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FORMULATION AND EVALUATION OF SUSTAINED RELEASE DOMPERIDONE HYDROCHLORIDE TRANSDERMAL PATCHES TO TREAT MOTION SICKNESS

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ABSTRACT

Objective: Transdermal route of drug delivery is superior than oral route because it avoids first pass effect, ensures better patient compliance, reduce dosing frequency especially in extended-release formulation and is easy to use. Domperidone HCl is DA2 receptor antagonistic and is used to prevent nausea and vomiting. The objective was to formulate a domperidone HCl extended-release transdermal drug delivery system (TDDS) to treat motion sickness. **Methods:** Five different formulations were formed using different solvents (methanol and dichloromethane) and polymers (HPMC and Eudragitl-100) by solvent evaporation method. 500mg of domperidone HCl was added in each patch and dibutyl phthalate was added as plasticizer. A 3% w/v PVA layer was used as backing. All these formulations were evaluated for their physicochemical properties (weight variation, thickness, folding endurance and tensile strength), in-vitro drug release, drug contents determination, any incompatibility between drug and excipients by FTIR and DSC and skin irritation. **Results:** All formulations exhibited good physicochemical properties and percentage drug release during 24 hours was 79.3%, 97.1%, 96.8%, 74.7% and 59.7% respectively. F-YM showed maximum in-vitro drug release. The optimized formulation (F-YM) followed Korsmeyer Peppas release model with n=0.383 showing that the system was following dissolution dependent drug release. No interaction between drug and excipients was detected by DSC and FTIR. No skin irritation was detected. **Conclusion:** The extended release transdermal patches of domperidone HCl to treat motion sickness were prepared and formulation F-YM showed optimized behavior with maximum in vitro drug release.

Keywords: Antiemetic patch, Extended release, D_2 antagonist, Domperidone, Transdermal drug delivery.

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INTRODUCTION

A transdermal patch is a method of delivering the drug through the skin for the purpose of curing and replacing other systems of drug delivery **[1]**. The TDDS is a non-invasive drug delivery system with the additional characteristic of being painless and is considered to have precedence over other conventional methods of drug delivery. In this system, the drug is delivered in discrete dosage form from a transdermal patch through the skin layers reaching to the systemic circulation **[2]**. The transdermal patches are the suitable methods with reduced adverse effects, increased bioavailability due to bypassing the first-pass effect, and sustained release technology **[3]**. The main advantage of TDDS is the avoidance of first-pass metabolism and delivering drugs without facing the harsh environment of GIT **[4]**. Among other advantages of TDDS are the low cost, controlled release of active drugs, and patient compliance. But the skin irritation has been noticed as one of the major issues associated with this delivery system. TDDS is further classified into three generations depending upon the drug particle size and the addition of some excipients called penetration enhancers which assist the drug molecules in crossing the skin layers and reaching the blood circulation **[5]**. TDDS is a non-invasive technique for the systemic delivery of drugs. The drug/API enters through the stratum corneum and then passes through the epidermis to the dermis without accumulation of the drug. It is a

patient-compliant and painless route **[6]**. TDSs allow controlled and prolonged drug molecule delivery into the systemic circulation. Two types are matrix type transdermal patch and reservoir type TDP **[7]**. Matrix-type TDS have active ingredients in an amalgam of adhesives and other ingredients. Scientists realized some major problems and concerns that limit the use of TDDS for some drugs. The drug enters by passive diffusion which depends on a combination of three major characteristics low weight, high lipid attraction, and low therapeutic dose **[8]**. Domperidone HCl (DMP) is an anti-emetic drug that enhances the motility of the GI tract. DMP has been a massively used drug as a treatment for emesis due to its antagonistic action on the dopaminergic receptors both in CTZ as well as at the gastric level **[9]**. It enhances the motility of the stomach and bowel to speed up the passage of food through the gut which helps in treating nausea and vomiting. DMP is often used to treat problems of gut motility and GERD in neonates, children, and adults and is generally considered to be a safe agent **[10]**. DMP cannot cross BBB which proves to be a very useful aspect of the drug that helps in treating vomiting and other related problems with less CNS-associated side effects which gives it a little favor against other agents like metoclopramide **[11]**. Domperidone HCl is absorbed quickly through the oral route and the peak level is achieved within 30 minutes of oral intake. But it has a considerable first-pass effect; causing low bioavailability ranging at 15% and a plasma half-life of 7 hours **[6]**. This extensive metabolism and low oral bioavailability mean that the plasma concentration of domperidone HCl at therapeutic levels is difficult to be maintained **[12]**. In order to maintain therapeutic levels of domperidone HCl in blood, frequent dosing is required and the primitive dosage forms available make patients non-compliant due to the requirement of 2-3 doses per day **[13]**. These problems can be eliminated by using the transdermal route of drug delivery for domperidone HCl. Domperidone HCl is lipophilic in nature and has properties that make it suitable for delivery through the transdermal route, i.e. 425.9g/mol molecular weight, low dose of 30 mg, and absolute bioavailability of 10-20 % **[14]**. Our study aims at evaluating the effect of using different polymers on the physical properties and drug release profiles of domperidone HCl patches. Drugs, enhancers, and polymeric matrix are the main components of TDDS and the drug release from this system depends upon the composition of the polymeric matrix. Various properties of transdermal patches i.e., sustained, controlled and targeted drug release, physical appearance, and mechanical strength depend on the polymers used to make the matrix of the patch. Different combinations of hydrophobic and hydrophilic polymers can be used in the transdermal formulations to obtain different goals of drug release patterns **[15].** Our study aims at evaluating the effect of using different combinations of polymers on the physical properties and drug release profiles of domperidone patches which may help in opening the way for the preparation of more customized DMP patches with better control over patch properties in the future.

MATERIALS AND METHODS

Materials

Domperidone HCl (10g), polyethylene glycol (PEG400), HPMC k15, Eudragit L-100, Eudragit S-100, Eucalyptus oil, oleic acid, and polyvinyl alcohol, ethyl cellulose, dibutyl phthalate, propylene glycol, were purchased from Merck pharma and Mansoor chemicals. Distilled water was used throughout the research.

Methods

Preparation of Backing layer

3% w/v aqueous solution of PVA was prepared by dissolving 3g of PVA in 100ml water by heating at 60 ºC with constant stirring for 40 min. The prepared solution was then poured on a petri dish of area 67.4cm^2 after oiling the inner bottom. The petri dish was covered with aluminum foil and allowed to dry for 24h at room temperature.

Preparation of Polymeric Drug Solution and Patch

All the ingredients mentioned in **Table 1** were weighed carefully on highly sophisticated analytical weighing balance (Shimadzu AP124W). Polymer solution was prepared with HMPC K-15 in mixture of methanol and dichloromethane in 1:1. The weighed amount of Eudragit L-100 0.72g is poured in it with plasticizer polyethylene glycol-400. The solution containing domperidone HCl and polymers was left to swell for 6h. After 24h the backing got dry and we poured our polymeric solution and let it to be dried in open air for next 24h. The patch obtained was cut into 9 cm^2 sections and wrapped in aluminum foil for further testing.

Pre-formulation Studies

The first step in formulation of a dosage form is to establish physico-chemical properties of drug. For doing so, the bulk characterization, pH determination, solubility analysis, determination of partition coefficient and drawing of calibration curve were carried out.

Bulk Characterization

To establish bulk characterization of domperidone HCl, first of all melting point was determined by using Fisher-John's melting point apparatus. Then hygroscopicity was determined by heating the sample in oven at 100°C for 10 minutes and

calculating the weight change of sample. The crystal habit of domperidone HCl was determined by observing it under microscope. Then flow properties (angle of repose, Carr's Index and Hausner's ratio) of domperidone HCl were determined by using fixed funnel method and tapping method respectively. The particle size and size distribution were determined through sieving method.

Solubility Analysis

We prepared buffers of pH 6.8 and determined solubility of domperidone HCl in the buffer using Gravimetric method. The solubility of domperidone HCl was also determined in organic solvents (n-octanol and dimethylformamide).

Partition Coefficient

Partition coefficient was determined by using separating funnel and checking solubility of drug in both aqueous solvent (6.8 pH buffer) and organic solvent (n-octanol) and calculating the log P value of the domperidone HCl.

Standard Calibration Curve

A stock solution of conc. 2 mg/ml was prepared from which a working solution was obtained by dissolving 2.5ml of stock solution in 47.5ml of 6.8 pH buffer giving a concentration of 100mcg/ml. From working solution, by diluting it with suitable volume of 6.8pH buffer, five different dilutions of conc. 5, 10, 15, 20 and 25mcg/ml were prepared. These dilutions were run in UV spectrophotometer (CE7400S) at 289.5nm wavelength and absorbance was recorded for each dilution. Then a calibration curve was drawn between absorbance and concentration.

Post-formulation Studies

Weight Variation

To determine the weight variation of the patches, the analytical weighing balance (Shimadzu AP124W) was used. In the first step, the balance was calibrated and then all of the patches were weighed individually and readings were noted down. The mean weight and the weight variations were calculated.

Thickness

The Vernier caliper (INOX 150mm TMT311501) was used to measure the thickness of 10 patches randomly selected and values were noted down.

Clarity Test

The patches were seen through a light source and their clarity was observed and noted down.

Folding Endurance Test

The patches were tested for their folding endurance with a roller. Patches were folded at the same position with roller and this process was repeated until the patch was broken at that position and the number of folds were counted and noted down.

Drug Content Test

Drug content assay was carried out by immersing the patch in buffer with pH of 6.8 for 24h with gentle shaking for 30 minutes while immersing the patch. After 24h, that media was centrifuged and the sample was drawn from the supernatant and was run in UV spectrophotometer (CE7400S) and absorbance was noted.

Table 1: The ingredients of all formulations manufactured.

Ingredients	F-MY	F-HM	F-MA	F-AJ	F-Y
Eudragit L-100 (mg)	-	-	720	100	370
Eudragit S-100 (mg)	-	-	-	250	-
HPMC K15 (mg)	-	-	180	-	93
Ethyl cellulose (mg)	1500	200	-	-	-
Polyvinyl pyrrolidone(mg)	750	-	-	-	-
Dibutyl phthalate (ml)	0.67	1.2	-	0.1	0.15
PEG-400 (ml)	-	1.2	0.3	-	-
Propylene glycol (ml)	-	-	-	0.1	0.15
Eucalyptus oil (ml)	-	-	0.1	-	-
Oleic acid (ml)	-	-	-	-	0.1
methanol (ml)	-	16	-	-	4
Dichloromethane(ml)	-	-	-	-	4
Chloroform (ml)	5	4	-	-	-
Water (ml)	-	-	-	-	5
Polyvinyl Alcohol as backing membrane (%w/v)	3	3	3	3	3
Domperidone HCl (mg/patch)	66	66	66	66	66

Dissolution Test

For this purpose, the paddle dissolution apparatus was used. The patch was tied to the paddle and immersed in the buffer media with volume of 450ml of buffer with pH of 6.8. The apparatus was operated at 50 rpm at 37 °C for 24 hours. The samples were taken the sampling syringe at 0.5h, 1h, 2h, 4h, 8h, 12h, 24h, 36h and 48h. These samples were diluted in reference solvent and were run in the UV spectrophotometer and their absorbance was noted down.

RESULTS AND DISCUSSIONS

Results from the pre-formulation studies indicated the chemicals which were used in formulation of patches were of analytical scale. Domperidone HCl was active in our formulation which is selected after multiple tests to confirm its compatibility with other polymers and effectiveness in transdermal delivery system. Stability in moist environment made it suitable to be remained of skin without degrading and losing its effectiveness.

Bulk Characterization

Table 2 shows that the melting point was very close to actual value which confirmed the purity of domperidone HCl and was stable hygroscopic solid showing very little tendency to change in physical properties due to hygroscopicity. The spherical crystallization of DOM imparted greater stability exhibited good flow properties which were helpful in the formulation. The particle size of drug was larger which affected solubility of DOM badly.

Solubility the phenomena of dispersing a solute in a solvent to form a uniform mixture, is one of the crucial criteria to achieve the desired drug concentration in systemic circulation for the required pharmacological effect. Low aqueous solubility is the most challenging aspect of formulation development. Domperidone HCl solubility in buffer PH 6.8 was 3.7 parts in 1000 parts (3.7mg/L) making it poorly soluble in aqueous solvents. The solubility analysis showed that domperidone HCl was slightly soluble in aqueous buffer while soluble in organic solvent indicating higher lipophilicity and poor hydrophilicity. Drug penetration through stratum corneum depends on lipophilic tendency of the drug. More lipophilic nature or low hydrophilicity makes domperidone HCl suitable candidate for efficient delivery to systemic circulation through blood.

This finding was further confirmed by determining partition co-efficient of drug using octanol and water in separating funnel the log-p value from analysis was 2.7 which is crystal clear evidence of highly lipophilic nature of the drug.

Post Formulation

Various criteria such as thickness, homogeneity of weight, folding endurance, and drug content were used to evaluate the films. These are crucial parameters for evaluating the dosage form in order to produce a formulation with batch-to-batch uniformity and consistency. Results was demonstrated in **Table 3**. The maximum weight variation among patches was 3%. In formulations F-MA to F-AJ the weight of the patches was different and F-HM, F-MY and F-YM the weight was nearly same. Thickness ranges from 0.08±0.75 to 0.126±0.98mm. The thickness and weight increased with more use of polymer which is indication of uniformity of thickness of patches. Excellent drug content uniformity in drug was observed in transdermal films as proved by drug content analysis through advance UV-spectrophotometer. The drug content was in range of 62% ± 0.14 to 92.08 ± 0.26. The drug content analysis of the developed formulations demonstrates that the techniques employed to prepare the patches in this study result in consistent drug content, little batch variability, and uniform thickness and weight **[16]**. The uniformity of drug content, consistency in weight, and uniformity of thickness demonstrate that the drug is well disseminated in the polymeric solution. However, only minor differences were identified in formulations, which may be related to differences in polymeric composition **[17].**

Table 2: Various pre-formulation studies of domperidone HCl.

S. No.	Characteristic	Finding
1.	Melting Point	241.5 °C.
2.	Hygroscopicity	stable hygroscopic solid
3.	Crystallinity	Spherical
4.	Angle of Repose	31.29° (Good Flow)
5.	Carr's Index	14.19 (Good Flow)
6.	Hausner's Ratio	1.15 (Good Flow)
7.	Particle size	1.625mm
8.	Solubility (6.8pH buffer)	3.7mg/l (Slightly soluble)
9.	Solubility (Dimethylformamide)	57.5mg/l (soluble)
10.	Solubility (methanol)	4.9mg/l (slightly soluble)
11.	Partition Coefficient	2.7

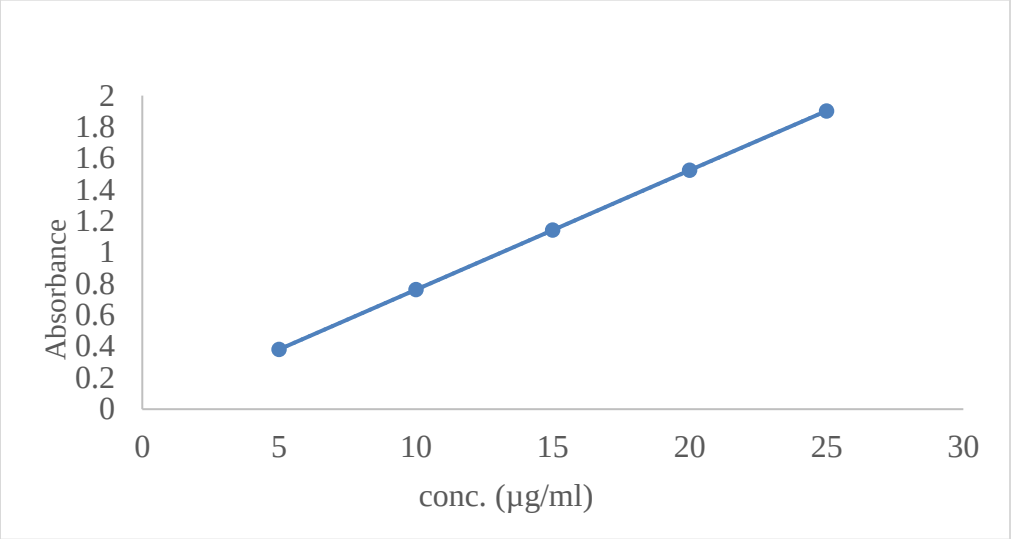

Figure 1: Standard calibration curve of domperidone HCl at 285.9nm wavelength.

Table 3: Post formulation tests of developed dosage forms.

Name of Test	F-MY	F-HM	F-MA	F-AJ	F-Y
Weight Variation (%)	0.81	0.42	3	3.35	1.17
Thickness (mm)	0.92	0.91	0.94	0.875	0.912
Clarity	Very slightly opaque	Transparent	Very slightly opaque	Transparent	Transparent
Folding Endurance	>200	>200	>200	>200	>200
Drug Content (%)	88.38	69.89	86.53	82.84	92.08

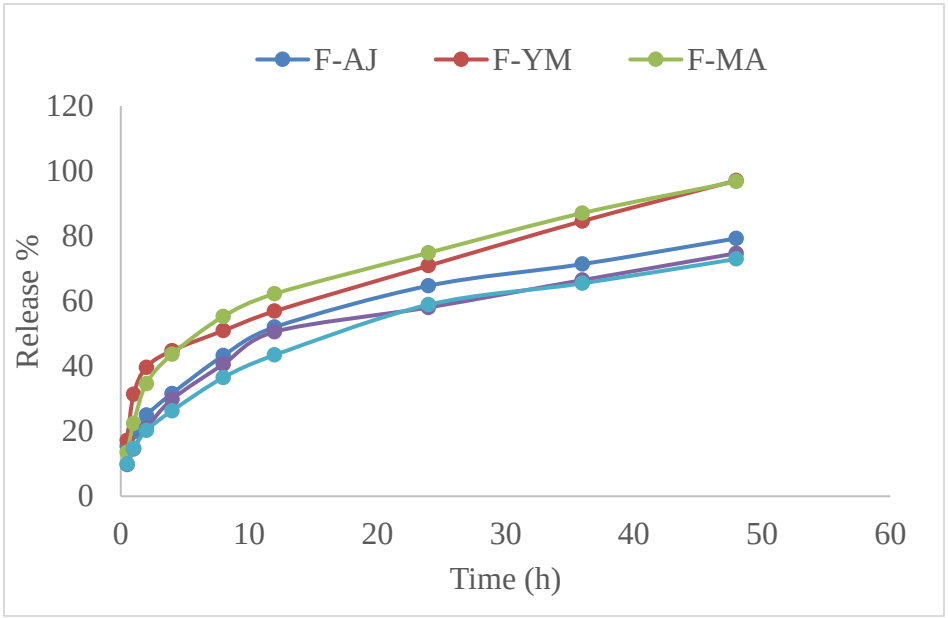

Figure 2: In vitro drug release profiles of formulations.

In-Vitro Drug Release

To estimate the reproducibility of rate and duration of drug release, release studies are required. Considering the impact of polymer breakdown on drug release from matrices is crucial for achieving sustained release performance. In vitro diffusion studies can be used to quantify the rate and magnitude of drug release from a transdermal patch **[18]**. The chemical properties of the drug, the mode of delivery, and the physiological and physicochemical qualities of the biological membrane govern the release of drug from transdermal patches. Drug concentration in the

Stability Studies

The patches of the best-optimized formulation were subjected to stability studies for six months. The temperature of 40± 2°C and the relative humidity of 75%± 5% were maintained throughout this period. Samples were taken at time intervals specified by ICH guidelines and their physical appearance and drug contents were evaluated.

matrix, chemical composition of matrix material, and device geometry are rate-controlling parameters **[6]**. Formulation F-HM showed minimum release 59.744% and F-YM showed 97.10% release of drug. Kinetic modeling of patches was performed which exhibited that all formulation was following Korsmeyer Peppas model with Fickian drug release pattern. F-HM in addition to Korsmeyer Peppas model was also following Higuchi model. The aforementioned outcomes were validated in terms of the linear regression coefficient (R^2) these indicated that the release from the patches were both diffusion and erosion method.

As shown in **Table 4**, no significant change was observed in the physical properties and drug content of patches throughout the testing period. From the results, it was concluded that all the formulations were physically and chemically stable under the testing conditions.

Table 4: Accelerated stability testing of domperidone transdermal patches.

Formulation code	% Drug content					
	Initial drug content	0.5 month	1 month	2 months	3 months	6 months
F-MY	88.3%	87.9%	87.2%	88.1%	89.2%	87.5%
F-HM	69.8%	69.4%	68.1%	68.4%	68.2%	69.7%
F-MA	86.5%	86.3%	86.7%	85.7%	85.4%	86.7%
F-AJ	82.8%	81.8%	82.5%	82.1%	83%	81.6%
F-Y	92.0%	92.4%	92.7%	91.8%	91.6%	91.5%

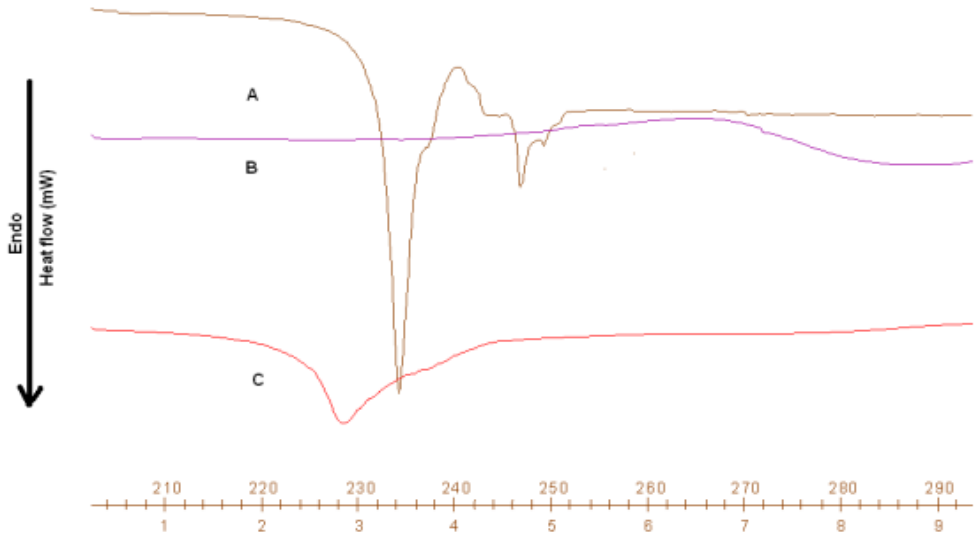

Figure 3: DSC thermogram of (a)DOM, (b) HPMC K-15 (c) Physical mixture of DOM and HPMC K-15.

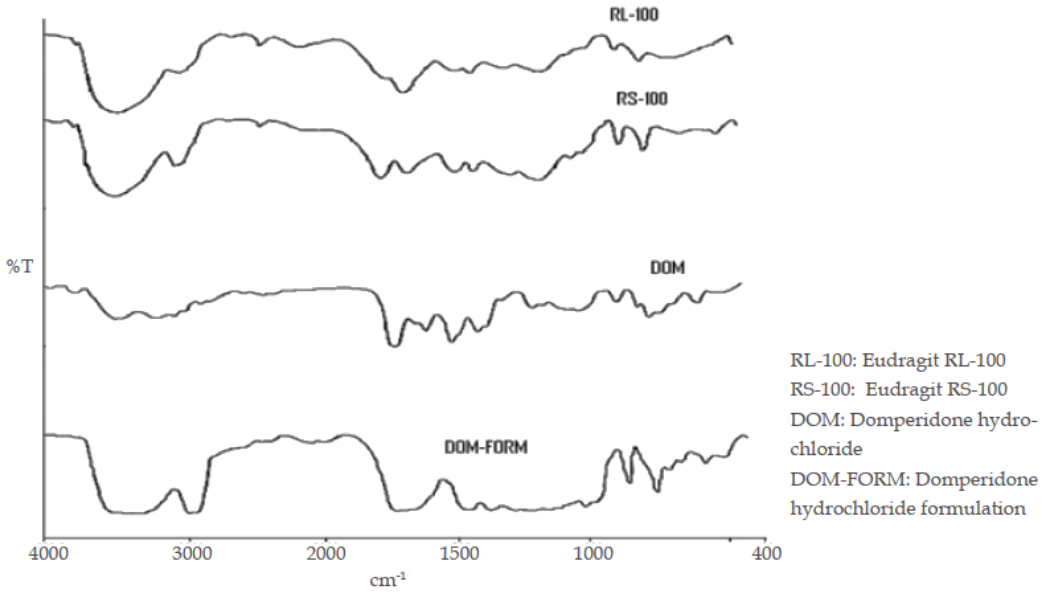

Figure 4: FTIR Spectrum of polymer, domperidone HCl and formulation.

FTIR and DSC Study

Fig. 3 depicts the DSC analyses of domperidone HCl, HPMC K-15, and the optimized formulation. A distinct melting peak with at temperature 234.6 ºC (H=138.9 J/g) of DOM demonstrated a sharp endothermic process. The thermal characteristics of HPMC K-15 did not indicate the presence of any transition region. The thermogram of the optimized formulation also showed the emergence of a peak related to the melting of DOM. In the presence of polymeric materials, the melting point of domperidone HCl did not alter substantially. The principal peaks of the FTIR spectra of DOM (**Fig. 4**) were at 3015.16 cm^{-1} (N-H stretching), 2718.27 cm^{-1} (asymmetric C-H stretching), 1715.31 cm^{-1}, 1684.32 cm^{-1} (C=O stretching), and 1432.15 cm^{-1} (N=C stretching peak) **[19]**. Additional distinctive peaks were observed at 1489.15 cm^{-1}, 1147.18 cm^{-1}, and 1062.18 cm^{-1}. The profile of the FTIR spectrum of Hydroxypropyl methylcellulose K-15 lacked distinct peaks. The optimized formulation and HPMC K-15 were nearly overlapped in the formulation. FTIR findings suggested that there was no interaction between the drug and polymer employed in this study **[19].**

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CONCLUSION

The present study showed that domperidone HCl patch containing HPMC K-15, Eudragit L-100 and plasticizer Dibutyl phthalate the intended goals of TDDS, such as, extended release, and administration frequency, and may serve as a more effective system for transdermal delivery.

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