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RESEARCH ARTICLE

Transdermal Delivery of Domperidone via Solid Dispersion: Formulation, Characterization, and Ex Vivo Permeation

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Abstract: Background: Transdermal drug delivery systems (TDDS) provide various advantages, including avoiding hepatic first-pass metabolism, ensuring prolonged drug release, and improving patient compliance. Domperidone, a dopamine antagonist with limited oral bioavailability due to significant first-pass metabolism, makes an excellent candidate for transdermal application.
Objective: Develop and test domperidone transdermal patches employing hydrophilic polymers like PVP K-30 and HPβCD to improve solubility and release.
Methods: Methods: Domperidone SDs were formulated with PVP K-30 and HPβCD in various ratios (1:1, 1:3, 1:5 w/w). FTIR and DSC were carried out to check compatibility and crystallinity. Transdermal patches were prepared following a solvent casting method with polymers (EC, HPMC, PVP) and plasticizers (PEG, DBP). Physicochemical properties like drug content, moisture content, tack, and diffusion were determined. In vitro release of the drug was analyzed through Franz diffusion cells, and release kinetics was determined. Skin irritability was determined through PII scoring.
Results: Domperidone's solubility rose dramatically (up to 4.75 times) with PVP K-30. The amorphous nature of SDs and successful complexation were verified by FTIR and DSC. When compared to pure drug patches, patches with SD (especially PVP K-30) demonstrated better drug release. Over eight hours, the cumulative release of the optimized patch (P6, 1:5 SD with 50% DBP) was 87±11.65%. Safety with PII < 2 was confirmed by skin irritation tests.
Conclusion: Transdermal patches of domperidone based on a solid dispersion matrix greatly enhanced the drug's solubility, release rate, and skin compatibility. As a patient-friendly, sustained-release substitute for oral domperidone therapy, the optimized SD patch formulation shows promise.

Keywords: Domperidone, Transdermal drug delivery, Solid dispersion, PVP K-30, HPβCD, Matrix patch, Drug release, Skin irritation

INTRODUCTION

Transdermal delivery patches, also referred as TDDS, release drugs at a pre-established, controlled rate across a patient's skin to produce systemic effects. It nullifies pulsed entry into the systemic circulation, which often culminates into unwanted side effects, and permits continuous input of drugs that own short biological half-lives. It also gives controlled, continuous delivery of drugs. [1]

Among novel drug delivery systems, the transdermal route has garnered significant attention for systemic therapy. It offers a means to circumvent the hepatic first-pass effect, thereby improving the bioavailability of drugs susceptible to extensive metabolism, while also enabling sustained drug release. Additional benefits such as ease of self-administration and the capacity to quickly halt treatment enhance both its practicality and patient acceptability. [2]

Domperidone is a dopamine receptor antagonist renowned for its antiemetic properties. Its therapeutic action is dualistic, combining peripheral gastrokinetic effects with the central inhibition of dopamine receptors in the chemoreceptor trigger zone (CTZ) of the area postrema. Following oral administration, domperidone is rapidly absorbed, achieving peak plasma concentrations within 30 to 60 minutes. However, its clinical utility is significantly limited by its pharmacokinetic profile, which includes low and pH-dependent solubility in the intestinal environment, an oral bioavailability of approximately 15%, and a plasma half-life of 7–9 hours. These limitations are particularly problematic for its indicated use in managing nausea and vomiting in parkinsonian patients, where treatment durations may extend to 12 weeks and necessitate sustained drug levels.

Consequently, to circumvent the substantial first-pass metabolism, enhance therapeutic efficacy, reduce dosing frequency, and minimize adverse effects, a transdermal drug delivery system was investigated as a superior alternative for domperidone administration. This route is anticipated to improve patient compliance by providing sustained, non-invasive delivery, thereby addressing the key pharmacokinetic challenges of the conventional oral formulation [3-6].

With the above facts under consideration, the current work intends to prepare matrix-based transdermal patches of domperidone from necessary polymers such as sodium CMC, HPMC, polyvinyl alcohol, polyvinylpyrrolidone, and ethyl cellulose.

MATERIAL AND METHOD

2.1. Materials

2.2. Tokyo Chemical Industry Co. Ltd., a Japanese company, provided the source of hydroxypropyl-β-cyclodextrin. Dibutyl phthalate (DBP), polyvinylpyrrolidone K-30, and PEG came from Merck Specialities Pvt. Ltd. as well as Loba Chemie, both located in Mumbai, India. Hydroxypropyl methylcellulose (HPMC) came from Sigma Aldrich Chemicals, while the ethyl cellulose (EC) was provided by Colorcon Asia Pvt. Ltd. located in Goa, India. Sigma Aldrich also provided the cellophane membranes that were defined by their molecular weight cut-off (MWCO) between 6000 to 8000. Ingredients used for the transdermal patch came from 3M Drug Delivery Systems located in the USA, including the CoTranTM 9698 nonwoven polyurethane adhesive tape, the 1022 fluoropolymer release liner, as well as the ScotchpakTM 9733 backing layer. Sodium hydroxide (NaOH) and domperidone came as sources from Yarrow Chem. Ltd. based in Mumbai. Analytical-grade chemicals and reagents only were used to secure high quality. Deionized distilled water (DDW) was used continuously during the studies to secure the consistency as well as the cleanliness of all preparations.

2.3. Methods

Crystals of domperidone were obtained by dissolving 0.175 g of the substance in double-distilled water (DDW). Neutralization was carried out on the solution using 1 N sodium hydroxide, causing precipitation, which led to the formation of a solid precipitate. Then, this resultant mixture was filtered through 150 mm Whatman filter paper and dried off in a hot air oven kept at 50°C before being left to cool. After constant agitation, the precipitate so obtained was combined with acetone kept at a temperature of 56°C, almost around its boiling point. This resultant mixture was filtered off to remove impurities and left to reach the ambient temperature. To allow the process of nucleation, the obtained mixture was cooled. Ultimately, the retrieved crystals were dried off at 50°C and kept in a desiccator as part of the preparation before undergoing further formulation as well as analysis.

2.3. Research on Pre-formulation

2.3.1.1 Domperidone λmax determination

λmax was also measured for domperidone after sonicating 10 mg in 100 mL DDW for 30 min. 0.1 mL of this stock was again diluted with DDW (100 mL) to get a stock of 10 µg/mL. A UV-Visible spectrophotometer (ANALAB UV-180) was used for scanning this vs. blank (100 mL DDW) between 200 to 400 nm, and the best absorption wavelength was taken as λmax.

2.3.1.2 Standard Calibration Curve Preparation

Ten milligrams of Domperidone were dissolved in ten milliliters methanol, the stock so prepared being diluted to a hundred milliliters either in DDW or phosphate buffer (7.4, 6.8, pH). Absorbance was measured at 248 nm following serial dilutions (2–16 µg/mL). The calibration curve was prepared by plotting the mean absorbance of the five samples vs. concentration.

2.4. Pre-formulation Characterization Additional Information

2.4.1 Finding the Melting Point

To determine the thermal stability and the degree of purity of the doperidone, a parameter vital for the formulation development, the melting point was determined using standard laboratory procedures.

2.4.1.1 Examination of Saturation Solubility

Solubility of domperidone was ascertained by addition of excess quantity of the drug to 5 mL DDW phosphate buffer (pH 7.4, 6.8) that followed incubation under sporadic shaking for 24 hr at 37 ± 0.5°C in a water bath. Centrifugal separation as well as filtration through Whatman paper followed the measurement of absorbance at 248 nm to determine the solubility.

2.4.1.2 Investigation of Phase Solubility

Phase solubility under 0–10% w/v HPβCD, PVP K-30, in DDW, buffers (pH 7.4, 6.8) was measured using the Higuchi-Connors method. Excess domperidone was introduced into 5 ml solutions, kept under agitation, at 30, 37, 40, 45 ± 0.5°C, during 24 hours, filtered through 11 µm Whatman paper, then analyzed at 248 nm. Molar concentrations of domperidone were plotted vs. concentrations of the solubilizants on a phase solubility diagram based.

Van't Hoff Equation [12,13.

$$K_{1:1} = \frac{Slope}{Intercept\,(1 - Slope)} \quad (1)$$

$$\ln\left(\frac{Ka_2}{Ka_1}\right) = \Delta H \frac{T_2 - T_1}{RT_2T_1} \quad (2)$$

where Ka_2 and Ka_1 are the stability constants at 30 and 37˚C and T_2, T_1 constitutes the corresponding temperature in Kelvin. $\Delta G = -2.303\,RT\,\log\,K$ denotes Gibbs free energy change and entropy (ΔS), $[\Delta G = (\Delta H - T\Delta S)]$ were also determined.

R is the universal gas constant $(R - 8.314\,J/mol/K)$ [12].

2.4.1.3 Transdermal Patch Manufacturing

Polyvinylpyrrolidone K30 (PVP K30, 50 mg), ethyl cellulose (EC, 10 mg), hydroxypropyl methylcellulose (HPMC, 5 mg), and dopamine (10 mg) were blended in a weight-to-weight ratio of 5:1:0.5:1 to prepare transdermal patches. To obtain a viscous product, dibutyl phthalate (DBP, 30–50% v/w) was added as a plasticizer after their dissolution in chloroform. In a subsequent preparation, polyethylene glycol (PEG) was used instead of DBP. Formulations were then spotted onto a 130 cm² SCOTCHPAK 9733 back coating layer after a wet film coating was performed through the help of a 350 µm wet film coating apparatus. Patches were then dried under vacuum after-application for a period of 24 hours at a temperature of 25°C, after which they were then overlaid with CoTranTM 9697 adhesive tape. Similar procedure was followed to prepare patches containing solid dispersion of Domperidone-PVP K30 (1:5 w/w, equivalent to 10 mg Domperidone). Theoretical values of the content of the drug were confirmed through assay.

Patch code	Carriers				Total weight of carrier (mg)	Chloroform (mL)	% DBP (total wt. of polymer)	% PEG (total wt. of polymer)	Drug (mg)
	PVP K-30 (mg)	HPMC (mg)	EC (mg)	SD (1:5w/w OND-PVP K-30) in mg					
P1	50	5	10	-	65	3	30% v/w	30% v/w	10
P2	50	5	10	-	65	3	40% v/w	40% v/w	10
P3	50	5	10	-	65	3	50% v/w	50% v/w	10
P4*	-	-	-	78	-	3	30% v/w	30% v/w	10
P5*	-	-	-	78	-	3	40% v/w	40% v/w	10
P6*	-	-	-	78	-	3	50% v/w	50% v/w	10

2.5 Transdermal Patch Evaluation

2.5 Assessment of Transdermal

To confirm performance and quality, patches were evaluated for drug content, moisture content, moisture absorption, thickness, adhesion, and drug distribution uniformity.

2.5.1.1 Investigation of Adhesion through Texture Analyzer Utilization

A Texture Analyzer (Texture Technologies Corp.) fitted with a 7 mm probe was employed to determine adhesive strength. Patches of DBP and PEG were fitted to a holder and maintained at a temperature of 25±1°C for a duration of a one-month interval. Analyzer calibration included a 50 g target force, set approach and return speed, a 10-second holding time, and a set trip distance. Characterization of tackiness involved contact of a probe with a patch (3 cm x 3 cm) such that it remained attached for its holding time and subsequently withdrawn. Work of adhesion determinations as well as separation distance and positive force area determinations were performed.

2.5.1.2 Drug Diffusion Study in Vitro

A 50 mL receptor chamber located in a Franz diffusion cell in phosphate pH 7.4 buffer which remained at 37±0.5°C and magnetically stirred served to follow drug release. Patches of surface area of 3.935 cm² were positioned between donor and receptor chambers so that orientation of release liner is facing downwards. Samples were transferred quantitatively and replacement of fresh buffer that ensued were analyzed by UV spectrophotometry at 248 nm. Release kinetics were calculated by employing zero-order, first-order, and Higuchi models.

2.5.1.3 SEM

The surface characterization of domperidone powders and patches was done through a scanning electron microscope (JSM-6700F, JEOL Ltd.). For obtaining high-resolution micrographs of surface structure, a thin layer of platinum coating under a 2.54 Pa vacuum was deposited and subsequently recorded at 10 kV and 25 mA.

RESULTS AND DISCUSSIONS

3.1. Determination of λ_{max} of Domperidone

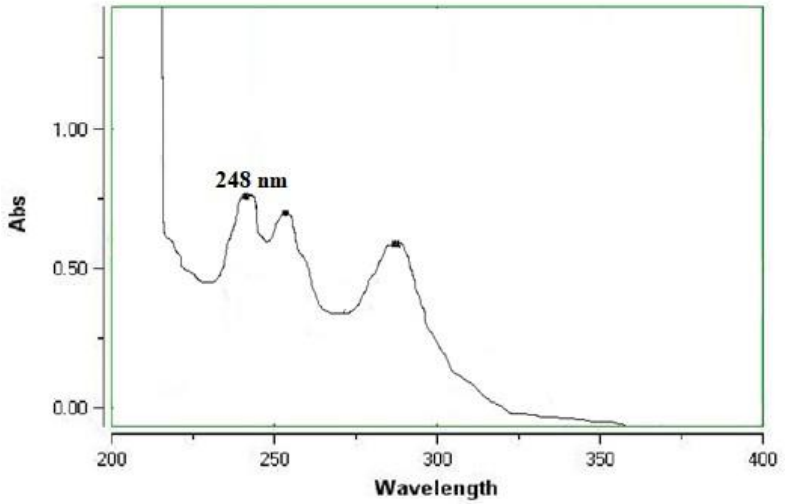


Fig. 1 UV spectrum of DOMPERIDONE in phosphate buffer pH 7.4

The maximum wavelength (λmax) of domperidone was determined by UV spectrophotometric scanning. As illustrated in Figure 1, a distinct λmax was observed at 248 nm.

3.2. Evaluation of linearity curves of DOMPERIDONE

To find out the concentration of DOMPERIDONE, standard curves have been made by using different solvents, namely deionized distilled water (DDW) and phosphate buffers of pH 7.4, 6.8, and 5.5. Linear relations defined by regression coefficient of each aqueous medium are given in Fig. 2. Values of absorbance (n=5) in correspondence to each profile are given in Table 5.4. Linear equations of curves of phosphate buffer of pH 7.4, phosphate buffer of pH 6.8, and DDW are given by following regression equations.

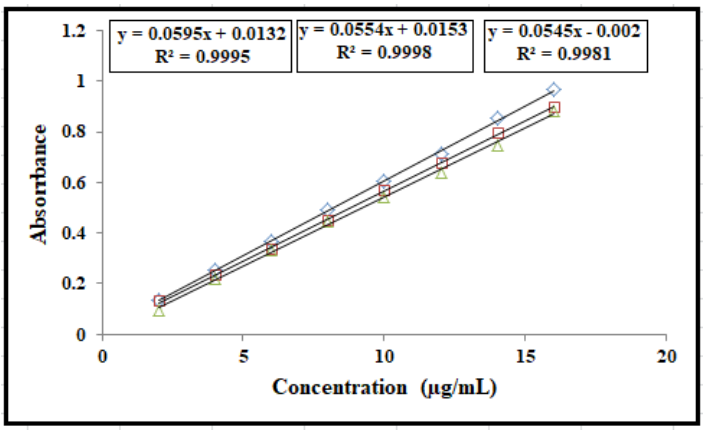


Table 4: Absorbance of Domperidone at 248 nm for different concentrations in phosphate buffer pH 7.4, pH 6.8, and DDW

Serial Number	Concentration (µg/mL)	Avg. Absorbance in pH 7.4	Avg. Absorbance in pH 6.8	Avg. Absorbance in DDW
1	2	0.1320 ± 0.0012	0.0978 ± 0.0008	0.1342 ± 0.0007
2	4	0.2370 ± 0.0007	0.2176 ± 0.0011	0.2532 ± 0.0014
3	6	0.3412 ± 0.0013	0.3352 ± 0.0023	0.3656 ± 0.0010
4	8	0.4546 ± 0.0008	0.4446 ± 0.0030	0.4932 ± 0.0011
5	10	0.5692 ± 0.0026	0.5458 ± 0.0031	0.6068 ± 0.0017
6	12	0.6800 ± 0.0012	0.6378 ± 0.0023	0.7142 ± 0.0027
7	14	0.7960 ± 0.0012	0.7464 ± 0.0024	0.8538 ± 0.0016
8	16	0.9004 ± 0.0030	0.8844 ± 0.0032	0.9670 .0014

3.3. Measurement of melting point

The melting point was found to be 231°C with the help of the melting point apparatus by adopting capillary method. On the other side, the melting point of Domperidone was found to be 186ºC indicated that form may contain some impurities which is eliminated by thorough crystallization of Domperidone

3.3.1.Saturation solubility study

It is evident that Domperidone is a weakly basic drug (pKa=7.4) and it is aqueous soluble under acidic pH (Salem et al., 2001). Based on solubility data, it was observed that the drug remains unionized at pH 7.4. Solubility of Domperidone in acidic pH was remarkably enhanced due to ionization. At 25˚ and 37˚C the concentration of Domperidone in each aqueous media (DDW, pH 7.4, pH 6.8) was found to be 187±0.007.
respectively. As large amount of unionized fraction of drug is present in basic media, the solubility is apparently decreased as compared to acidic media.

3.3.2. Partition coefficient

In accordance with OECD guideline 107 (OECD, 1995), the shake flask method (log Ko/w) was used to obtain the log P values of doperidone and SDs. The range of the results was 2.36±0.003 to 2.78±0.001.

3.4. Identification of pure Domperidone and polymers

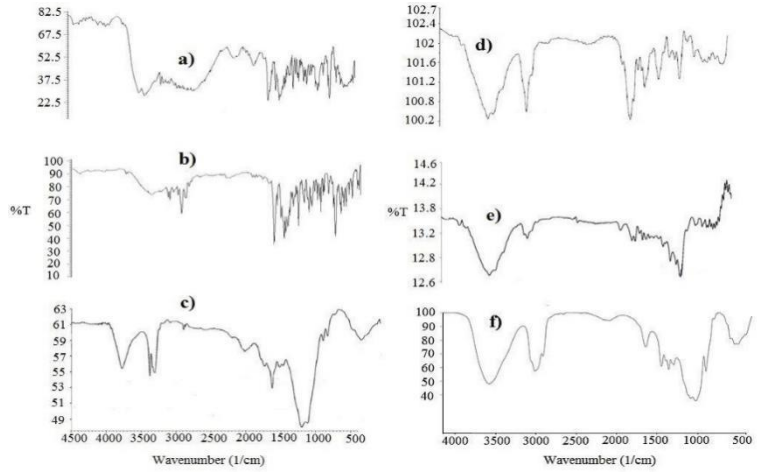


Fig. 3 FTIR spectra of a) Domperidone b) EC c) PVP K-30 d) HPβCD e) HPMC

FTIR spectroscopy was used to investigate how domperidone interacted with certain polymeric materials in a solid state. The hydroxyl functional groups were demonstrated by the distinctive O–H stretching band of 3412 to 3245.31 cm^{-1} in the doperidone hydrochloride FTIR spectrum (Fig. 5.3a). Strong C=O stretching was detected at 1639.49 cm^{-1}, while C–H stretching vibrations were detected at 2976.16 cm^{-1}, which is consistent with previously published literature (Patil et al., 2015).

The peaks showed a significant variation in the Domperidone pure sample (Fig. 5.3b). While the C=O stretching appeared at 1622.13 cm^{-1}, the C–H stretching bands appeared between 2935.66 cm^{-1} and 2987.74 cm^{-1}. These shifts, which are roughly 17.36 cm^{-1} for C=O and 11 to 40 cm^{-1} for C–H, indicate that the drug's molecular structure was somewhat changed during the purification process. The aromatic peaks in the EC spectra (Fig. 5.3c) at 579.18 to 918.78 cm^{-1} were used to identify phenol units. Peaks for C–OH stretching and CH_3 bending were found at 1112.60 cm^{-1} and 1381.17 cm^{-1}, respectively. Weak aldehyde signals were seen at 2875.85 cm^{-1} and 2979.03 cm^{-1}, while the broad band at 3484.97 cm^{-1} showed stretching of alcohol and amine (N–H).

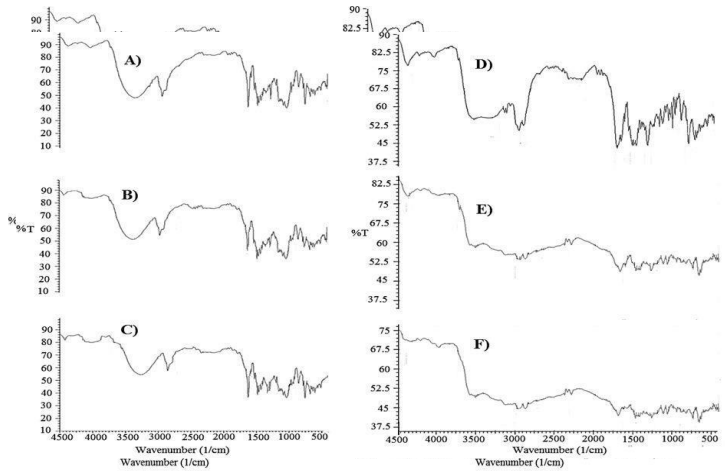
When compared to aliphatic C-H signals, Polyvinylpyrrolidone K-30 (PVP K-30) revealed a wide band of O-H stretching from 2935.66 to 3099.61 cm^{-1} (refer Fig. 5.3d). Peaks appeared to be located at 1639.10 cm^{-1} due to

C=O stretching as well as at 2926.77 cm^{-1} due to C–H stretching. A wide band due to appearance of moisture as reported earlier appeared at 3403.87 cm^{-1} (Paradkar et al., 2004).
Distinct absorption bands were observed at 3401.89 cm^{-1} corresponding to O–H stretching, at 2932 cm^{-1} indicative of C–H stretching, and at 1593 cm^{-1} attributed to aromatic C–C stretching in the hydroxypropyl β-cyclodextrin (HPβCD) spectrum (Fig. 5.3e). Additional signals were recorded at 1156 cm^{-1} for C–H stretching and at 1031 cm^{-1} for C–O stretching. Furthermore, hydroxypropyl methylcellulose (HPMC) (Fig. 5.3f) exhibited C=C bending within the range of 1378.06–1457.81 cm^{-1} and aromatic C–H bending at 610.35 cm^{-1}. A broad band at 3457.18 cm^{-1} was indicative of alcoholic O–H and amine (N–H) groups, implying the potential for hydrogen bonding within the polymer, while an alkyl C–H stretch was detected at 2928.28 cm^{-1}.Table 5: Thermodynamic parameters in binding of binary systems of Domperidone with carriers PVP K30 and HPβCD, over a temperature range in various aqueous media.

Carrier	**Temp. in °C**	**Temp. in K**	**DDW (kJ/mol)**			**pH 7.4 (kJ/mol)**			**pH 6.8 (kJ/mol)**		
			Ka (M^{-1})	ΔG	ΔH	ΔS	Ka (M^{-1})	ΔG	ΔH	ΔS	Ka (M^{-1})
PVP K-30	25	303	7160.9	–22.36	4.42	0.088	31571.6	–20.29	60.82	0.267	1156.7
	37	310	7450.53	–22.97	13.32	0.11	54460.1	–22.17	79.14	0.326	1478.4
	40	313	7829.13	–23.33	1.77	0.08	7309.83	–23.15	84.82	0.344	1886.39
	45	318	7913.6	–23.73	—	—	12203.6	–24.87	—	—	2950.37
HPβCD	25	303	54.43	–10.06	2.06	0.010	158.66	–12.76	6.23	0.075	58.21
	37	310	65.49	–10.77	19.77	0.098	173.62	–12.39	10.83	0.083	60.31
	40	313	70.49	–11.07	34.65	0.146	181.81	–13.53	8.00	0.059	61.35
	45	318	86.91	–11.80	—	—	187.57	–13.83	—	—	63.65

3.4.1.Determination of aqueous solubility of Domperidone

Poor solubility of Domperidone was found in doubly distilled water (~187±0.007 µg/mL, 25˚C and 253.10±0.004, 37˚C). When SD fraction of PVP K-30 is increased, linearly DOMPERIDONE solubility is found to be increasing. As drug quantity was constant (100 mg), solubility is improved up to drug-carrier ratio 1:5 (w/w). For all PVP K-30-DOMPERIDONE binary systems, drug solubility is found to be higher compared to that of HPβCD-DOMPERIDONE binary system at 25 and 37˚C. Compared to pure drug in pH 7.4 solubility enhancement is found 4.0-4.5 folds higher. Moreover, in DDW (~ pH 6) it is found ~ 4.75 folds. (Fig. 5.6).
Mole ratio of drug and carrier is very important in case of inclusion complex. When inclusion complex is formed with 1:1 mole ratio then total complexation is possible. In case of SD with 1:5 (w/w) ratio the mole ratio is calculated as 0.97:1 ~ equal to 1:1. The data of solubility study of each system were depicted in Table 6.



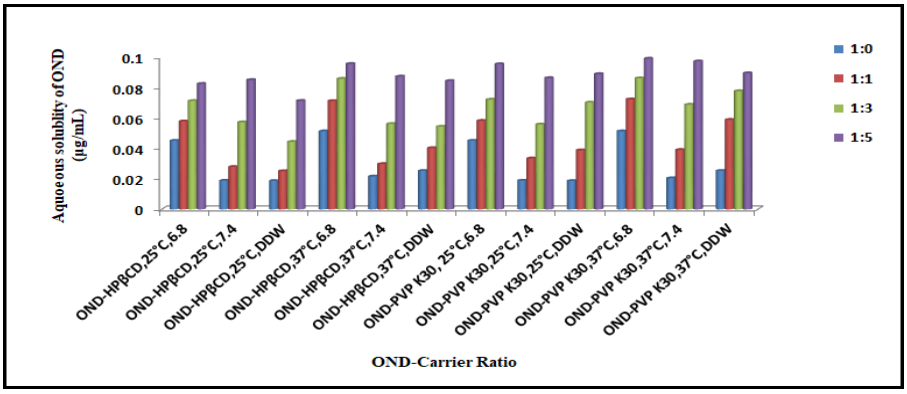


Fig. 6: Comparison of aqueous solubility of Domperidone in various binary mixtures, various aqueous media and at temperatures 25 and 37˚C

3.4.2.Identification of Solid Dispersions

Fig. 7: FTIR spectra of A) Domperidone -HPβCD 1:1 binary complex; B) Domperidone - HPβCD 1:3 binary complex; C) Domperidone -HPβCD 1:5 binary complex D) Domperidone -PVP K-30 1:1 binary complex; E) Domperidone -PVP K-30 1:3 binary complex; F) Domperidone -PVP K-30 1:5 binary complex

The spectra of SDs prepared with Domperidone -HPβCD (1:1, 1:3, 1:5 w/w) showed distinct peaks at 2942, 2935.66 and 2920.60 cm-1 indicated the presence of C-H stretching vibrations (Fig. 5.7 A-C). The presence of O-H band is indicated by the peaks present at 3319.49, 3299 and 3251.07 cm-1 Major frequencies of shifting of wave number and lowering of intensity of peaks were observed in both cases because of physical binding between drug and carrier molecules which may not cause any chemical incompatibility. Drug and carrier molecules are molecularly dispersed, so some of their functional groups come in contact with other causing physical bonding due to weak forces such as Van der Walls force. The solid binary systems have successfully established an inclusion complex between the drug and the carrier, based on the above findings.

3.5. DSC analysis of solid dispersions

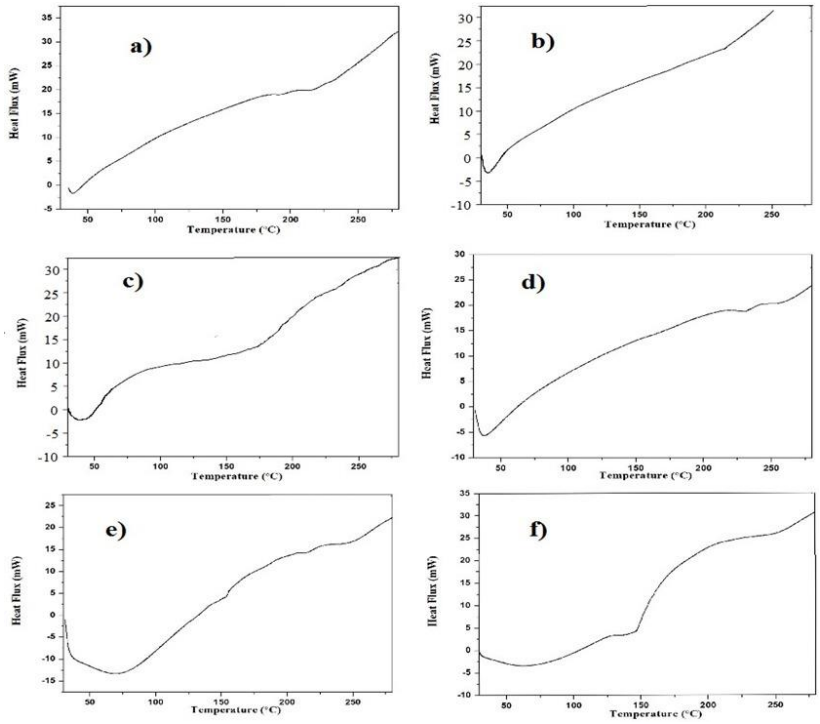


Fig. 8 Differential scanning calorimetry study.

The peak of DOMPERIDONE has nearly vanished, according to the DSC thermogram of solid binary systems (Fig. 8a-f). The crystalline drug DOMPERIDONE changes to an amorphous state in SD, which may indicate that the drug is molecularly dispersed with PVP K-30 and may bind into the cyclodextrin cavity to form an inclusion complex. During the DSC experiment, both the drug and the carrier are heated to high temperatures, which promotes the drug's amorphization.

Table 7 Data of Percentage moisture content, percentage moisture absorption and percentage drug content of patches (n=3)

Patch Code	% Moisture Content (PEG)	% Moisture Content (DBP)	% Moisture Absorption (PEG)	% Moisture Absorption (DBP)	% Drug Content (PEG)	% Drug Content (DBP)
P1	1.29 ± 0.06	1.11 ± 0.032	3.14 ± 0.2	1.28 ± 0.71	91.39 ± 1.04	94.53 ± 0.02
P2	1.28 ± 0.045	1.21 ± 0.51	3.37 ± 0.31	1.92 ± 0.32	92.18 ± 1.81	96.91 ± 2.36
P3	1.31 ± 0.02	1.06 ± 0.035	1.97 ± 0.15	1.01 ± 0.2	87.45 ± 1.81	93.76 ± 4.92
P4	2.77 ± 0.047	1.89 ± 0.043	3.64 ± 0.04	1.90 ± 0.023	92.18 ± 1.34	96.12 ± 2.09
P5	3.10 ± 0.023	2.22 ± 0.31	3.83 ± 0.052	2.62 ± 0.02	94.54 ± 1.81	95.33 ± 1.04
P6	2.41 ± 0.04	1.23 ± 0.012	2.79 ± 0.046	2.10 ± 0.031	92.18 ± 3.63	95.33 ± 3.78

3.5.1. In Vitro Release Study Using a Modified Diffusion Cell

The in vitro release of domperidone was evaluated using a modified Keshary-Chien diffusion cell. The receptor compartment was filled with 50 mL of phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C. For an initial baseline study, a solution containing 302.69 µg of domperidone (equivalent to the drug content in a 3.935 cm² patch) dissolved in 3 mL of chloroform was placed in the donor compartment. A cellophane membrane was mounted between the donor and receptor chambers, sealed with the patch's release liner.

This donor solution served as a control to represent the maximum release potential without formulation constraints. Over 8 hours, this solution released 36.07 ± 0.31% of the loaded drug (Table 5.10). The retarded release profile is attributable to the inherent lipophilicity of domperidone, which limits its diffusion into the aqueous receptor medium. This baseline data confirms that a well-designed patch formulation is necessary to modulate the release kinetics for optimal therapeutic control.

Subsequently, the formulated transdermal patches (P1–P6) were evaluated under the same conditions to assess their ability to control the drug release rate. The drug release profile from the transdermal patches was governed by several formulation variables, including the properties of the polymer matrix, the type and concentration of plasticizers, and the inclusion of permeation enhancers. Initial drug diffusion studies provided critical insights for the selection of appropriate polymer blends.

To achieve an optimal balance between drug release and patch flexibility, plasticizers—specifically polyethylene glycol (PEG) and dibutyl phthalate (DBP)—were incorporated. As illustrated in Figure 9 (a–b), higher plasticizer concentrations resulted in faster drug release. Patches formulated with PEG demonstrated superior release performance compared to those with DBP, which is attributable to the inherent hydrophilic nature of PEG that enhances drug diffusion and solubility.

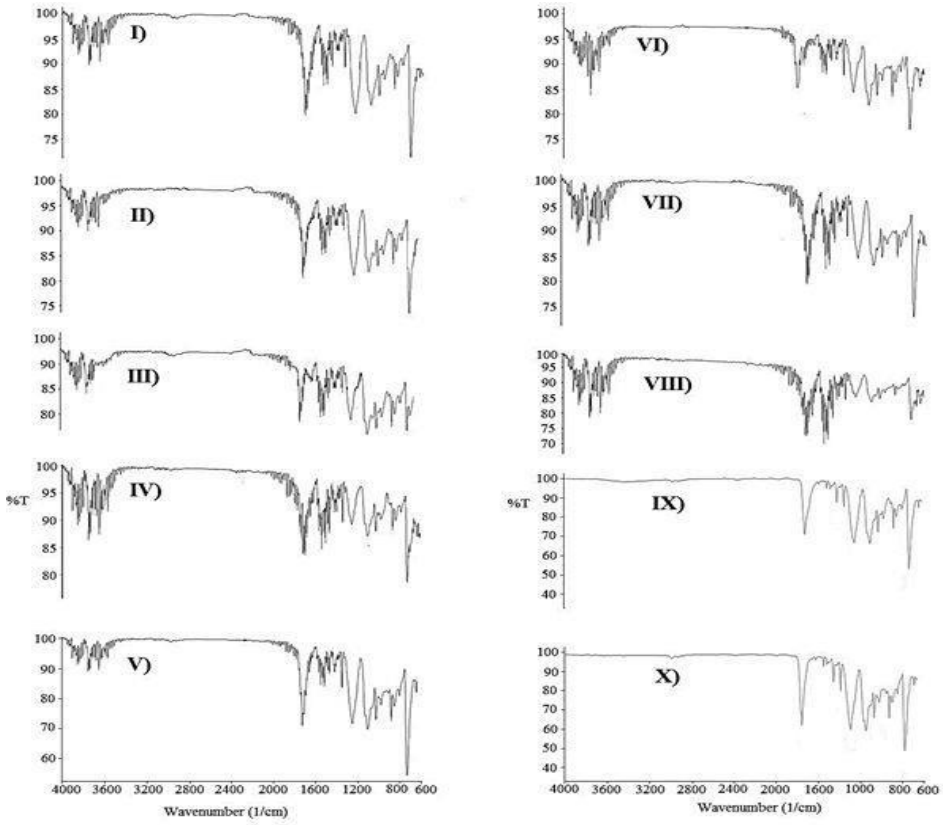
Polyvinylpyrrolidone (PVP K30) was added to the formulation to stabilize the system and prevent crystallization of the lipophilic drug. Furthermore, the inclusion of the hydrophilic polymer low-viscosity hydroxypropyl methylcellulose (HPMC) served to facilitate the release of the weakly water-soluble domperidone. The combination of PVP K30 and HPMC produced a synergistic effect, significantly accelerating the rate of drug release. Despite the incorporation of ethyl cellulose (EC) to provide structural integrity, the patches consistently exhibited low permeability, enabling a prolonged release of the drug over an extended period.

The formation of a composite matrix by ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC) has been reported to create hydrophilic pores that facilitate regulated drug diffusion (Patel et al., 2009). This principle was observed in the current study, where the drug release was significantly influenced by the type and concentration of plasticizer.

For patches plasticized with DBP, the cumulative drug release increased with higher plasticizer concentration: formulations P1, P2, and P3 (30%, 40%, and 50% v/w DBP, respectively) released 58.41 ± 3.22%, 65.10 ± 4.74%, and 74.65 ± 10.58% of the domperidone load. Patches plasticized with PEG demonstrated a more pronounced release, with P1 and P2 (30% and 40% v/w PEG) achieving 73.21 ± 4.55% and 79.25 ± 3.16% release, respectively. This enhanced performance is attributed to PEG's hydrophilic nature, which increases polymer chain mobility and drug diffusion.

The incorporation of domperidone as a solid dispersion (SD) further augmented the release rate across all formulations. SD-PEG patches at 30% and 40% v/w (P4, P5) released 80.59 ± 6.11% and 93.79 ± 7.81%, respectively. Similarly, SD-DBP patches (P4-P6) showed concentration-dependent release, with 65.30 ± 7.45%, 74.58 ± 5.23%, and 87.00 ± 11.65% release at 30%, 40%, and 50% v/w DBP. This phenomenon is consistent with literature indicating that plasticizers enhance molecular mobility and drug flow within the polymer matrix (Bergo and Sobral, 2006).

However, patches containing 50% w/w PEG (P3 and P6) were excluded from further development due to poor mechanical properties, exhibiting rough surfaces and weak adhesion, underscoring the need to balance release performance with practical patch characteristics.



3.5.2. Identification test of patches

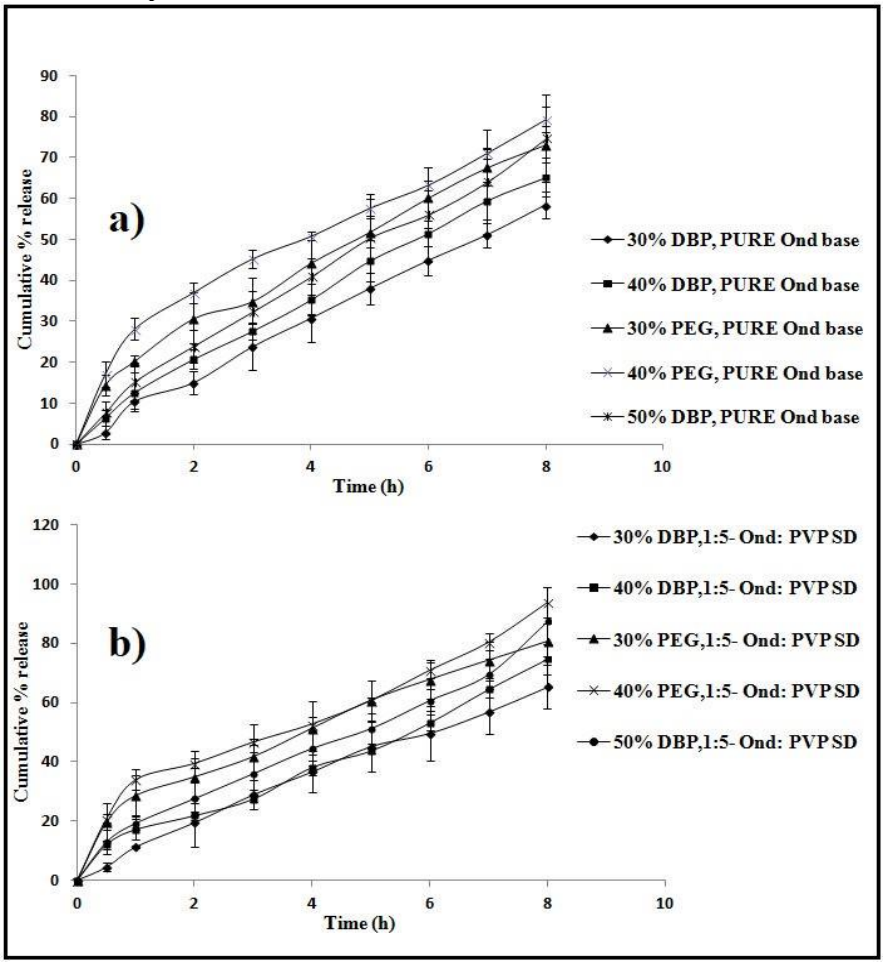


Figure 11: FTIR spectra showcasing different patch formulations: I) Patch with pure Domperidone and 30% PEG; II) Patch with pure Domperidone and 40% PEG,;III) Patch with pure Domperidone and 30% DBP,;IV) Patch with pure Domperidone and 40% DBP,;V) Patch with pure Domperidone and 50% DBP,;VI) Solid dispersion (SD) patch with 30% PEG,;VII) SD patch with 40% PEG,;VIII) SD patch with 30% DBP,;IX) SD patch with 40% DBP; X) SD patch with 50% DBP.

The potential for interaction between domperidone and the transdermal patch components was assessed using Fourier Transform Infrared (FTIR) spectroscopy. The spectrum for pure domperidone (Fig. 5.11 I) displayed characteristic functional group vibrations, including: aromatic C=C stretching at 1542 cm^{-1}, a sharp ketone (C=O) stretch at 1733.69 cm^{-1}, and strong conjugated phenyl ring vibrations at 719.6 cm^{-1} and 670.2 cm^{-1}. Other significant peaks were consistent with methyl group bending (1458.32 cm^{-1}), NO_2 stretching (1343.2 cm^{-1}), and C–O–C stretching (1248 cm^{-1}).

FTIR analysis revealed formulation-dependent interactions. Increasing PEG concentration to 40% induced minor shifts (~2-3 cm^{-1}) in the NO_2 and C–O–C peaks (Fig. 5.11 II), indicative of weak physical interactions. In contrast, DBP-based patches showed preserved phenyl vibrations, confirming the stability of the aromatic ring system. More significant changes were observed in solid dispersions (SD). SD-PEG patches (Fig. 5.11 VI, VII) showed peak broadening in the C–H region (~2946-3044 cm^{-1}) and a shift in the C=O stretch to 1639–1644 cm^{-1}, suggesting stronger drug-polymer interactions that alter the molecular environment of domperidone.

The most profound spectral alterations were observed in the solid dispersion (SD) patches plasticized with DBP (Fig. 5.11 VIII–X). In these formulations, the characteristic C–H stretching peak of domperidone disappeared entirely, concurrent with substantial bathochromic shifts of the C=O stretching peak by approximately 79, 90, and 92 cm^{-1} for the 30%, 40%, and 50% DBP concentrations, respectively. These findings provide conclusive evidence of a strong drug-carrier interaction, which is strongly indicative of the formation of an amorphous state. This transition is critical, as it inhibits drug crystallization and promotes a homogeneous distribution, thereby potentially enhancing the solubility and in vitro release of domperidone from the transdermal system.

3.6. SEM analysis Solid dispersion and patches

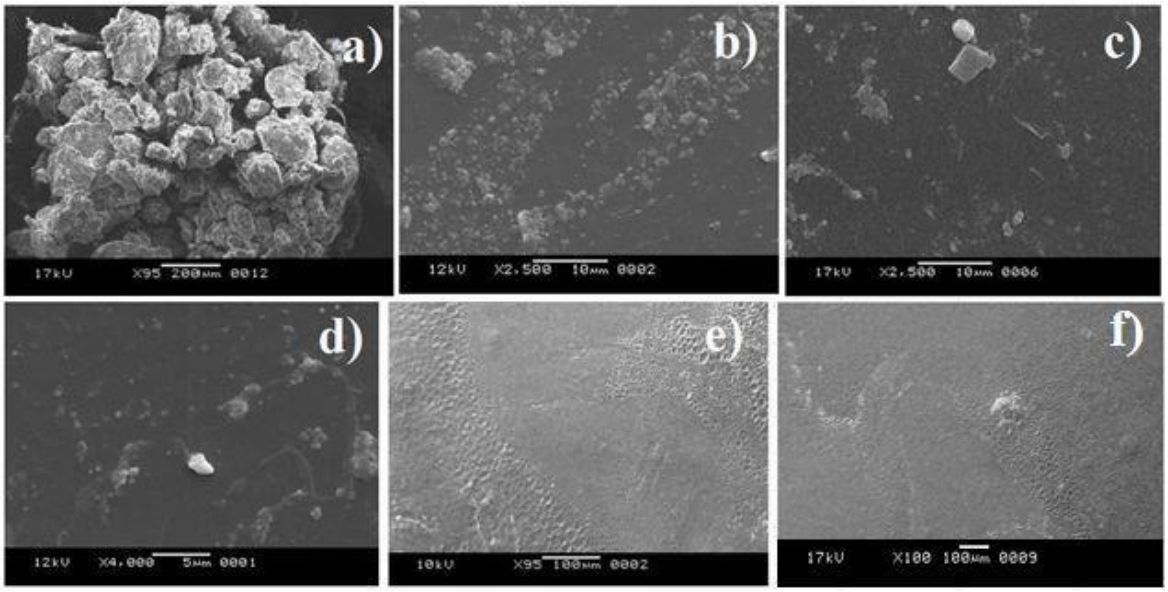


Fig. 12 Scanning electron micrographs

SEM morphology of Domperidone -PVP K-30 (1:5 w/w) SD showed rough wrinkled surface (Fig. 12). This is due to homogeneous dispersion of drug within the carrier. Surface morphology of blank patch (Fig. 12).

Consistent with the findings of Pattnaik et al. (2011), who reported the spherulitic crystallization of domperidone from chloroform solutions, the SEM analysis in this study revealed distinct morphological differences. Micrographs of patches containing the pure drug (with PEG or DBP) displayed a rough, heterogeneous matrix (Fig. 12), indicative of drug crystallization. In contrast, patches formulated as solid dispersions (SD) exhibited a smooth, amorphous morphology (Fig. 12), confirming the uniform distribution of domperidone within the polymer blend. This transition to a homogeneous matrix is attributed to the inclusion of PVP K-30, which functions as an effective antinucleating agent, suppressing drug crystallization. These results collectively demonstrate that the solid dispersion strategy successfully inhibits the inherent crystallinity of domperidone when processed with chloroform, leading to a more favorable and consistent patch microstructure.

3.7. Skin irritation test

A skin irritancy test was conducted to evaluate the safety of the optimized formulation. The study comprised three groups: a control group (no treatment), a standard group treated with a pure drug-loaded patch (P3, 3.935 cm^2), and a test group treated with the optimized solid dispersion patch (P6, 3.935 cm^2, Domperidone:PVP K-30, 1:5 w/w).

The safety of a transdermal formulation is confirmed when the Primary Irritation Index (PII) value is below 2, as established by Soliman et al. (2011). In accordance with this criterion, the optimized P6 patch was found to be non-irritating, with a calculated PII value of less than 2. The detailed results are presented in Table 16, confirming the topical safety of the selected formulation.

Table 16 PII Scores of Skin Sensitivity Study

Patch Code	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	PII
	Er	**Ed**	*Er*	**Ed**	*Er*	**Ed**	*Er*	**Ed**
Control	0	0	0	0	0	0	0	0
P3	0	0	0	0	0	0	0.5	0.5
P6 (DBP)	0	0	0	0	0	0	0.5	0.5
P6 (PEG)	0	0	0.5	0.5	1	0	1	0.5

DISCUSSION

The present investigation was undertaken to formulate a transdermal drug delivery system for domperidone. The primary challenge of poor solubility was overcome by employing solid dispersion (SD) technology, aiming to improve dissolution, bioavailability, and achieve controlled release kinetics. Furthermore, the impact of various polymers and plasticizers on the physicochemical and mechanical characteristics of the patches was systematically evaluated to identify an optimal formulation.

Analytical Method Validation and Solubility Profiling

The maximum absorbance (λmax) of domperidone was confirmed at 248 nm, which is consistent with published data, thereby validating the suitability of the UV spectrophotometric method for analysis. Solubility studies demonstrated a pH-dependent profile, with significantly greater solubility observed in acidic medium (pH 6.8) compared to basic conditions. This aligns with the weakly basic nature of domperidone (pKa = 7.4), as a lower pH promotes ionization, thereby enhancing aqueous solubility. A positive correlation between solubility and temperature was also established.

Phase Solubility and Thermodynamic Analysis

Phase solubility studies demonstrated an AL-type diagram, where domperidone solubility increased linearly with rising concentrations of both HPβCD and PVP K-30. This linear relationship is indicative of the formation of soluble inclusion complexes. Thermodynamic parameters revealed that the complexation process was both spontaneous and endothermic for both polymers. However, the PVP K-30 systems, particularly at a 1:5 drug-to-polymer ratio, exhibited superior complexation efficiency and stability compared to HPβCD.

Solid Dispersion Formation and Characterization

The successful formation of amorphous solid dispersions was confirmed through comprehensive characterization. FTIR spectroscopy showed significant shifts in characteristic drug peaks, while DSC analysis revealed the complete disappearance of the crystalline domperidone melting endotherm. These findings collectively confirm strong drug-polymer interactions and a transition to the amorphous state. SEM micrographs provided further validation, showing a uniform, smooth morphology in the SD-loaded patches, which is consistent with effective suppression of drug crystallinity.

Physicochemical Evaluation of Patches

The fabricated patches were systematically evaluated for critical quality attributes, including moisture content, drug content uniformity, and mucoadhesive strength. Patches plasticized with PEG exhibited higher moisture content and a faster drug release rate compared to those with DBP, a direct consequence of PEG's inherent hydrophilicity and its role in enhancing polymer chain plasticity. Among all formulations, the optimized patch (P6, containing 50% DBP and the solid dispersion) demonstrated an ideal balance, exhibiting superior drug content uniformity, a controlled release profile, and excellent physical characteristics.

In Vitro Release and Kinetic Analysis

In vitro diffusion studies confirmed that solid dispersion (SD)-loaded patches achieved a significantly higher cumulative drug release than those containing the pure drug. The maximum release (93.79 ± 7.81%) was observed with formulation P5 (40% PEG). The hydrophilic polymers PVP K-30 and HPMC synergistically enhanced drug dissolution, while ethyl cellulose (EC) provided a structural framework that modulated release through its low permeability. The inclusion of plasticizers, particularly PEG, was critical in increasing free volume and molecular mobility within the polymer matrix, thereby enhancing release efficiency. Kinetic modeling indicated that the

release mechanism followed anomalous (non-Fickian) transport, governed by a combination of drug diffusion and polymer chain relaxation.

Skin Irritation Test: The optimized SD patch (P6) was found to be non-irritating with a primary irritation index (PII) of <2, indicating it is safe for dermal application and potentially suitable for clinical use.

CONCLUSION

This study successfully developed and characterized a transdermal patch for domperidone utilizing solid dispersion (SD) technology to address its primary challenges of poor solubility and low oral bioavailability. The approach centered on using hydrophilic polymers, PVP K-30 and HPβCD, with the 1:5 (w/w) domperidone-PVP K-30 SD demonstrating the most significant enhancement—a 4.75-fold increase in aqueous solubility.

The novelty of this work lies in the strategic integration of SD technology within a matrix-type transdermal system, optimized through a balanced blend of polymers (PVP K-30, HPMC, EC) and plasticizers (PEG, DBP). The optimized formulation, P6 (1:5 SD with 50% DBP), exhibited excellent physicochemical properties, including a smooth morphology, high drug content uniformity (95.33 ± 3.78%), and a sustained release of 87.00 ± 11.65% over 8 hours. Comprehensive characterization (FTIR, DSC, SEM) confirmed the formation of an amorphous solid dispersion, with the complete suppression of drug crystallinity and uniform distribution within the polymer matrix. Drug release followed a non-Fickian (anomalous) transport mechanism, indicating a coupled process of diffusion and polymer relaxation. Furthermore, the formulation demonstrated excellent topical safety, with a Primary Irritation Index (PII) well below the established irritancy threshold.

In summary, the domperidone-loaded transdermal patch presented herein represents a promising, patient-compliant alternative to conventional oral therapy. It offers a viable strategy for enhancing bioavailability, ensuring controlled delivery, and improving patient compliance for poorly soluble drugs, with potential applicability beyond domperidone.

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Conflict of interest

The authors have no conflict of interest.

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