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Original Research Article

Development and *In vitro* Evaluation of Self-Adhesive Matrix-Type Transdermal Delivery System of Ondansetron Hydrochloride

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Abstract

Purpose: *To develop and evaluate self-adhesive matrix-type ondansetron hydrochloride (OND) transdermal formulation.*
Methods: *OND transdermal patches were prepared using solvent casting method. The matrix polymer composition was Eudragit E 100, polyvinyl pyrrolidone and either propylene glycol or dibutyl sebacate as plasticizer. Mean patch thickness, tensile strength, moisture content, water absorption capacity and drug content of the patches were studied. In vitro release and permeation of the patches were determined using Franz diffusion cell.*
Results: *Mean patch thickness, moisture content, and water uptake increased with increased contents of polyvinyl pyrrolidone (PVP) and plasticiser. Higher levels of PVP and plasticiser increased drug release. Addition of release modifier such as succinic acid (SA) and myristic acid (MA) to the patch formulations produced a significant increase in drug release from the patch. Higuchi plots for patches containing propylene glycol (PG) were non-linear (r^2 = 0.9564), indicating that they did not follow Higuchi release model whereas the plots for most of the patches containing dibutyl sebacate (DBS) followed Higuchi release model (r^2 = 0.9974).*
Conclusion: *DBS is a superior plasticiser to PG for OND matrix patches while succinic acid (SA) is a more effective release modifier than myristic acid (MA) for PG patches.*

Keywords: *Ondansetron hydrochloride, Drug release, Release modifier, Transdermal, Dibutyl sebacate, Succinic acid, Higuchi model, Plasticizer*

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect encountered by cancer patients during chemotherapy treatment. Ondansetron is a serotonin subtype 3 (5-HT3) receptor antagonist used in CINV management. Orally administered OND undergoes extensive hepatic first-pass metabolism, which accounts for its low bioavailability and short half-life [1]. It tends to be vomited before being absorbed and has limited use in patients with difficulty swallowing after chemotherapy [2,3]. Polymers act as the backbone of systems for transdermal delivery and promote drug release in a pre-designed manner. Plasticiser is added to improve flexibility, thus reducing patch brittleness [4-7]. OND was selected as the model candidate for this study because it possesses several ideal characteristics for transdermal delivery system such as low molecular weight and the desired range of log P, Pka value and melting point [8].

Gwak *et al* investigated the effects of vehicles on *in vitro* permeation of OND liquid formulations across mouse skin and found that ethanol and water were the most effective vehicles [9]. However, they do not mix well with pressure-sensitive adhesive (PSA) and so a further study was carried out using different vehicles to develop OND transdermal PSA matrix formulations [10]. Krishnaiah *et al* prepared hydroxypropyl cellulose gel drug reservoir formulations of OND and evaluated the effect of menthol (a penetration enhancer) on drug permeation across rat epidermis. Pattnaik *et al* reported that chloroform was a preferred casting solvent for OND in transdermal films [10]. OND matrix type transdermal patches were prepared by Swain *et al* using different ratios of ethyl cellulose (EC) and polyvinylpyrrolidone (PVP) polymers [2].

The objective of this study was to develop the transdermal formulation of OND with a capacity to provide the required therapeutic drug concentration.

EXPERIMENTAL

Materials

Ondansetron hydrochloride (OND) was a gift from Aurobindo Chemicals, India. Eudragit E100 was a gift from Evonik Rohm GmbH Pharma Polymers, Germany. Polyvinylpyrrolidone (PVP, K-30) was purchased from BASF Chemical Company, Germany. Propylene glycol (PG) and succinic acid (SA) were purchased from Merck Chemicals, Germany while dibutyl sebacate (DBS) was obtained from Sigma-Aldrich Chemie GmbH, Riedstr, Germany. Myristic acid and eugenol were purchased from Spectrum Chemical Mfg Corp, USA. All the solvents used were of analytical reagent grade.

Preparation of the patches

The composition of the patches are shown in Table 1. The patches were prepared by dissolving 500 mg Eudragit E100 in 3 mL chloroform followed by addition of PVP with slow, uniform magnetic stirring at room temperature. Plasticiser (either PG or DBS) and 16 mg OND was added to the solution and stirred for 15 – 20 min. Release modifier (either SA or MA) was then incorporated. Finally, eugenol was added and the solution stirred for 30 min, poured slowly into the centre of a stainless steel ring with aluminium foil as a backing layer, and then dried at room temperature for 24 h.

Determination of patch thickness

Patch thickness was measured using a digital micrometer (Mitutoyo, Japan). A mean of six readings was obtained. The results reported a mean of six measurements (Table 1).

Determination of tensile strength

The tensile strength of the patches was evaluated using Instron 4204 Tensile tester, with a 50 KN load cell (Instron, UK). Six samples of each formulation were tested at an extension speed of 5mm/min [18]. The test was carried out at 25 ± 2 °C and 56 ± 2 %RH and tensile strength calculated as in Eq 1.

$\tau = L_{max}/A_i$ …………………………………….. (1)

where τ is the tensile strength; L_{max} is the maximum load; and A_i is the initial cross sectional area of the sample. The results are reported as mean of six readings (Table 1).

Evaluation of drug content

A known area of each patch was weighed accurately and dissolved in 2 mL chloroform followed by dilution with distilled water and then filtered. Drug content was analysed by UV spectrophotometer (PerkinElmer, USA) at 249 nm. A drug-free film was used as control. A mean of three readings was recorded. The results are reported as mean of six readings (Table 2).

Measurement of moisture content

Each patch was weighed and kept in a desiccator containing fused calcium chloride at 40 °C for 24 h. The patches were reweighed until a constant weight was obtained. A mean of three readings was taken. The results are reported as mean of six readings (Table 2).

Water absorption studies

Each patch was weighed and kept at room temperature for 24 h with exposure to two relative humidities of 75 % (containing saturated sodium chloride solution) and 93 % (containing saturated ammonium hydrogen phosphate solution) in different desiccators. The patches were reweighed until a constant weight was obtained. A mean of three readings was recorded. The results are reported as mean of six readings (Table 2).

In vitro release studies

In vitro release studies were carried out in a Franz diffusion cell (PermeGear, USA). A piece of circular matrix patch about 3cm^2 was mounted on receptor compartment, which was filled with freshly prepared phosphate buffered saline (pH 7.4). Temperature was maintained at 32 ± 0.5 °C. A sample (0.5 mL) was withdrawn every hour for 8 h and replaced immediately with the same volume of saline solution. The withdrawn samples were diluted and analysed by UV spectrophotometry at 249 nm [Shimadzu UV-1700, UK]. A mean of three readings was recorded (Table 3).

In vitro permeation studies

A matrix patch was bound intimately with a section of freshly excised albino mouse abdominal skin on the receptor compartment. The skin's dermal side was kept in contact with the receptor liquid at all times to ensure continuous drug permeation. All other analysis conditions were similar to those used for *in vitro* release studies above. A mean of three readings was recorded (Table 3).

Attenuated total reflectance-Fourier transform infrared (ATR-FTIR) studies

The patches were analyzed by attenuated total reflectance-Fourier transform infrared (ATR-FTIR) studies on a Magma-IR™ Spectrometer 750 (Nicolet Instrument Corp.), equipped with a Golden Gate Single Reflection Diamond ATR. Spectra were recorded on mean of 32 scans of transdermal patch at a resolution of 4 cm^{-1} and in the frequency range of 400 - 4000 cm^{-1}.

Statistical analysis

The results obtained were treated statistically using one-way analysis of variance (ANOVA). Post-hoc Tukey-HSD (Honestly Significant Difference) test was performed when there was a statistically significant difference, which was set at $p \leq 0.05$.

RESULTS

Physicochemical and mechanical characteristics of patches

The mean thicknesses of the films varied from 0.08 to 0.18 mm while mean tensile strength ranged from 4.36 to 6.93 MPa. Transdermal patches with a combination of lower thickness, higher tensile strength, optimal range of peel adhesion value (40 to 200 cN/cm) were subjected to *in vitro* release and permeation studies.

Moisture content, water absorption and drug content

Table 3 shows that the mean content of OND in all the patches was > 99 % while moisture content and water absorption capacity were dependant on type and concentration of plasticizer used in the study. Since patch with too much of water is prone to microbial growth while too less amount of water is prone to cracking and chances to absorb water from our skin. From the Table 2 it is clear that PG containing patches have higher percentage of moisture content and water absorption (> 1) compare to DBP containing patches but drug contents of both the categories are equally distributed. Therefore, it is important to perform physicochemical studies in order to determine the suitable patch therapy over longer period of time without losing integrity of the polymeric composition of the transdermal patches.

Table 1: Mean thickness and tensile strength of patches

Patch code	PVP (mg)	Plasticiser	(%)	Mean thickness (mm)	Mean tensile strength (MPa)	Peel adhesion (cN/cm)
E1	0	PG	10	0.09	4.36 ± 0.40	242 ± 3
E2	0		20	0.10	4.80 ± 0.30	231 ± 12
E3	50		10	0.10	4.95 ± 0.70	114 ± 20
E4	50		20	0.13	6.73 ± 0.50	39 ± 2
E5	100		10	0.16	5.15 ±0.30	37 ± 3
E6	100		20	0.18	6.89 ±0.40	15 ± 0
E7	0	DBS	10	0.08	4.90 ± 0.40	287 ± 14
E8	0		20	0.09	4.92 ±0.60	275 ± 7
E9	50		10	0.09	5.01 ±0.70	209 ± 3
E10	50		20	0.11	6.57 ± 0.30	97 ± 5
E11	100		10	0.13	5.69 ± 0.20	88 ± 4
E12	100		20	0.15	6.93 ± 0.50	41 ± 8

Note: *For all formulations, the Eudgragit :OND ratio was 500 :16 (mg)*

Attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectra

A comparison of the ATR-FTIR spectra of the individual patch components (Eudragit E 100, PVP and OND) as well as the patch itself is presented in Figure 1. The FTIR spectra of the formulation containing E 100: PVP: OND showed all the peaks for the polymers. The characteristic peaks of E 100 and PVP were observed at 2953cm^{-1} and 1723cm^{-1}, 1653cm^{-1}, 1657cm^{-1}, 1641cm^{-1}, 1437cm^{-1}, and 843cm^{-1} respectively. No significant shifts in the peaks corresponding to the drug or polymers were observed in the formulation matrix. Some characteristic peaks corresponding to the drug were found to overlap those of the polymer.

***In vitro* drug release**

The results of cumulative percent release, release rate (µgm/cm^2/hr) and drug release kinetics after 8 hours are shown in Table 3 and Figures 2 and 3, respectively. The regression correlation, r^2 value for release kinetic models for all formulations was given in Table 5.

Table 2: Moisture content, water absorption capacity, and mean drug content of patches

Patch Code	Moisture content (wt %)	Water absorption (wt %)		Mean drug content (µgm/cm2)
		75% RH	93% RH	
E1	1.43±0.14	1.63±0.37	1.75±0.26	426.12±7.15
E2	1.62±0.12	1.76±0.12	1.82±0.14	426.36±4.89
E3	1.75±0.50	1.82±0.17	1.96±0.10	426.43±6.82
E4	2.03±0.38	2.08±0.19	2.14±0.20	426.56±9.69
E5	2.42±0.27	2.31±0.27	2.48±0.17	426.63±8.37
E6	2.74±0.13	2.65±0.30	2.95±0.11	427.26±7.48
E7	1.02±0.25	1.05±0.07	1.15±0.09	426.18±6.62
E8	1.08±0.43	1.08±0.09	1.18±0.06	426.28±11.93
E9	1.16±0.19	1.14±0.10	1.44±0.13	426.51±13.05
E10	1.21±0.20	1.19±0.03	1.76±0.20	426.21±8.60
E11	1.32±0.19	1.28±0.09	1.83±0.16	426.42±9.02
E12	1.51±0.21	1.34±0.12	2.04±0.18	426.43±5.81

Table 3: Cumulative drug release and release rate at 8 h with or without release modifier

Patch code	Drug release (%)			Release rate (µg/cm2/h)		
	-	Release modifier (4%)		-	Release modifier (4%)	
		S	M		S	M
E1	5.92	41.29	19.43	2.86	13.92	1.70
E2	10.84	54.34	22.19	0.02	10.66	23.92
E3	7.27	44.63	28.80	1.73	16.21	14.33
E4	16.53	54.67	31.81	1.94	9.07	14.83
E5	14.54	45.51	34.04	1.32	10.18	14.72
E6	18.06	57.27	38.27	1.08	11.38	7.10
E7	26.32	-	29.91	8.52	-	6.29
E8	29.98	-	30.15	9.76	-	5.72
E9	37.66	-	38.88	12.09	-	32.10
E10	42.85	-	43.58	20.74	-	21.57
E11	48.57	-	42.53	10.84	-	16.90
E12	47.66	-	43.86	15.21	-	14.10

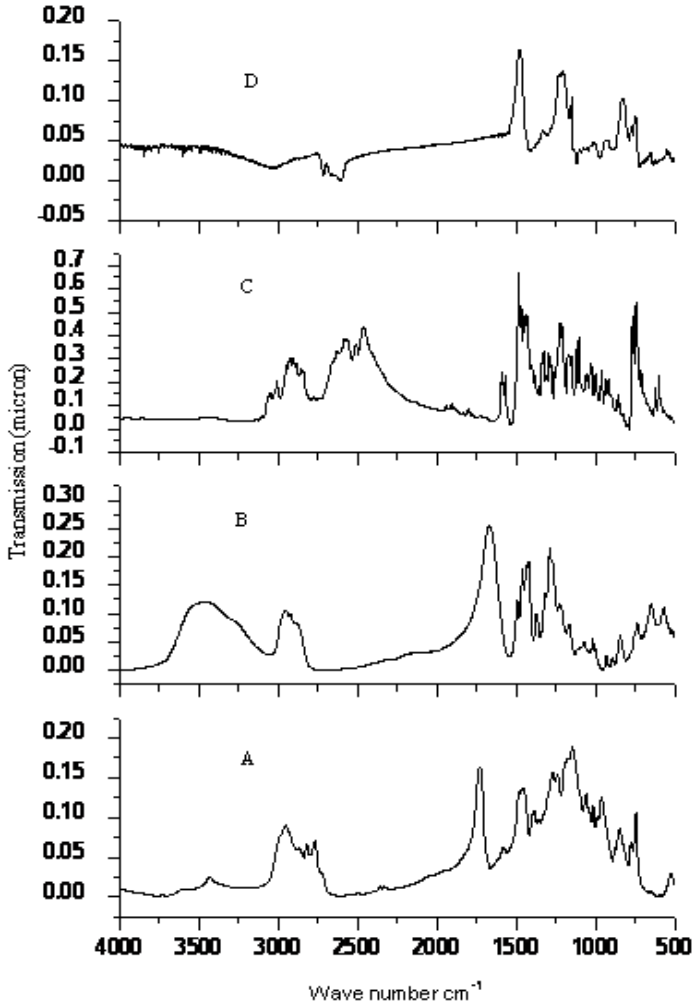

Figure 1: ATR – FTIR spectra of patch and patch components. A: Eudragit E 100, B: poly vinyl pyrrolidone, C: pure Ondansetron HCl, D: E 100:PVP:OND matrix patch

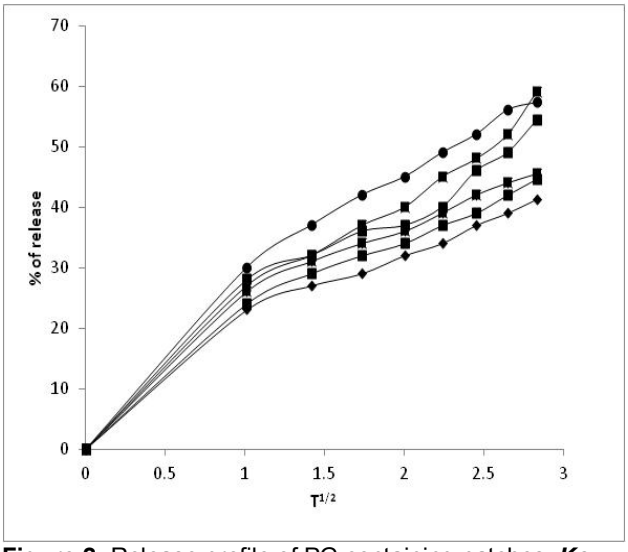

Figure 2: Release profile of PG containing patches. ***Key:*** Formulations E 1 (♦), E 2 (■), E 3 (▲), E 4 (x), E 5 (*), E 6 (●)

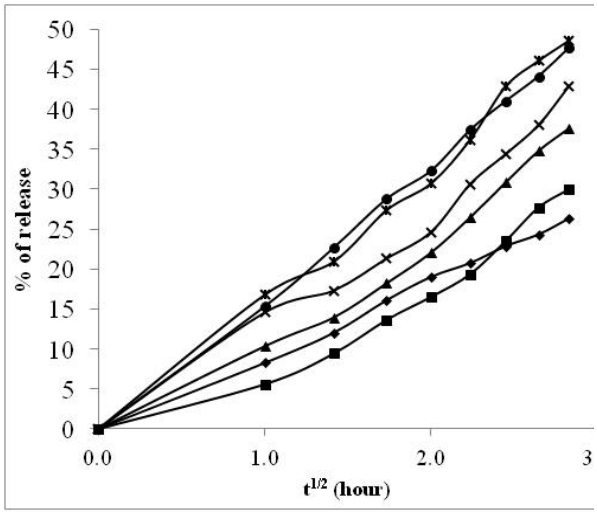

Figure 3: Release profile of DBP containing patches. ***Key:*** Formulations E 1 (♦), E 2 (■), E 3 (▲), E 4 (x), E 5 (*), E 6 (●)

Table 4: Kinetic drug release data for the patches; Q = cumulative amount of release at 8 h

Patch code	Zero order: $Q = k_0t+c$			Higuchi: $Q = k_Ht0.5 +c$			Weibull distribution: log [ln (1/1-*m*)] = β log (*t*) – log(*a*)		
	K_o	c	r2	K_H	c	r2	β	r2	a
E1	09.32	29.85	0.9523	43.92	02.63	0.8565	0.48	0.9830	2.59
E2	08.66	26.36	0.9543	40.66	03.58	0.9346	0.53	0.9353	2.85
E3	07.84	24.51	0.9276	36.21	04.73	0.9564	0.37	0.9576	2.29
E4	07.23	21.68	0.9189	29.07	05.61	0.9498	0.41	0.9879	5.78
E5	06.98	18.04	0.9387	20.18	07.48	0.9255	0.53	0.9871	4.62
E6	06.88	14.17	0.9254	19.38	08.06	0.9117	0.73	0.9837	5.83
E7	05.98	25.71	0.9845	16.34	06.93	0.9909	0.82	0.9905	6.92
E8	05.34	20.35	0.9775	14.72	07.48	0.9955	0.85	0.9826	7.42
E9	04.67	18.58	0.9723	15.83	08.17	0.9953	0.84	0.9847	6.39
E10	04.13	13.08	0.9545	19.59	01.85	0.9835	0.63	0.9798	5.62
E11	03.97	12.33	0.9985	20.83	06.29	0.9596	0.59	0.9845	4.93
E12	03.76	03.76	0.9753	15.03	09.73	0.9974	0.74	0.9974	7.93

t = time in hr, k_0 = zero order constant; c = intercept, k_H = Higuchi constant, β = shape parameter; a = scale parameter

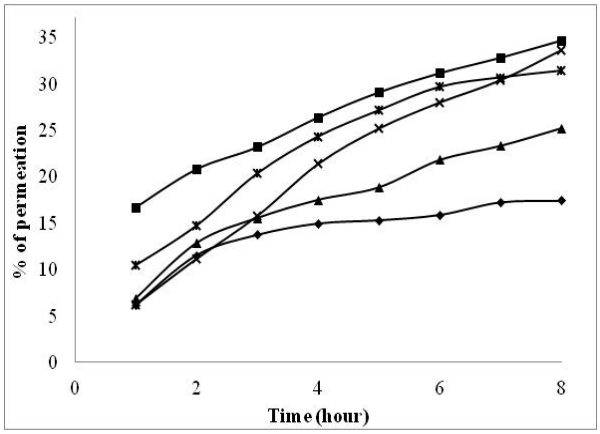

Figure 4: Release profile of PG containing patches. ***Key:*** Formulations E 2S (♦), E 4 S (■), E 6 S (▲), E 6 E (x), E 6ME (*)

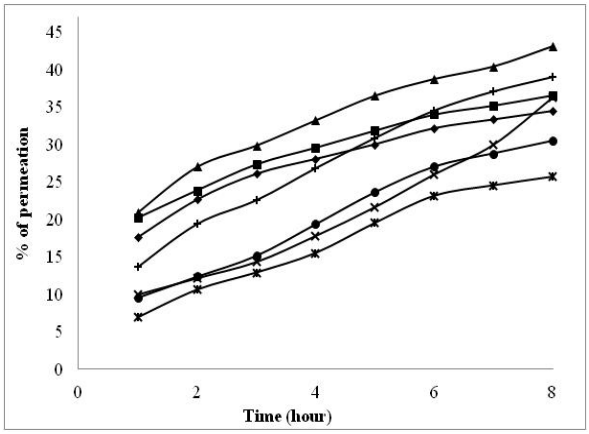

Figure 5: Release profile of DBP containing patches. ***Key:*** Formulations E 10 (♦), E 11 (■), E 12 (▲), E 10M (x), E 12M (*), E 10 ME (●) E 12 ME (ı)

percentage of permeation against time in Figure 4 and 5 show a fairly constant rate of drug permeation over time, and followed concentration-dependent first-order kinetics.

DISCUSSION

According to American Society for Testing Materials (ASTM), materials with tensile strength > 4.0 MPa possess an elastic characteristic [22]. Patches should be elastic in order to withstand external forces such as wear and tear during handling, storage or use [6]. There was no significant difference in the tensile strength between patches containing PG and DBS.

Higher plasticizer levels increase the free volume between polymer chains thus enabling more moisture/water to be absorbed. This increases patch bulkiness and thickness, as shown in Table 1 which explains why the patches with higher plasticizer content were also thicker. Similarly, increase in plasticizer concentration also enhanced peel adhesion [22] due to softening effect exerted by the plasticizers.

Patches containing hydrophilic plasticizer (PG) showed higher moisture content and water absorption than those containing hydrophobic DBS. patches because the former allow water freely into the patch In hydrophobic nature DBS patches have difficulty to hydrate the patch during the moisture content and water absorption studies especially in higher percentages. This also explains why moisture content and water absorption capacity increased with increase in

the content of plasticizer. This is because plasticizer can embed in between polymer chains and thus relax the chains, increasing free volume [14,22]. Also, PVP is hydrophilic and therefore allows water to easily diffuse into the patch, leading to higher uptake of moisture and water absorption [16]. The relatively more hydrophobic DBS-containing patches would be more difficult to hydrate and hence their lower moisture content and water absorption.

Patch thickness should also be appropriate because increased film thickness will increase compaction and reduce the mobility of molecules, which can decrease drug release from the patch [14]. Low moisture content in the formulations helps to maintain patch stability and reduce patch brittleness [4]. Besides that, water uptake should be low in order to prevent microbial contamination and decrease patch bulkiness [4].

Drug release increased with increase in the content of PVP due to the hydrophilicity of PVP which facilitates water absorption thus promoting drug dissolution and drug release from the patch [4]. Furthermore, as PVP leaches out, pores are created in the matrix for drug to diffuse out of the patch; thus, drug release is increased [4].

In an earlier report [16], it was stated that plasticizers form secondary bonds with polymer chains, which decrease inter-chain cohesive forces and increase mobility of macromolecules [6,17]. The higher the concentration of plasticizer in the patch, the greater the number of plasticizer molecules available to produce relaxation of polymer chains, and hence increase in drug release out of the patch [18]. Drug release was higher for patches containing DBS than those containing PG because the hydrophilic nature of PG promotes water uptake which causes the plasticizer to leach out from the matrix [17,19]. As a result, there is a decreased amount of plasticiser to relax the polymer chains and so drug diffusion decreases [17].

When drug release was plotted against the square root of time ($t^{1/2}$), drug release from the patches followed a diffusion-controlled pattern. However, when the plots for patches containing PG were extrapolated to the origin, the plots were non-linear, indicating that they did not follow Higuchi release. On the other hand, the plots for patches containing DBS are were linear and thus followed Higuchi release (except for E10 and E11; Table 4). Weibull equation adequately describes the in vitro release profiles of all the transdermal formulations. The shape of the parameter, β, characterizes the curve and its β values are < 1 in these plots, and also have high initial slopes [19]. The values of β, r^2 and a are presented in Table 4. The β values of all the formulations were < 1.

Incorporation of release modifiers, succinic acid (SA) or myristic acid (MA) into formulations containing PG resulted in a significant increase in drug release ($p < 0.05$). This contradicts results in other studies which found that MA increased drug release while SA decreased it [20,21]. Gondaliya *et al* explained that SA might cross-link with Eudragit E100 to form a rigid matrix and thus retard drug diffusion from the matrix [21,23]. However, no co-polymer was added to the formulations in their study. Therefore, in the present study, it is believed that addition of PVP prevents the formation of cross-link between SA and Eudragit E100, and hence drug can diffuse freely out of the matrix.

SA produced higher drug release than MA in PG-containing patches. This may be due to smaller molecular size of SA which enables its molecules to penetrate between polymer chains more easily and disrupt the continuity of polymer chains. As a result, matrix rigidity decreases thus increasing drug release from the patch. For patches containing DBS, SA failed to dissolve completely in the solution due to incompatibility with DBS. Besides chloroform, different solvents (acetone, methanol, and ethanol) were tested but incompatibility still occurred. Thus, no patch was generated and hence there was no significant difference between drug release before and after addition of MA for patches containing DBS.

Incorporation of eugenol produced resulted in increase in drug release for patches containing PG. However, the effect of eugenol in DBS-containing patches was not significant.

CONCLUSION

DBS is superior to PG for the preparation of OND transdermal formulations in terms of mechanical and controlled release of drug over a long period of time. Furthermore, succinic acid is a suitable release modifier for OND patches containing PG. The optimised patches (E12 and E12 ME) may be further developed for actual applications by evaluating their pharmacokinetic and pharmacodynamic studies in appropriate animal models.

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