For this assay, a sample of pure doxofylline and physical mixture of doxofylline, HPMC E-50, and PVP were characterized by the ATR and DSC.

Infrared (IR) absorption spectroscopy of doxofylline exhibited sharp peaks on 1642.59/cm, 1534.23/cm, and 1219.23/cm due to of C=O stretching, C=N stretching, and C-O stretching, respectively, as presented in Fig. 1. From the IR spectra of physical mixture of drug with polymers, it was observed that there were no modifications/variations in these major peaks of doxofylline as shown in Fig. 2.

DSC enables the quantitative detection of all processes, in which energy is required or produced (i.e., endothermic or exothermic phase transformations). The thermograms of doxofylline and their physical mixture with HPMC E-50 and PVP are presented in Fig. 3. The doxofylline showed a melting peak at 145.31°C. Peak of doxofylline at 145°C was present at the same position, i.e., near to 145°C in the physical mixture of drug with both HPMC and PVP polymers. This certified the physicochemical stability of drug with the formulation excipient used in the study.

The physicochemical evaluation study reveals that all formulations possessing weight and thickness with low deviation from average values. The thickness of the patches varied from 0.630±0.012 mm to 0.793±0.008 mm and order of the thickness of films is F1>F2>F6>F5>F3>F4. The weight variation was to be in the range of 204.06±0.900 mg to 214.71±0.941 mg and order of weight variation of films is F1>F2>F6>F5>F3>F4. The values for all the formulations are enumerated in Table 2. As there was increasing in PVP, there is consistent increase in weight and thickness which may be due to hydrophilic nature of PVP that absorbs water from the atmosphere and thus retains the mass (Figs. 4 and 5).

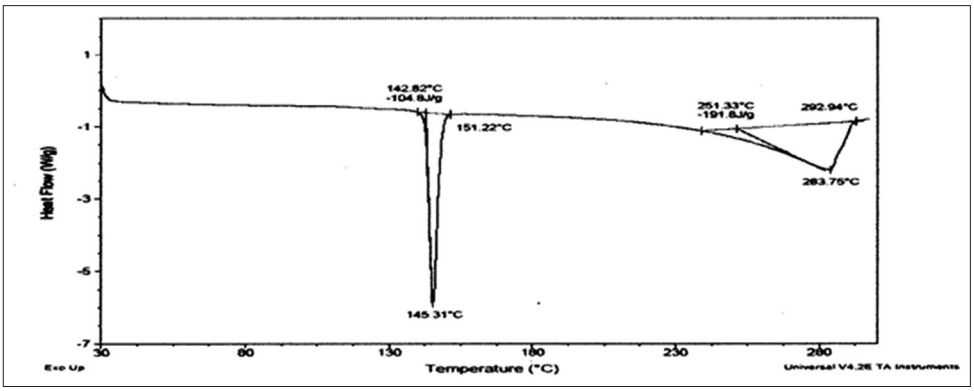

Fig. 3: Differential scanning calorimetry of doxofylline

Table 2: Physical parameters of doxofylline transdermal patches with varying concentrations of HPMC E-50 and PVP

Formulation code	Weight variation (mg) mean±SD	Thickness (mean±SD)	Folding endurance	Area	Flatness (%)
F1	204.06±0.900	0.630±0.012	>200	32.18	100
F2	208.05±0.911	0.725±0.005	>200	32.18	100
F3	211.28±0.830	0.738±0.004	>200	32.18	100
F4	214.71±0.941	0.793±0.008	>200	32.18	100
F5	210.21±0.730	0.734±0.0005	>200	32.18	100
F6	208.83±0.708	0.730±0.0008	>200	32.18	100

PVP: Poly vinyl pyrrolidone, HPMC E-50: Hydroxy propyl methyl cellulose E-50, SD: Standard deviation

Table 3: Percentage moisture absorption studies of the transdermal patches for doxofylline formulations with varying concentrations of HPMC E-50 and PVP

Formulation code	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Percentage moisture absorption
F1	203.3	206.8	208.3	210.8	213.1	213.1	4.820
F2	207.1	209.9	210.6	211.3	213.3	215.1	3.862
F3	212.8	215.5	217.2	218.9	219.8	219.9	3.336
F4	215.8	218.5	219.9	219.9	221.8	221.4	2.594
F5	211.5	212.5	212.9	213.1	213.6	214.6	1.465
F6	210.1	210.3	210.7	211.7	212.2	212.4	1.0947

PVP: Poly vinyl pyrrolidone, HPMC E-50: Hydroxy propyl methyl cellulose E-50

Table 4: Percentage moisture loss studies of the transdermal patches for doxofylline formulations with varying concentrations of HPMC E-50 and PVP

Formulation code	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Percentage moisture loss
F1	205.3	204.8	204.3	203.8	203.1	203.1	1.07
F2	209.1	208.9	208.6	207.3	207.3	206.9	1.05
F3	212.8	211.5	211.2	211	210.8	210.4	1.12
F4	215.8	215.5	214.9	214.9	213.8	213.3	1.15
F5	211.5	210.5	210.2	210	209.6	209.5	0.94
F6	210.1	209.1	208.7	208.7	208.2	208.2	0.90

PVP: Poly vinyl pyrrolidone, HPMC E-50: Hydroxy propyl methyl cellulose E-50

The folding endurance value of all the patches was found to be adequate which assures that patches prepared employing PEG-400 were acquired excellent flexibility and were not brittle (Table 2).

The results of flatness study showed that none of the formulation had the difference in the strip lengths before and after their cuts, thus indicating 100% flatness. It indicates 0% constriction in the patches, and thus, they could maintain a smooth surface when applied to the skin leading to intimate contact and hence better drug permeation.

The moisture absorption of all the formulations showed that with the increase in the concentration of hydrophilic polymer HPMC E-50 percentage moisture absorption increased (Table 3). Among all the patches, the formulation F6 (HPMC E-50: PVP =1:1) showed the lowest percent moisture absorption than other formulations. This is because of the low concentration of hydrophilic polymer HPMC E-50 as compared to all other formulations. A low moisture uptake preserves the material from microbial contagion and bulkiness of the patches (Fig. 6)

The moisture content studies furnish information with regard to stability of the formulations. The low moisture content in the formulations aid them to persist stable and from being a completely dried and brittle film. The result indicated that percentage moisture content was found to be maximal for formulation F4, whereas minimal for formulation F6. The results are documented in Table 4 and shown graphically in Fig. 6. The moisture content in the formulations was found to increases with increasing concentration of hydrophilic polymer (HPMC E-50) because it attributed to the hygroscopic nature (Fig. 7).

Table 5: Drug content studies of the transdermal patches for doxofylline formulations with varying concentration of HPMC E-50 and PVP

Formulation code	Drug content (%)
F1	99.3±0.25
F2	92.6±0.37
F3	89.35±1.54
F4	87.66±1.53
F5	92.81±0.90
F6	90.41±1.47

PVP: Poly vinyl pyrrolidone, HPMC E-50: Hydroxy propyl methyl cellulose E-50

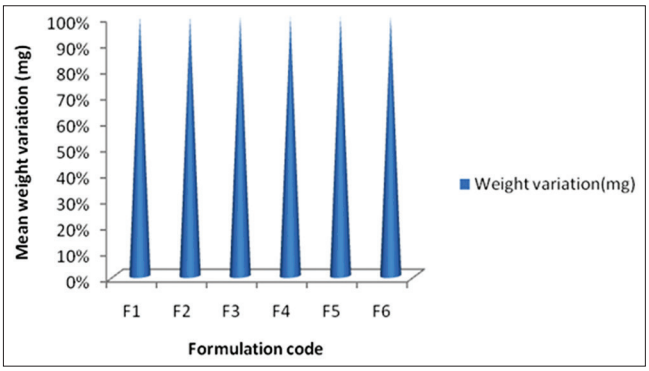

Fig. 4: Mean weight variation for comparison of different formulations

Table 6: *In-vitro* release studies of the transdermal patches for doxofylline formulations by using Franz diffusion cell

Time (h)	Percentage release					
	(F1)	(F2)	(F3)	(F4)	(F5)	(F6)
0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.25	12.576	40.065	11.39585	11.19903	9.230838	8.509166
0.5	12.773	40.19712	12.64238	13.82329	13.56087	12.51116
0.75	13.495	41.83728	19.72788	19.07182	15.79149	13.49526
1	14.020	42.0341	32.12751	36.12951	17.30044	14.34815
2	25.37004	42.29653	38.81938	39.47545	20.44955	19.20303
3	30.29053	42.69017	40.85318	41.70607	21.43365	19.85909
4	31.9307	43.0182	43.0838	45.18321	23.00821	21.04001
5	35.34223	43.67426	47.34823	45.31443	23.33624	22.02411
6	37.76968	44.85518	48.33233	46.69216	23.59867	22.74578
7	38.68817	50.0381	48.72597	47.74187	24.32034	23.07381
8	39.93469	51.35023	49.25082	48.33233	25.17322	24.71398
9	45.24882	56.0739	52.0719	57.32042	30.88099	27.01021
10	58.30452	64.73396	56.40193	64.01229	51.02219	38.75377
11	97.66843	91.17339	86.64654	84.41591	84.67834	80.15149
12	96.22509	90.51732	86.05608	83.95667	81.39801	79.82346
13	95.89706	89.46762	84.61273	83.62864	79.62664	79.42982
14	95.76584	88.68034	84.48152	83.56303	79.42982	77.46162

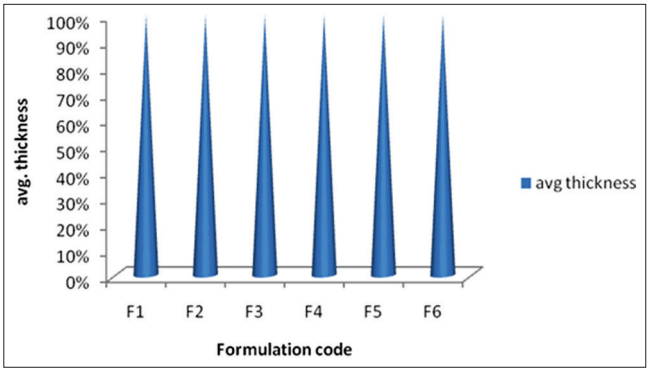

Fig. 5: Average thickness comparison of different formulations

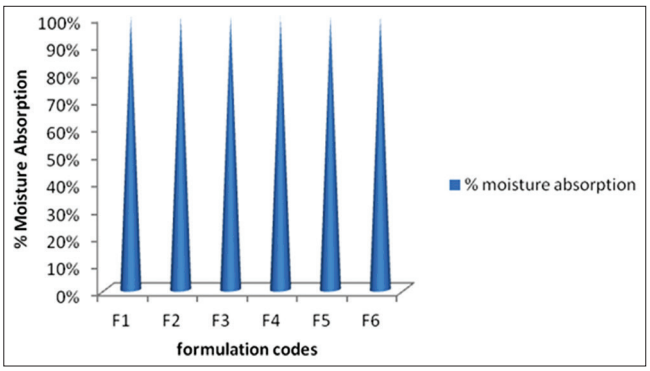

Fig. 6: Percentage moisture absorption for comparison of different formulations

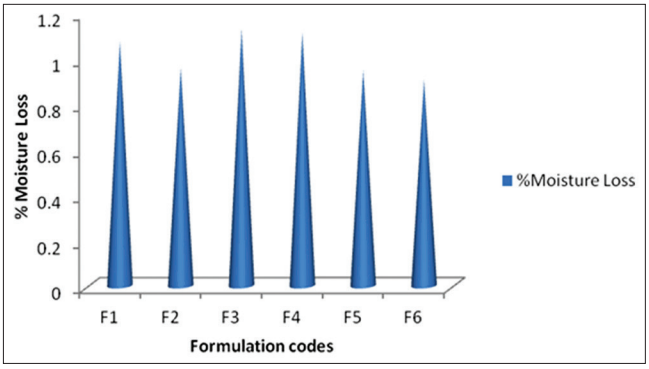

Fig. 7: Percentage moisture loss for comparison of different formulations

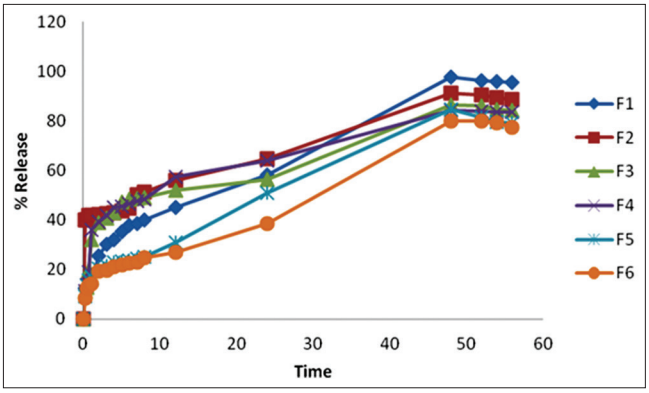

Fig. 8: Drug-release profile of all doxofylline transdermal patches using Franz diffusion cell

The drug content was found in the range from 87.66±1.53 to 99.3±0.25 (Table 5). The drug content analysis of the patches has shown that the process employed to prepared patches was capable of giving uniform drug content and minimum batch variability.

The release profile of doxofylline patches in phosphate buffer solution pH 7.4 showed in Table 6 and Fig. 8, appeared that the patches containing HPMC E-50 lone exhibited maximum percentage drug release and sustained release up to 48 hrs (97.66%) emerging as a best formulation by fulfilling the requirement of better and sustained release which was not possible with HPMC E-50 and PVP combination, whereas the patch containing HPMC E-50 and PVP in ratio (1:1) showed very low percentage release rate (only 80.15%). The percentage release of doxofylline from transdermal patches was significantly increase with increase in the concentration of hydrophilic HPMC E-50 in the polymer matrix. From the % release data versus time profile, it was observed that different batches of the formulation were able to release up to about 48 hrs.

CONCLUSION

The main objective of formulating the doxofylline transdermal system was to prolong the drug release time, reduce the frequency of administration, and to improve patient compliance. Six formulations were prepared using two polymers in different ratios along with plasticizers and penetration enhancer. The results show that patches of doxofylline obtained by the solvent evaporation method had acceptable physicochemical characteristics and satisfactory percentage drug release.

REFERENCES

1. Shingade GM, Quazi A, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, *et al.* Review on: Recent trend on transdermal drug delivery System. J Drug Deliv Ther 2012;2(1):66-76.
2. Dhiman S, Singh TG, Rehni AK. Transdermal patches: A recent approch to new drug delivery system. Int J Pharm Pharm Sci 2011;3(5):26-34.
3. Sangster J. Octanol-water partition coefficients of simple organic compounds. J Phys Chem 1989;18(3):1111-226.
4. Kadajji VG, Betageri GV. Water soluble polymers for pharmaceutical applications. Polymer 2011;3(4):1972-2009.
5. Kavya L, Murthy GL, Roosewelt C. Formulation design and evaluation of doxycycline hyclate film coated tablets. World J Pharm Res 2014;3(10):942-50.
6. Vora N, Lin S, Madan PL. Development and *in-vitro* evaluation of an optimized carvedilol transdermal therapeutic system using experimental design approach. Asian J Pharm Sci 2013;8(1):28-38.
7. Patel RP, Patel G, Baria A. Formulation and evaluation of transdermal patch of aceclofenac. Int J Drug Deliv 2009;1:41-51.
8. Ng SF, Rouse J, Sanderson D, Eccleston G. A comparative study of transmembrane diffusion and permeation of ibuprofen across synthetic membranes using Franz diffusion cells. Pharmaceutics 2010;2(2):209-23.