Original Research Article

Formulation development and investigation of domperidone transdermal patches

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Abstract

Aim and Background: Domperidone is a dopamine antagonist with antiemetic properties having a plasma half life of 7-9 h with 15% oral bioavailability. In the present work transdermal patches of domperidone were prepared with the objective to improve its therapeutic efficacy, patient compliance and to reduce the frequency of dosing and side effects, as well as to avoid its extensive first pass metabolism of the drug. **Materials and Methods:** The patches were prepared using ethyl cellulose (EC): Poly vinyl pyrrolidone (PVP), poly vinyl alcohol (PVA): Poly vinyl pyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC): Sodium (carboxy methyl cellulose) CMC as polymers in combination. The physicochemical parameters like thickness, drug content, weight variation, moisture absorption and drug permeation studies were evaluated for the prepared patches. No significant difference in thickness, average weight and in the drug content among the patches. **Results:** It was observed that from hydrophilic polymers the drug release was found to be faster compared to (F5 and F6 & F3 and F4) combination of hydrophilic and lipophilic polymers used in the study. Patches containing HPMC and Sodium CMC (F5 and F6) showed faster release as the patches showed maximum percentage amount moisture absorption. The *in vitro* release data was treated with kinetic equations and it followed Higuchi's diffusion mechanism. The *in vivo* bioavailability study was performed in rats and observed that, drug reached to the peak in approximately 60 min (16%) after oral route of administration. However, approximately same amount of drug was found in the serum from transdermal formulation in 6 h and further increase in the amount of drug in the serum, indicated that the drug 5 bioavailability could be better and hence the hepatic metabolism can be avoided, as it is evident from the data. Further, the decrease in the amount of drug present in the serum 45 min after oral administration also indicated that major amount of drug might have got metabolized and the bioavailability is reduced. However, the transdermal patch released further amount of drug (33%) at the end of 24 h. **Conclusion:** The present study can be concluded that transdermal patch can extend the release of drug for many hours with better bioavailability and also can avoid the first pass effect.

Key words: Domperidone, *in vitro* and *in vivo* release study, transdermal patch

INTRODUCTION

Transdermal drug delivery system (TDDS) is topically administered medicamentsin the form of patches that deliver drugs across a patient's skin for systemic effects at a predetermined and controlled rate. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects.[1]

Among the wide variety of novel drug delivery systems, the transdermal delivery of drugs for the systemic treatment of diseases has acquired increasing interest in recent years due to its potential in avoiding the hepatic first pass effect, thus achieving high systemic bioavailability of drugs, which undergo either considerable or extensive first-pass metabolism and they are capable of sustaining the drug release for prolonged period of time. Moreover, it provides suitability for self-administration and rapid termination of drug effect if needed, leading to better patient acceptance and compliance.[2]

Domperidone is a dopamine antagonist with antiemetic properties. Its antiemetic effect is due to a combination of peripheral (gastro kinetic) effect and antagonism of central dopamine receptors in the chemo-receptor trigger zone, which lies in the area postrema. It is rapidly absorbed following oral administration and peak plasma concentration is reached within 30−60 min. The solubility of domperidone is related to pH, and is showing poor solubility in

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intestinal pH. Plasma half- life of domperidone is 7–9 h with 15% oral bioavailability. In the treatment of nausea and vomiting in parkinsonian patients, domperidone therapy may be continued for a maximum of 12 weeks, which requires the necessity of sustained formulation. Hence, to improve its therapeutic efficacy, patient compliance and to reduce the frequency of dosing and side effects, as well as to avoid its extensive first pass metabolism, transdermal drug delivery approach was considered to be better suitable for domperidone.[3,4]

In view of the above facts, in the present investigation, an attempt is made to develop matrix type transdermal patches of domperidone using suitable polymers like polyvinyl alcohol, polyvinylpyrrolidone, HPMC, sodium CMC, ethyl cellulose.

MATERIALS AND METHODS

Materials

Domperidone was obtained as a gift sample from Torrent Pharmaceutical, Ahmedabad. Poly vinyl alcohol (cold) was procured from CDH Laboratory reagent, Mumbai; Poly vinyl pyrolidone K-30 from Ozone International, Mumbai; Ethyl cellulose from Sulab Reagent, Baroda; Sodium Carboxymethyl cellulose from Loba Chemical Pvt. Ltd., Mumbai; Hydroxy propyl methylcellulose from Reachem Laboratory Chemicals Pvt. Ltd., New Delhi. All other chemicals and reagents used were of analytical reagent grade.

Formulation of transdermal patches

In the present study, matrix type transdermal patches of domperidone were prepared by molding technique. A flat square shaped, aluminum foil coated glass molds having surface area of 25 cm^2 were fabricated for casting the patches.

Preparation of casting solutions

For Ethyl cellulose and PVP (F1 and F2)

The casting solutions were prepared by dissolving weighed quantities [Table 1] of polymers in chloroform. The drug is dissolved in DMF and added to the above polymer solution along with Di-butylphathalate, as plasticizer, thoroughly mixed to form a homogeneous mixture. The volume was made up to 10 ml with chloroform. Entrapped air bubbles were removed by applying vacuum.

For PVA and PVP Polymers (F3 and F4)

The casting solutions were prepared by dissolving weighed quantities [Table 2] of polymers in water by heating on water bath. The drug is dissolved in DMF and added to the above polymer solution along with Di-butylphathalate, as plasticizer, thoroughly mixed to form a homogeneous mixture. The volume was made up to 10 ml with water. Entrapped air bubbles were removed by applying vacuum.

For HPMC and Sodium CMC (F5 and F6)

The castings solutions were prepared in similar way as described for PVA: PVP solution by using HPMC and sodium CMC polymers [Table 3].[5,6]

Preparation of transdermal patches

Ten milliliter of the casting solution was poured into glass moulds and dried in hot air if necessary after 24 hours of controlled evaporation at room temperature for 24 hours for solvent evaporation. The patches were removed by peeling and cut into square dimension of 3 cm × 3 cm (9 cm^2). These patches were kept in desiccator for 2 days for further drying and wrapped in aluminum foil, packed in self-sealing covers.

Table 1: Formulation of EC and PVP combination

Code	Polymer ratio EC/PVP	Ethyl cellulose (mg)	Polyvinyl pyrrolidone (mg)	Domperidone (mg)	Di-butyl phathalate (ml)	DMF	Water
F1	9:1	900	100	250	0.1	0.5	10
F2	8:2	800	200	250	0.1	0.5	10

EC: Ethyl cellulose, PVP: Poly vinyl pyrrolidone

Table 2: Formulation of PVA and PVP combination

Code	Polymer ratio PVA/PVP	Poly vinyl alcohol (mg)	Polyvinyl pyrrolidone (mg)	Domperidone (mg)	Di-butyl phathalate (ml)	DMF	Water
F3	1:1	250	250	250	1	0.5	10
F4	1.25:1	278	222	250	1	0.5	10

PVP: Poly vinyl pyrrolidone

Table 3: Formulation of HPMC and sodium CMC combination

Code	Polymer ratio HPMC/Sodium CMC	HPMC (mg)	Sodium CMC (mg)	Domperidone (mg)	Di-butyl phathalate (ml)	DMF	Water
F5	1:1	250	250	250	1	0.5	10
F6	1.25:1	278	222	250	1	0.5	10

HPMC: Hydroxyl propyl methyl cellulose, CMC: Sodium carboxy methyl cellulose

Evaluation of transdermal patches

Physicochemical parameters

Physical appearance

All the transdermal patches were visually inspected for color, flexibility, homogenecity, and smoothness.

Film thickness

The thickness of the patches was measured at five different places on a single patch of each formulation using a screw gauge and the mean values were calculated.[6]

Weight variation

A set of three patches from each batch having a diameter of 1 cm^2 were weighed on a digital balance and the mean values were calculated. The tests were performed on films which were dried at 60^0C for 4 h prior to testing.[7]

Drug content uniformity

The patch (1 cm^2) was transferred into a graduated glass stopper flask containing 100 ml of phosphate buffer 6.8. The flask was shaken for 4 h in a mechanical shaker. Then the solution was filtered and 1 ml diluted to 10 ml with of phosphate buffer and the absorbance was measured at 283 nm using the placebo patch solution as blank and the drug content was calculated.[8]

Folding endurance

A strip of 2 cm × 2 cm (4 cm^2) was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed and the values were reported.[9]

Elongation and tensile strength

These mechanical properties were evaluated using Instron universal testing instrument (model F. 4026), Instron Ltd, Japan, NITK, surathkal) with a 5 kg load cell. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamps at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Two mechanical properties, namely tensile strength and percentage elongation, were computed for the evaluation of the film. Tensile strength is computed from the following equation[10]

$$\text{Tensile strength} = \frac{\text{Break force}}{\text{Initial cross sectional are of the sample } (mm^2)}$$

Percentage elongation can be obtained by following equation:

$$\%\ \text{Elongation at break} = \frac{\text{Increase in length} \times 100}{\text{Original length}}$$

Hardness

To determine the hardness of the patches, an apparatus was designed in our laboratory to study the hardness of the films using the literature report. It consists of a wooden stand of 11 cm height and top area of 16 cm × 16 cm. A small pan was fixed horizontally to one end of the 2 mm thick iron rod whose other end is reduced to a sharp point. A hole of 0.2 cm was made at the center of tip area of wooden stand, which was supported on the pan rod. An electric circuit was developed through a 3 volt battery in such a way that the bulb glows only when the circuit is completed through the contact of a metal plate and sharp end of the rod. The film was placed between the metal plate and sharp end of the rod. The weights were gradually added at an interval of 10 seconds for the stabilization of the force till the bulb was glow. The final weight was considered as a measure of hardness.[11]

Moisture absorption

Films (1 cm^2) of each formulation were accurately weighed and exposed to atmospheric conditions of temperature (average temp 34^0C) and humidity (75%) for three days. After three days, the films were again weighed and % moisture absorption was calculated. Average % moisture absorption of each film was calculated.[12]

$$\%\ \text{Moisture absorption} = \frac{(\text{Final weight} - \text{Initial weight}) \times 100}{\text{Initial weight}}$$

In vitro drug release studies

In vitro drug release profiles were carried out by using modified Keshery – Chein diffusion cell with cellophane membrane. The cell consists of two compartments, the donor and the receptor compartment. The donor compartment was in contact with ambient conditions of the atmosphere. The receptor compartment was in contact with a solution in the receptor compartment (phosphate buffer pH 6.8) and the contents were stirred by a rod-shaped magnetic bead driven by a magnetic stirrer. One patch of 1 cm^2 was placed in the donor compartment of the diffusion cell. The receptor fluid (5 ml) was withdrawn at predetermined time intervals and replaced immediately with same volume of phosphate buffer pH 6.8. The samples were analyzed for drug content at 283 nm using UV-visible spectrophotometer (Shimadzu, Japan) after suitable dilution with phosphate buffer pH 6.8.[12]

In vivo drug release studies

The *in vivo* experimental protocol described in this study was approved by the Institutional Animal Ethical Committee (KSHEMA/AEC/066) and was in accordance with the guidelines of the Committee for Purpose of Control and Supervision of Experiments on Animals, Ministry of Social Justice and Empowerment, Government of India. All efforts were made to minimize animal suffering and to limit the number of animal used.[13] In this study, six rabbits weighing 1.5 kg were selected for each group (control and drug). After cleaning the dorsal surface, hair was removed. The dose of domperidone was calculated according to the body weight. Transdermal patch of 4.1 cm^2 was placed on the dorsal surface of the rabbit and immediately secured with an adhesive tape. Blood samples (0.5 ml) were withdrawn

from the marginal ear vein into heparinized glass vessels at predetermined time intervals for the estimation drug in plasma. The blood samples were immediately centrifuged at 2000 rpm for 10 min and plasma was separated and extracted with ethyl acetate followed by final preparation of sample with mobile phase (mixture of buffer: acetonitrile: methanol (55:35:10) at 1 mL/min flow rate) analyzed for drug content by HPLC (instrumentation comprises of A Shimadzu's HPLC (LC-2010-HT, Shimadzu, Singapore) equipped with UV-Visible Detector, phenomenex, C18, ODS column (250 mm X 4.6 mm; 5μ.), Hamilton 20 μL).[14]

Compatibility studies

In the present study, compatibility studies were carried out to assess any incompatibility between the drug and polymers. The IR studies were performed to check the compatibility of excipients. Spectra of the pure drug, PVA, PVP, sodium CMC, HPMC, ethyl cellulose and the formulated patch were taken individually by the potassium bromide pellet method.[15]

Stability studies

The short term stability studies of the formulated transdermal patches were carried out on prepared films at different temperature and humidity according to ICH guidelines: 25 ± 2°C (60%RH) and 45 ± 2°C (75%RH) a period of 60 days. The patches were wrapped in aluminum foil and stored in desiccator for stability study. The patches were characterized for drug content and other parameters at regular intervals.[15,16]

Skin irritancy studies

Patches were applied to the shaved skin on one side of the back of rabbit and secured using adhesive tape. On other back side of the rabbit, control patch (without drug) was secured in a similar way. The animal was observed for any sign of erythema or edema for a period of 48 h.

Lamination of transdermal patch

The transdermal patch of 3 cm diameter was cut and placed on an aluminum foil of 3.5 cm diameter that serves as the backing membrane. A solution of polyisobutylene was applied along the circumference of the aluminum foil and dried at room temperature for 10 h. The patch was covered with silicone-coated release liner.[16]

RESULT AND DISCUSSION

All the patches prepared with different polymer concentration were found to be flexible, smooth, opaque, non-sticky, and homogeneous in nature. Thickness and average weight of the patches did not show any significant difference. All the six formulations have showed good folding endurance indicated that the patches have good flexibility [Table 4].

Water absorption studies revealed that as the concentration of PVP and HPMC increased, the amount of water absorption also increased. Among the patches, F6 patch (HPMC: Sod. CMC 1.25: 1) showed higher moisture absorption. This may be due to the hydrophilic nature of the sod. CMC. The least percentage of moisture absorption was observed for F3 patch (PVA: PVP 1: 1) as compared to F6. The concentration of polymer exhibited significant effect on the percentage elongation, tensile strength. It was found that as the concentration of PVP increased the percentage elongation and tensile strength was also increased along with hardness. It was also found that the patches containing high concentration of plasticizer (0.1% with EC: PVP compared to 0.01% with HPMC: sod. CMC and PVA: PVP) the percentage of elongation and tensile strength were found to be increased [Table 5]. There was no significant difference in the drug content among the patches indicated content uniformity [Table 6].

In vitro drug release study showed that from hydrophilic polymers the drug release was found to be faster compared to (F5 and F6 & F3 and F4) combination of hydrophilic and lipophilic polymers used in the study [Figure 1]. Patches prepared with PVP and EC as polymers it was found that more the amount of PVP better the drug release due to the hydrophilic nature of PVP. No significant change in drug release was observed from patches containing PVP and PVA irrespective of the polymer

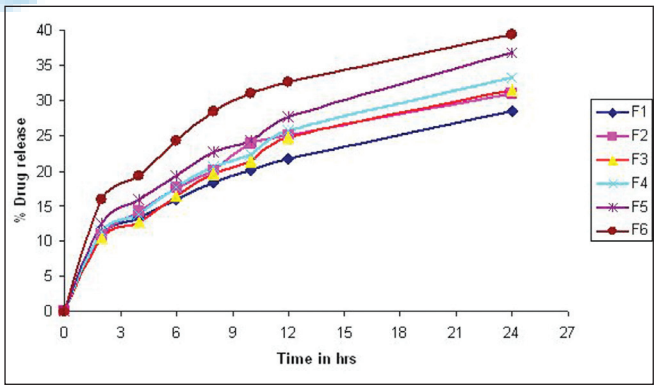

Figure 1: Comparison of *in vitro* % drug release of formulations.

Table 4: Physicochemical properties of the prepared transdermal patches

Code	Flexibility	Smoothness	Transparency	Stickiness	*Folding endurance	*Weight (mg) AM ±SD
F1	Flexible	Smooth	Opaque	Non-sticky	182-215	31.000±2.000
F2	Flexible	Smooth	Opaque	Non-sticky	182-215	32.333±2.516
F3	Flexible	Smooth	Opaque	Non-sticky	182-215	31.333±1.154
F4	Flexible	Smooth	Opaque	Non-sticky	182-215	33.667±1.154
F5	Flexible	Smooth	Opaque	Non-sticky	199-245	30.667±1.527
F6	Flexible	Smooth	Opaque	Non-sticky	199-245	31.333±2.518

*Average of three determinations

Table 5: Physicochemical properties of the prepared transdermal patches

Formulation code	*Hardness (kg) AM±SD	*Thickness (mm) AM±SD	*Width (mm) AM±SD	*Initial length (mm) AM±SD	*Final length (mm) AM±SD	*Elongation (mm) AM±SD	%Elongation AM±SD	*Weight required to break (kg) AM±SD	*Tensile strength (kg/mm) AM±SD	*% Moisture absorption
F1	0.422±0.030	0.323±0.025	5.0±0.0	10.0±0.0	15.667±1.527	5.667±1.527	83.724±15.275	0.367±0.016	0.457±0.054	5.32
F2	0.401±0.015	0.333±0.015	5.0±0.0	10.0±0.0	18.667±1.526	8.667±1.527	86.117±15.275	0.444±0.018	0.497±0.042	5.21
F3	0.428±0.024	0.320±0.026	5.0±0.0	10.0±0.0	16.667±1.154	6.667±1.154	66.667±11.547	0.373±0.007	0.492±0.067	3.64
F4	0.392±0.035	0.336±0.025	5.0±0.0	10.0±0.0	18.667±2.516	8.667±2.516	86.781±25.166	0.453±0.024	0.505±0.098	4.63
F5	0.340±0.018	0.320±0.021	5.0±0.0	10.0±0.0	16.00±1.000	6.00±1.000	60.000±10.00	0.398±0.033	0.357±0.009	5.6
F6	0.352±0.020	0.336±0.015	5.0±0.0	10.0±0.0	17.667±2.081	7.667±2.081	76.667±20.817	0.460±0.025	0.384±0.080	5.63

*Average of three determinations

ratio (F3 and F4). Patches containing HPMC: sod. CMC (F5 and F6) showed faster release as the patches showed highest % of moisture absorption which might have lead to faster release of drug from the patches. This may be attributed to hydrophilic nature of the polymer which has more affinity for water results in increased thermodynamic activity of the drug in the film. Further, the drug release study (F6) was when conducted for 48 h, it was observed that approximately 75% of drug was released. Hence, transdermal patches can be used for extended period of time.

The *in vivo* drug release study was performed in rabbits and the data was compared with that of in vitro drug release data. In this study, drug was administered to animal in the form of suspension in water by oral route as well as in the form of transdermal patches same dose was maintained in both formulations. It was observed that the drug reached to the peak in approximately 60 min (16%) from oral route. However, approximately same amount of drug was observed in the serum from transdermal formulation in 6 h [Figure 2] and further increase in the amount of drug in the serum, indicated that the drug bioavailability could be better and hence the hepatic metabolism can be avoided, as it is evident from the data.

Further, the decrease in the amount of drug present in the serum 45 min after oral administration also indicates that major amount of drug might have got metabolized and the bioavailability is reduced. However, the transdermal patch released further amount of drug (33%) at the end of 24 h. Hence, from the present study it can be concluded that transdermal patch can extend the release of drug for many hours with better bioavailability and also can

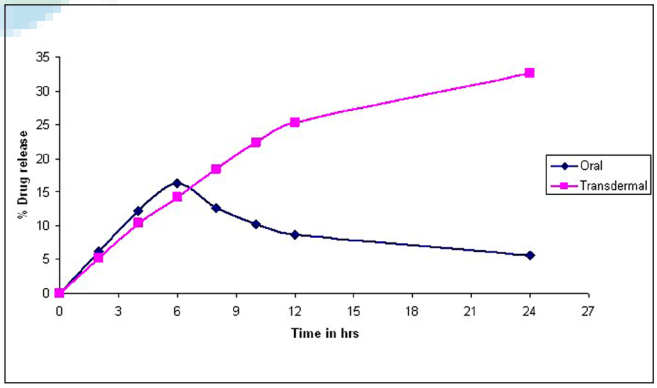

Figure 2: Comparison of oral and transdermal route formulation.

Table 6: Drug content of the prepared transdermal patches

Formulation code	Amount in 1 cm² (mg)	Percentage drug content In 1 cm²
F1	9.45±0.0212	94.50±0.4124
F2	9.32±0.0354	93.25±0.6256
F3	9.15±0.0241	91.57±0.5325
F4	9.60±0.0428	96.06±0.4546
F5	9.26±0.0295	92.57±0.7412
F6	9.80±0.0374	98.31±0.5125

*Average of three determinations

avoid the first pass effect as the drug undergoes extensive first pass effect approximately 80%.

To understand order of release and release mechanism of the drug from the prepared films, obtained release data was processed into the zero and first order kinetics. The data from *in vitro* release studies of transdermal patches did not fit into zero order kinetics. Further to know mechanism of release, plotted Higuchi plot, which indicated diffusion as dominating mechanism of drug release [Table 7].

IR studies were done for pure drug, HPMC, sodium CMC, PVA, PVP, EC and formulated films to know the interaction between drug and polymers. From these spectra's it was observed that there was no significant change in the original peak of the drug, polymers when compared with the spectra's of formulated films and this indicates that there is no interaction between drug and polymers [Figure 3].

Stability studies showed that, there is no significant change in physical characteristics and drug content [Table 8]. Based on these results it was concluded that the formulated transdermal

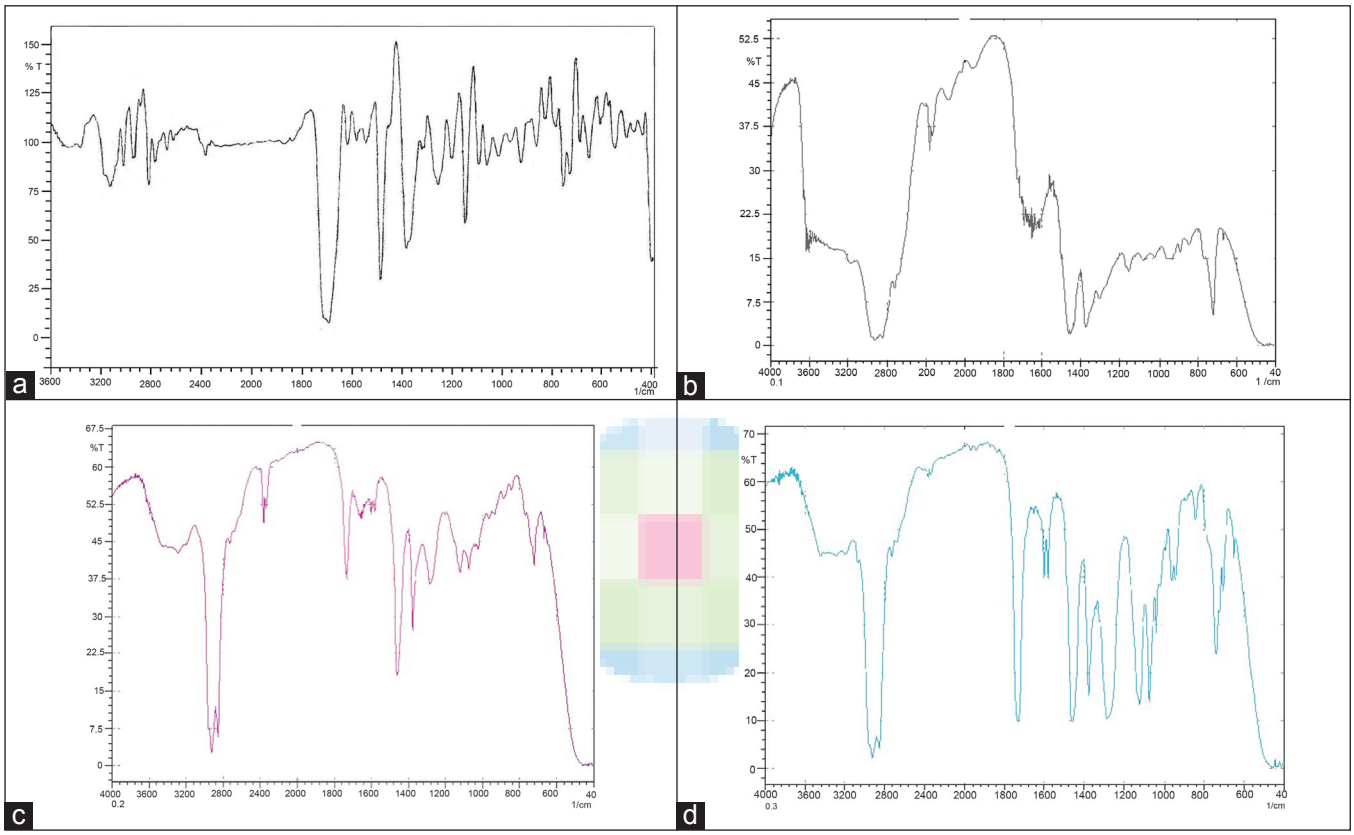

Figure 3: a) IR spectra of domperidone (b) IR spectra of EC:PVP formulation (c) IR spectra of PVA:PVP formulation (d) IR spectra of HPMC: Sodium CMC formulation

Table 7: R^2 values of all the prepared transdermal patches

Code	F1	F2	F3	F4	F5	F6
Zero order	0.9105	0.7957	0.8497	0.8443	0.8512	0.7440
First order	0.8552	0.7649	0.8244	0.8397	0.8398	0.7163
Higuchi model	0.9967	0.9701	0.9850	0.9906	0.9965	0.9595

Table 8: Stability study of transdermal patches at various temperature and humidity

Code	Initial % drug content	25±2°C (60±5%RH)			40±2°C (75±5%RH)		
		15 days	30 days	60 days	15 days	30 days	60 days
F1	94.5	94.2	94.3	93.9	94.2	94.3	92.1
F2	92.5	92.1	92.3	90.8	92.3	92.1	91.9
F3	91.57	91.28	92.08	90.36	90.35	92.09	90.54
F4	98.3	97.21	98.06	97.24	98.2	97.07	96.35
F5	93.25	93.15	93.06	92.25	93.12	93.09	91.52
F6	96.06	96.12	96.09	95.36	96.21	95.24	95.11

patches were found to be physically and chemically stable during the study period (60 days).

Results of skin irritancy study revealed that neither blank patch nor patch containing domperidone causes any noticeable sign of erythema or edema on rabbit skin throughout the period of 48 h. Hence, the patches were found to be compatible with the skin.

CONCLUSION

Di-butylphthalate was used as plasticizer at a concentration of 0.01% v/v for F4 and F5 and 0.1% v/v for F1, F2, F5, and F6 which exhibited good flexibility, tensile strength, hardness and handling property. DMF was included as permeation enhancer at a concentration of 0.04% v/v, which enhanced the drug release through cellophane membrane and rabbit for *in vivo* study. Based on the physicochemical parameters and *in vitro* release studies, formulation F5 and F6 were considered as the best formulations which exhibited the drug release of 36.83% and 39.38% through cellophane membrane and 32.56% through rabbit by *in vivo* study at the end of 24 h, respectively. While comparing the rate of permeation of drug through the cellophane membrane and rabbit *in vivo* study, the cellophane membrane has shown the best permeation. Based on the encouraging results, the domperidone transdermal patch can be used as controlled drug delivery system in the treatment of nausea and vomiting, where the drug is made available for an extended period of time, so frequency of administration can be minimized. Though the efforts were made for the development of domperidone transdermal patch, long term pharmacokinetic and pharmacodynamic studies are needed to undertake the establishment of the usefulness of these patches.

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