



FORMULATION AND EVALUATION OF ONDANSETRON TRANSDERMAL GELS

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The aim of this study was to develop and evaluate ondansetron gels for transdermal effect using in-vitro and ex-vivo permeation methods.

Ondansetron gels were prepared using; sodium carboxymethyl cellulose (Na CMC), hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), sodium alginate, and pluronic F- 127 as gelling polymers. Polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG) 400 were used as solubility enhancers. Oleic acid, ethyl alcohol, menthol, isopropyl myristate and propylene glycol were evaluated as penetration enhancers. The effect of the employed gel bases and permeation enhancers on the physicochemical characterization and drug permeation through cellophane membrane and rat skin were determined.

The results showed that both polymers and their concentrations affect the permeation of drug, by increasing the polymer concentration in the formulation, viscosity increased and in-vitro permeation of ondansetron decreased. Formula containing 16% of hydroxyl propyl cellulose with PVP/PEG400 (1.5/5% w/w) showed the highest amount permeation (95% over a 6 hrs period) through cellophane membrane. Both formulae containing 16% of hydroxyl propyl cellulose with PVP/PEG400 (1.5/5% w/w) and 7% of sodium alginate with PVP/ PEG400 (1.5/5% w/w) showed the best permeation through rat skin (amount permeated about 345.06 $\mu\text{g}/\text{cm}^2$) over a 6-hr period. PVP/PEG400 (1.5/5% w/w) showed the optimum solubilization enhancement.

INTRODUCTION

Ondansetron is a 5-HT₃ receptor antagonist indicated for the treatment and/or prophylaxis of postoperative, chemotherapy- or radiotherapy-induced emesis. It is a possible therapy for nausea and vomiting of acute or chronic medical illness or acute gastroenteritis¹⁻³. It is used off-label to treat hyperemesis gravidarum in pregnant women safely⁴. It is effective in decreasing frequency of hypotension and bradycardia in patients receiving spinal anesthesia⁵. It is well absorbed orally and undergoes first-pass metabolism⁶. The oral bioavailability of ondansetron is almost 59%, and peak plasma about 0.03–0.04 $\mu\text{g}/\text{mL}$ is obtained after 1.5 to 2 hrs of administration⁷.

Although ondansetron exhibits excellent emesis-inhibiting effects, its oral administra-

tion has several drawbacks that limit its usefulness; as oral administration during vomiting is difficult and the absorption through the digestive system is highly susceptible to the influence of pH in the gastro-intestinal tract. Administering drug through the transdermal route avoids hepatic first-pass metabolism, the delivery of ondansetron to the systemic circulation via the transdermal route could improve its systemic bioavailability.

Some studies were performed on transdermal ondansetron like Amish *et al.*⁸ who studied the *in-vitro* skin permeation and irritation of transdermal ondansetron hydrochloride matrix patch and also Malakar *et al.*⁹ who formulated ondansetron hydrochloride microemulsions for transdermal delivery and evaluated the *in-vitro* skin permeation. Also, Uttarwar¹⁰ developed *in-situ* gelling system for nasal administration for an antiemetic drug

ondansetron hydrochloride. Koland *et al.*¹¹ evaluated chitosan buccal films of ondansetron hydrochloride, but no of these formulations were marketed over the world; there is no transdermal formulation of ondansetron available to use till now.

This study was designed to investigate the effect of gelling polymers and penetration enhancers on ondansetron permeation through rat skin in order to evaluate the potential of a transdermal gel formulation system.

MATERIALS AND METHODS

Materials

Ondansetron was kindly provided by Adwia Co., Cairo, Egypt, Spectra/Por[®] dialysis membrane 12000 to 14000 molecular weight cut off (Spectrum Laboratories Inc., USA), sodium alginate (Na alginate) (Judex Laboratories Reagent, England), sodium carboxymethyl cellulose (Na CMC) (30000 M.Wt.), hydroxypropylmethyl cellulose (HPMC) (Aldrich Chem. Co., USA), Pluronic[®] F-127 (Sigma Chemical Co., USA), hydroxypropyl cellulose (HPC) (Kolmar Company, California, USA), polyvinyl pyrrolidone, polyethylene glycol 400, oleic acid, ethyl alcohol, menthol, isopropyl myristate and propylene glycol (Adwic, EL-Nasr Pharmaceutical Chemicals Co., Egypt) were used.

Methods

Ondansetron solubility determination

An excess amount of the drug was added to each of flasks containing; 10 ml water, phosphate buffers of different pH values ranged from 4 to 8 or an aqueous mixture of polyvinyl pyrrolidone PVP (1.5% w/w) and polyethylene glycol PEG 400 (5% w/w).

The mixtures were agitated at 100 rpm in a thermostatically controlled shaking water bath (Gallenkamp, England) at 34±0.5°C for 24 hrs left for equilibrium, filtered through filter disk 0.45 µm (Sartorius), diluted and measured spectrophotometrically at 304nm using UV spectrophotometer (Jenway 6305, U.K) against a blank similarly treated.

Preparation of ondansetron gels

Ondansetron gel formulations are presented in table 1. The gels were prepared by dissolving an accurately weighed 0.5 gram of ondansetron powder in a mixture of 5 grams PEG 400 and 1.5 grams PVP and 50 ml of distilled water using magnetic stirrer (except formulae F16 and F17 which contained different percentage of PVP and PEG 400). The remaining amount of distilled water required to prepare 100 g of the gel was added to the specified amounts of the gelling polymers; Na CMC (2-4% w/w), Na alginate

Table 1: Composition of the prepared ondansetron gel formulations (F1- F24).

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24
Ondansetron	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Na CMC	2	3	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HPMC	-	-	-	2	3	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HPC	-	-	-	-	-	-	16	17	18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PL.F-127	-	-	-	-	-	-	-	-	-	20	25	30	-	-	-	-	-	-	-	-	-	-	-	-
Na alginate	-	-	-	-	-	-	-	-	-	-	-	-	7	8	9	7	7	7	7	7	7	7	7	7
Oleic acid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.5	-	-	-	-	-	-
Isopropyl myristate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.5	5	-	-	-	-
Ethanol	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	16.2	17.2	15.6	-	-
Menthol	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8	8	-
Propylene glycol	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	35
water up to	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

^a All formulations contained PVP/ PEG 400 (1.5/5% w/w) except formulae F16 and F17 which contained (1.5/10% w/w) and (5/5% w/w) of PVP and PEG 400 respectively.

(7-9% w/w), HPMC (2-4% w/w) and HPC (16-18% w/w) and then soaked overnight for complete polymer solvation. The drug mixture was added slowly to the previously soaked polymer and continuously stirred to get the required gels using magnetic stirrer¹². Pluronic F-127 gels (20-30% w/w) (F10-F12) were prepared by the cold method described by Schmolka¹³ as the required amount of pluronic F-127 was dissolved in drug, PVP:PEG 400 mixture and cold water mixture prepared as previously mentioned using magnetic stirrer. The solution was left in a refrigerator overnight; a clear transparent gel was obtained when the solution was left at room temperature.

For formulae (F16-F24) ondansetron gels were prepared by using the same previous procedure using Na alginate (7% w/w) as gelling agent then each of different penetration enhancers (oleic acid, menthol, isopropyl myristate and propylene glycol) was added with continuous stirring¹⁴. In formulae F20-F22, the ethyl alcohol was finally added in the last step very slowly with continuous stirring to prevent coalescing of the gel. Different amounts of ethyl alcohol were used to give 20:80 w/w % of ethanol-water vehicle that showed high solubility of ondansetron according to Krishnaiah *et al.*¹⁵.

Evaluation of the prepared ondansetron gels

1- Cosmetic and aesthetic criteria of the prepared gels

The prepared gels were inspected visually for their color, appearance and homogeneity.

2- Determination of spreadability of the prepared gels

Spreadability of the prepared gels was determined according to El-Houssieny and Hamouda¹⁶. Samples of 0.25 g of each formula was pressed between two glass slides and left for 5 minutes to ensure no more spreading. Diameters of the spreaded sample circles were measured in centimeters and taken as comparative values for spreadability. Results obtained were the average of three measurements.

3- Determination of the pH of the prepared gels

The pH of the prepared medicated gels was determined directly after preparation using a pH meter (Jenway 3505, UK)¹⁷.

4- Determination of the actual drug content in the prepared gels

Drug content was determined by dissolving accurately weighed 0.25 g of gel in 50 ml phosphate buffer pH 5.5 using magnetic stirrer for 3 hours in order to get complete solubility of the drug. The mixture was then quantitatively transferred into volumetric flask 100 ml and completed the volume with phosphate buffer. The same method was adopted for the plain gel and used as a blank. The absorbance was recorded using UV-Spectrophotometer at λ_{\max} 304 nm⁸.

5- Determination of the viscosity of the prepared gels

The viscosity of the prepared gels was determined (Brookfield viscometer, USA) using T-bar spindle numbers 96 and 94 at temperature 25°C using 50 g sample at 10 rpm¹⁷.

6- Permeation studies of ondansetron from the prepared gels

***In-vitro* permeation through cellophane membrane**

The *in-vitro* permeation of ondansetron from each of the prepared gels was studied using dialysis membrane method (formulae F1-F15). One gram sample of each gel was accurately weighed and placed on a semipermeable cellophane membrane (previously soaked in phosphate buffer pH 5.5 for 24 hrs) to occupy a circle of 2.4 cm diameter. The loaded membrane (donor compartment) was firmly stretched over the lower open end of a glass tube of 2.4 cm diameter and made water tight by rubber band. The tube was then immersed in a beaker (receptor compartment) containing 50 ml of the permeation medium (phosphate buffer pH 5.5). The system was maintained for 6 hrs at 34±0.5°C in a thermostatically controlled shaker water bath at 25 rpm. Samples of 5 ml were withdrawn at intervals of 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5 and 6 hrs. The volume of each sample was replaced by the same volume

of fresh buffer (kept at the same temperature) to maintain constant volume. Samples were analyzed for ondansetron content spectrophotometrically at λ_{\max} 304 nm against blank similarly treated.

Ex-vivo permeation through rat skin

1- Skin Preparation

Animals were sacrificed immediately before the start of the experiment. A full thickness of skin was excised from abdominal site of dead rat and then was washed with water. The fatty tissue layer was removed as thoroughly as possible to minimize variation between the tissue specimens. The hair was plucked and skin was washed with cold phosphate buffer solution (pH 5.5). The membrane was stored in cold phosphate buffer (pH 5.5) and used within 1 h after removal.

2- Experimental Details

Accurately weighed 1gm gel was spread uniformly on the epidermal surface of excised rat abdominal skin which was then stretched over the lower open end of the tube with epithelial side facing upwards and the dermal side facing downwards into the receptor compartment¹⁸. The permeation medium was 25 ml of phosphate buffer pH 5.5, the permeation procedure was completed as mentioned under the *in-vitro* permeation procedure.

3- Permeation data assessment

The permeation data was assessed to determine the permeation parameters through both cellophane membrane and rat skin.

Permeation Flux: The effect of different polymers and penetration enhancers on permeation of ondansetron through rat skin was studied. The average cumulative amounts of ondansetron permeated per unit surface area ($\mu\text{g}/\text{cm}^2$) were plotted against the function of time (hrs). The slope and intercept of the linear portion of plots were derived by regression. The permeation flux for each gel was calculated as the slope divided by the skin surface area¹⁹.

$$P = J_{ss}/C_d$$

Where,

P = Permeability coefficient.

J_{ss}= Flux.

C_d = Concentration of the drug in the donor side.

The drug flux at steady state (J_{ss}) ($\mu\text{g}/\text{cm}^2/\text{min}^{-1}$) was calculated from the slope of the straight line.

Statistical analysis

Ondansetron *in-vitro/ex-vivo* permeation results in concern with different concentrations and types of polymers with and without permeation enhancers were analyzed by one way ANOVA and Post Hoc Tukey-Test at a significance level of 0.05. The statistical software used for analysis was Graph-Pad Prism Software Version 5.0²⁰.

RESULTS AND DISCUSSION

Ondansetron solubility

The determined solubility of ondansetron in water was found to be 0.75 ± 0.11 mg/ml which is almost similar to the value reported (0.724 mg/ml) by Suthar *et al.*²¹. As shown in table 2 the solubility of ondansetron decreased by increasing pH^{22&23}. Solubility of ondansetron in phosphate buffer pH 5.5 (permeation medium) was 2 ± 0.32 mg/ml. For enhancing water solubility of ondansetron to ensure complete solubility of the desired drug concentration in the prepared gels, a mixture of PVP (1.5% w/w) and PEG 400 (5% w/w) in water was used. Ondansetron solubility in this mixture was investigated and found to be equal to 18.73 ± 0.43 mg/ml.

Table 2: Solubility of ondansetron in various vehicles at 34°C after 24 hrs.

Vehicles	Solubility (mg/mL) ^a
Water	0.75 ± 0.11
Phosphate buffer pH 4	4.83 ± 0.81
Phosphate buffer pH 5	2.489 ± 0.79
Phosphate buffer pH 5.5	2 ± 0.32
Phosphate buffer pH 6	1.735 ± 0.19
Phosphate buffer pH 7	0.132 ± 6.03X10 ⁻³
Phosphate buffer pH 8	0.0539 ± 9.6X10 ⁻⁴
PVP (1.5 % w/w) and PEG 400 (5 % w/w)	18.73 ± 0.43

^aMean ± S.D. (n = 3)

Evaluation of the prepared ondansetron gels

1- Cosmetic and aesthetic criteria of the prepared gels

All prepared ondansetron transdermal gels were transparent and showed good visual appearance and odor, acceptable cosmetic criteria as well as suitable consistency and homogeneity. The physical appearance of all the prepared gels is shown in table 3.

2- Spreadability of the prepared gels

Table 3 shows the differences in spreadability of the prepared gels due to different polymers types and concentrations. From the table, it is noticed that the prepared gels give relatively acceptable spreadabilities which were concomitant with their viscosities; gels with low viscosities, showed high spreadabilities, also increasing the polymer concentration led to decrease in spreaded circle diameter which could be attributed to the increase in the viscosity.

3- pH of the prepared gels

The pH values of different ondansetron gels were determined immediately after preparation and they are listed in table 3. It was found that the pH of different gels lied in the range of 5.8-6.8 (near the normal pH of the skin) and therefore no skin irritation is expected upon application of any of them.

4- Actual drug content in the prepared gels

The actual drug content of all the prepared ondansetron gels ranged from 96-103.7% of the claimed amount.

5- Viscosity of the prepared gels

The viscosities of the prepared ondansetron gels varied according to the type and concentration of the gelling agents and they are listed in table 3. It is obvious that pluronic F-127 (30% w/w) gel exhibited the highest viscosity while Na alginate (7% w/w) gel exhibited the lowest viscosity from the prepared gels.

Table 3: Color, spreadability, pH, viscosity and physical appearance of the prepared gels containing 0.5 % ondansetron.

Formulae		Color	Spreaded circle diameter (cm)	pH	Viscosity (cps)	Homogeneity & Appearance
Polymer type & conc. (% w/w)						
F 1	Na CMC 2%	Transparent	3.76	6.45	16371	All gel formulations are homogenous and clear
F 2	Na CMC 3%	Transparent	2.68	6.36	65166	
F 3	Na CMC 4%	Transparent	2.23	6.7	108500	
F 4	HPMC 2%	Transparent	4.43	5.89	10225	
F 5	HPMC 3%	Transparent	3.15	5.95	35200	
F 6	HPMC 4%	Transparent	2.63	6.1	89533	
F 7	HPC 16%	Transparent	3.78	6.18	15500	
F 8	HPC 17%	Transparent	3.54	6.23	19500	
F 9	HPC 18%	Transparent	3.35	6.58	33300	
F 10	Pl.F-127 20%	Transparent	2.00	6.34	63750	
F 11	Pl.F-127 25%	Transparent	1.80	6.8	94000	
F 12	Pl.F-127 30%	Transparent	1.51	6.8	140000	
F 13	Na alginate 7%	Brownish	3.84	6.29	6800	
F 14	Na alginate 8%	Brownish	3.09	6.53	11133	
F 15	Na alginate 9%	Brownish	2.28	6.55	14333	
F 16	PVP/PEG400(1.5/10% w/w)	Brownish	3.97	6.20	8693	
F 17	PVP/ PEG 400 (5/5 % w/w)	Brownish	3.85	6.45	7747	
F 18	Oleic acid (2.5%)	Yellowish brown	4.05	6.08	9641	
F 19	Isopropyl myristate (2.5%)	Brownish	3.98	6.17	9261	
F 20	Ethanol- water (20:80 w/w %) + Isopropyl myristate (5%)	Brownish	3.17	5.98	11533	
F 21	Ethanol- water (20:80 w/w %)	Brownish	3.02	5.90	10587	
F 22	Ethanol- water (20:80 w/w %) + Menthol 8%	Yellowish brown	3.45	5.80	12101	
F 23	Menthol 8 %	Yellowish brown	4.32	5.82	10208	
F 24	PG (35 %)	Brownish	4.19	6.7	9450	

Permeation of ondansetron from the prepared gels

1- *In-vitro* permeation of ondansetron through cellophane membrane

From figures 1&2 and table 4, it is observed that the permeation of ondansetron from the prepared gels containing the same initial drug concentration (0.5% w/w ondansetron) decreased as polymer concentration increased and the permeation of ondansetron from HPC 16% gel base exhibited the highest amount permeated. Similarly, the percent of ondansetron permeated from the prepared Na CMC gels decreases significantly ($P < 0.001$) by increasing the polymer concentration from 2% to 4%. This result is similar to those reported by Mohammed²⁴ and Tas *et al.*²⁵ using diclofenac sodium and chlorpheniramine maleate, respectively. This may be attributed to increase Na-CMC concentration which leads to the formation of matrix of polymer molecules and consequently increasing viscosity. These results explain the higher permeation of ondansetron from 2% w/w Na-CMC compared to 4% w/w Na-CMC. Moreover the density of the polymer chain increases as the polymer concentration increases and this limits the drug movement and subsequently diminishes the drug permeation²⁶.

The percent of ondansetron permeated from the prepared Na alginate gels decreased significantly ($P < 0.001$) by increasing the polymer concentration from 7% to 9%. An analogous situation has been reported by Ahuja *et al.*²⁶, Al-Kubati²⁷ and Fetih²⁸. This permeation profile may be explained as increasing the concentration of sodium alginate increased the viscosity of the gel bases which imparts a resistance for drug molecules to be permeated.

The percent of ondansetron permeated from HPMC gels did not differ significantly ($p > 0.05$) upon changing the concentration of the polymer from 2 to 4% w/w in spite of the increase in the viscosity. This result is in agreement to those reported by Mekkawy *et al.*²⁹ who explain this result due to the lower percent of modification in the polymer concentration.

The percent of ondansetron permeated from HPC gels was found to decrease significantly ($P < 0.001$) with increasing the

polymer concentration from 16% to 18%. This result is in agreement with that of Andrews *et al.*³⁰ who reported that a decrease in permeation rate was observed upon increasing HPC concentration in gels.

The percent of ondansetron permeated from pluronic F-127 gels is shown in figures 1&2. The permeation of ondansetron from the prepared gel was found to decrease significantly ($P < 0.001$) upon increasing the pluronic concentration. This may be explained as follow; the drug permeation from pluronic gels depends on the number and size of the micelles which affect the number and size of water channels in the gel matrix, so the change in pluronic concentration affects the diffusional pathways and thus the drug permeation. Moore *et al.*³¹ explained that behavior by the increase in the number of micelles at higher pluronic concentrations that results in a more entangled system and a more rigid gel. This inverse relationship between the pluronic concentration and the drug permeation has been shown for varies drugs previously studied and reported by several investigators³²⁻³⁸.

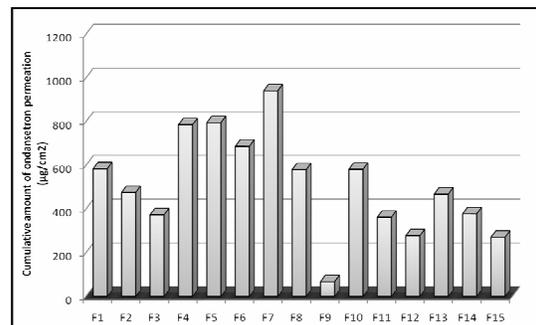


Fig. 1: Cumulative amount of ondansetron permeated through standard cellophane membrane from different gels after 3 hours.

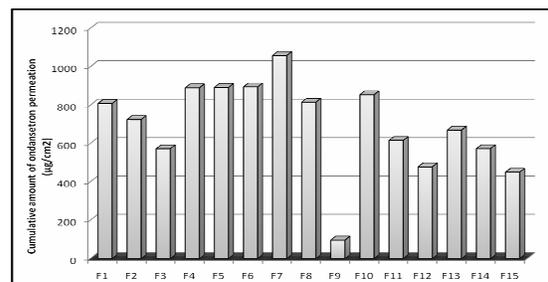


Fig. 2: Cumulative amount of ondansetron permeated through standard cellophane membrane from different gels after 6 hours.

Table 4: Permeation parameters of ondansetron through cellophane membrane from various gels (formulae F1-F15).

Formula			Permeation parameters ^a	
	Polymer type	Conc. (%w/w)	J ($\mu\text{g}/\text{cm}^2/\text{h}$)	K_p ($\times 10^3$)(cm/h)
F 1	Na CMC	2	132.09 \pm 0.11 ^b	26.18 \pm 0.25
F 2	Na CMC	3	120.58 \pm 0.34	24.61 \pm 0.26
F 3	Na CMC	4	96.75 \pm 0.87	19.04 \pm 0.41
F 4	HPMC	2	124.71 \pm 0.57	24.91 \pm 0.23
F 5	HPMC	3	130.47 \pm 0.64	26.10 \pm 0.37
F 6	HPMC	4	145.21 \pm 0.76	29.13 \pm 0.42
F 7	HPC	16	168.76 \pm 0.34	33.75 \pm 0.18
F 8	HPC	17	125.85 \pm 0.42	25.11 \pm 0.76
F 9	HPC	18	13.38 \pm 0.67	2.68 \pm 0.080
F 10	Pl.F-127	20	136.55 \pm 0.97	27.88 \pm 0.39
F 11	Pl.F-127	25	101.43 \pm 0.64	20.48 \pm 0.24
F 12	Pl.F-127	30	78.87 \pm 0.22	15.63 \pm 0.20
F 13	Na alginate	7	107.41 \pm 0.75	21.53 \pm 0.32
F 14	Na alginate	8	103.91 \pm 1.23	20.2 \pm 0.70
F 15	Na alginate	9	90.49 \pm 0.54	18.12 \pm 0.21

^aJ: Drug flux, K_p : permeability coefficient.

^bMean \pm S.D. (n = 3).

In general, the inverse relation between polymer concentration and ondansetron permeation is in agreement with lauffer's molecular diffusion theory of polymer gels³⁹. The theory states that the diffusion of a solute is inversely proportional to the volume fraction occupied by the gel forming agent. Welin-Berger *et al.*⁴⁰ found that an increase in the macro viscosity may affect the permeation rate of the active compound inversely^{22&24-25&41}.

It is obviously clear from the previous mentioned results that all prepared ondansetron gels with the different polymers showed permeation of most of the drug at six hours. HPC 16% gel showed a significantly ($P < 0.05$) higher drug permeation over all the other polymers of about 95%.

2- *Ex-vivo* permeation of ondansetron through skin rat

The effect of polymer type on permeation of ondansetron using the five polymers: Na CMC (2% w/w), HPMC (2% w/w), HPC (16% w/w), pl. F-127 (20% w/w) and Na alginate (7% w/w)(formulae F1, F4, F7, F10 and F13, respectively), these formulae were prepared using the lowest concentration of each polymer

and gave the highest amount of the drug permeated.

Figures 3&4 and table 5 show the comparison of ondansetron permeation from different gels. It is obviously clear that the amount of drug permeated from HPMC was significantly ($p < 0.001$) lower than the amount permeated from other polymer gels nearly at all-time intervals.

On the other hand, Na alginate and HPC gels showed a significantly ($p < 0.05$) higher drug permeation over the other polymers. Both gels showed no significance difference in the ondansetron amount permeated over most of the time intervals.

It is pointed out that an appropriate choice of the polymer and its concentration used in preparing the gel is important for achieving the desired drug permeation profile.

From the previous results, F13 which containing PVP/PEG 400 (1.5/5% w/w) and Na alginate (7% w/w) gel was selected for further evaluation as it exhibited the highest spreadability and permeation of the ondansetron through skin among all the other formulations.

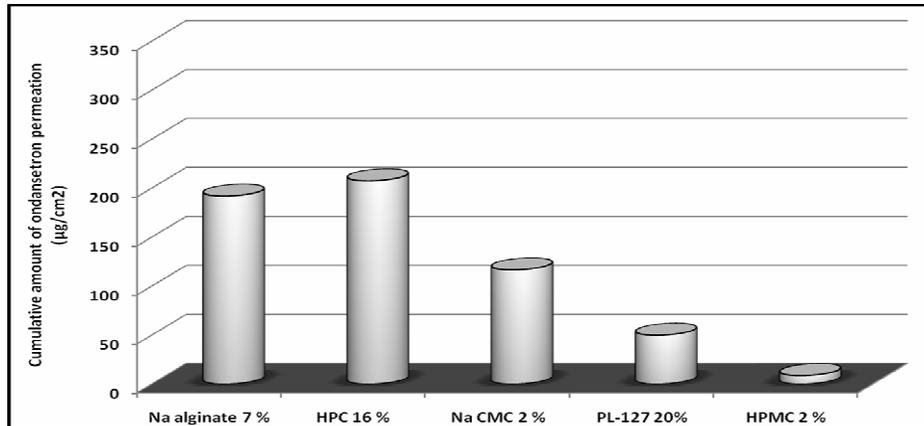


Fig. 3: Cumulative amount of ondansetron permeated through excised rat skin from various gels after 3 hours.

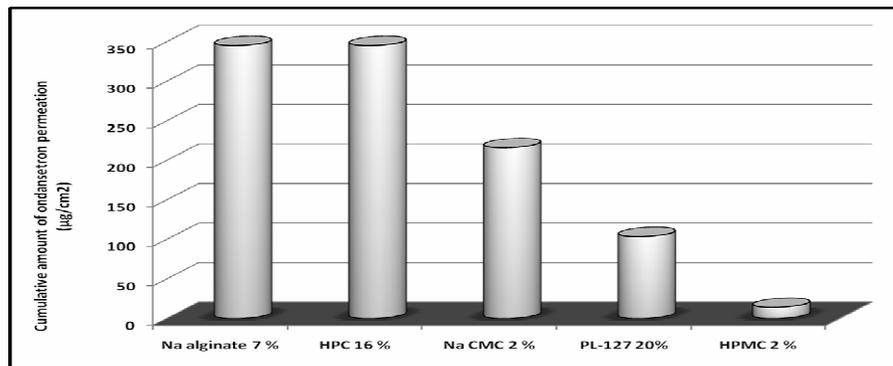


Fig. 4: Cumulative amount of ondansetron permeated through excised rat skin from various gels after 6 hours.

Table 5: Permeation parameters of ondansetron through excised rat skins from various gels: (Na alginate (7% w/w), HPC (16% w/w), Na CMC (2% w/w), PL. F-127 (20 %) and HPMC (2% w/w)).

Formula		Permeation parameters ^a	
		J (µg/cm ² /h)	K _p (×10 ³) (cm/h)
F 1	Na CMC 2 %	34.468±0.39 ^b	6.88±0.27
F 4	HPMC 2%	2.0391±1.2	0.41±0.19
F 7	HPC 16%	52.601±2.03	10.50±0.85
F 10	PL. F-127 20%	19.181±0.81	3.86± 0.23
F 13	Na alginate 7 %	53.076±1.77	10.52±0.41

^aJ: Drug flux, K_p: permeability coefficient.

^bMean ± S.D. (n = 3).

Effects of different penetration enhancers on ondansetron permeation

The results of the selected ondansetron-Na alginate (7% w/w) gels subjected to the addition of penetration enhancer are shown in figures 5&6 and the permeation parameters are presented in table 6.

Generally, It can be seen that F13 which containing PVP/ PEG 400 (1.5/5% w/w) and Na alginate (7% w/w) gel showed the highest permeation profile among the studied gels containing various penetration enhancers and it may be attributed to the rapid dissolution of the drug in water and the possible solubilizing effect on the drug^{42&43}.

Figures 5&6 show the effect of menthol and ethyl alcohol (F21-F23) on the penetration of ondansetron across the abdominal rat skin compared to the control gel (F13). Statistically, there is a significant decrease ($p < 0.01$) in ondansetron permeation from menthol (F22, F23) compared to F13. This result is in agreement with that obtained by Ismael⁴⁴ who reported a decrease in the permeation of naproxen from gels containing menthol as penetration enhancer and explained that behavior on the basis of cooling effect exhibited by the terpenes in the Na alginate gels.^{44&45}

Also there is a significant decrease ($p < 0.001$) in ondansetron permeation from menthol and ethyl alcohol (F22) compared to F13, especially after 4 hrs of permeation. Moreover the cooling effect due to the evaporation of ethyl alcohol may results in retardation from permeation from such formulation⁴⁴.

Figures 5&6 show the effect of increasing the concentration of IPM from 2.5% (F19) to 5% w/w and using ethyl alcohol (F20) on the permeation of ondansetron. It can be seen from the figures that the permeation of the drug from F13 control gel was significantly ($p < 0.001$) higher than F19 & F20 containing IPM. This might be attributed to the increased viscosity of the formulations upon increasing the IPM concentration and these results are in agreement with that obtained by Lakshmi *et al.*⁴⁶ who reported a decrease in permeation of ibuprofen from gels at higher concentration of IPM. Also, it was found that adding ethyl alcohol to F20 did not improve the permeation of ondansetron especially after 2.5 hrs from permeation due to its cooling effect.

Table 6: Effect of penetration enhancer on permeation parameters of ondansetron through excised rat skins from various gels.

Penetration enhancer		Permeation parameters ^a	
		J ($\mu\text{g}/\text{cm}^2/\text{h}$)	K _p ($\times 10^3$) (cm/h)
F 13	PVP/ PEG 400(1.5/5 % w/w)	53.076 \pm 1.77 ^b	10.615 \pm 0.41
F 16	PVP/ PEG 400(1.5/10 % w/w)	11.619 \pm 0.9	2.324 \pm 0.40
F 17	PVP/ PEG 400(5/5 % w/w)	8.089 \pm 0.6	1.618 \pm 0.33
F 18	Oleic acid (2.5%)	16.209 \pm 0.64	3.242 \pm 0.66
F 19	Isopropyl myristate (2.5%)	14.472 \pm 0.81	2.894 \pm 0.34
F 20	Ethanol- water (20:80 w/w %) + Isopropyl myristate (5%)	4.557 \pm 0.85	0.911 \pm 0.19
F 21	Ethanol- water (20:80 w/w %)	9.215 \pm 1.15	1.843 \pm 0.2
F 22	Ethanol- water (20:80 w/w %) + Menthol 8%	32.694 \pm 1.58	6.539 \pm 0.29
F 23	Menthol 8 %	45.083 \pm 0.9	9.016 \pm 0.36
F 24	PG- water (35%)	8.928 \pm 0.82	1.786 \pm 0.18

^aJ: Drug flux, K_p: permeability coefficient.

^bMean \pm S.D. (n = 3).

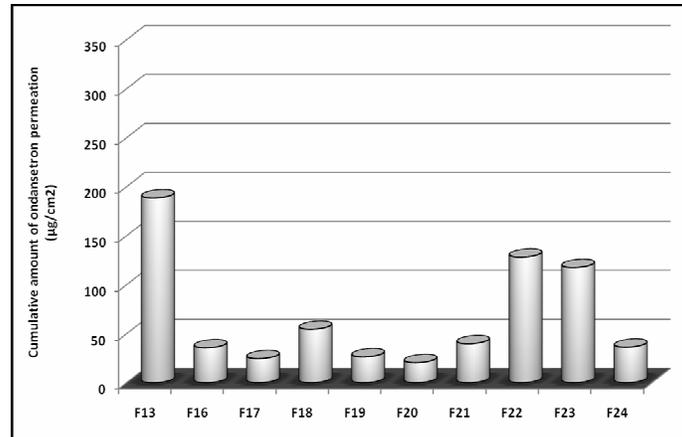


Fig. 5: Cumulative amount of ondansetron permeated through excised rat skin from various gels after 3 hrs.

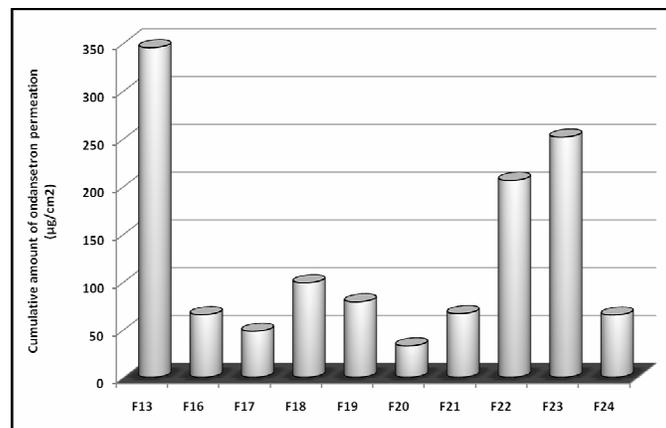


Fig. 6: Cumulative amount of ondansetron permeated through excised rat skin from various gels after 6 hrs.

The permeation of ondansetron from propylene glycol is significantly ($p < 0.05$) less than control gel. These findings are in agreement with the data obtained by Patel *et al.*⁴⁷ who found that upon using high concentration of propylene glycol as penetration enhancer, the flux and permeability coefficient of aceclofenac in Na alginate gels decrease. Trottett *et al.*⁴⁸ studied the permeation of drug (loperamide) linked with propylene glycol dose loading. He found that a large difference in the size of propylene glycol and loperamide (molecular weight 76 and 447, respectively), lipophilicity and solubility characteristics effect on permeation, as propylene glycol found to cross the skin barrier more quickly than loperamide. A large molecule more likely to be delayed compared to a smaller one because of specific binding or interaction with the different elements of the

stratum corneum. (N.B. molecular weight of ondansetron is 293)

The amount of ondansetron permeated from hydrophilic enhancer gels is significantly ($p < 0.05$) more than gels containing lipophilic vehicles (F18- F20) which contain oleic acid and IPM as shown in figures 5&6 as in case of using lipophilic vehicles, the medium became non-polar and immiscible with the polar diffusion medium; hence retardation of drug permeation is expected. Also this low permeation may be attributed to the closing of the pores with the vehicles and prevention of penetration of the acceptor medium through the membrane to dissolve the drug⁴⁹.

Permeation profile of ondansetron from different concentrations of PVP/PEG 400 (F16, F17) was illustrated in figures 5&6. It is clear that there is a high correlation between the viscosity and the permeation rate of ondansetron on increasing the concentration of

either of PVP or PEG, the viscosity was increased and consequently a significant ($p < 0.001$) decrease in the permeation.

Conclusion

The results obtained showed that the gels had good physical characteristics and acceptable ondansetron permeation; that could be considered for further evaluation a promising transdermal alternative for the treatment of nausea and vomiting.

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نشرة العلوم الصيدلانية جامعة أسيوط



صياغة وتقييم مستحضرات هلامية عابرة للجلد لعقار الأندانسترون

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يعتبر الأندانسترون الدواء الأول لمنع الغثيان والتقيؤات الناتجة عن المعالجة الكيميائية (العلاج الكيماوي) والمعالجة الإشعاعية (العلاج بالأشعة) لعلاج الأورام السرطانية، كما أنه يستعمل لمنع الغثيان والقيء للحوامل وأيضاً بعد العمليات الجراحية.

نظراً لخطورة الغثيان والقيء المستمر وتسببه في بعض الأعراض الخطيرة مثل: الجفاف وما يصحبه من إختلال في الديناميكية الدموية التي يمكن أن تؤدي إلى هبوط حاد في الدورة الدموية وعدم انتظام ضربات القلب وزيادة قلوية الدم، بالإضافة إلى متلازمة مالوري - وايس (نزف هضمي يلي القيء الشديد)، التهاب المرئ والمعدة، تفتت الأسنان، وسوء التغذية.

ونظراً لأهمية عقار الأندانسترون في علاج هذه الأعراض وجد أنه من الضروري إعداد صياغات عبر جلدية (هلاميات) منه وذلك لتجنب الأعراض الجانبية التي تنتج من إستخدام عقار الأندانسترون عن طريق الفم مثل الإسهال أو الإمساك، وإرتفاع في انزيمات الكبد، أو عن طريق الحقن الوريدي مثل الإحمرار والألم والحرقان في مكان الحقن، كما أنه يؤثر على ضربات القلب إذا أعطى بجرعة كبيرة بشكل وريدي مباشر، إلى جانب أن الصياغات عبر الجلدية للعقار تعتبر أكثر ملاءمة للمريض لسهولة إستخدامه، وتجنب إعطاؤه عن طريق الجهاز الهضمي لأنه غير مناسب خاصة في حالة القيء أو الغثيان.

وعلى ضوء ذلك كان الهدف من الدراسة الحالية هو صياغة مستحضرات هلامية خلال جلدية من عقار الأندانسترون وتقييمها من حيث المظهر الخارجى وقياس الأس الهيدروجيني وكذلك المحتوى الدوائى والزوجة وقابلية البسط. كما تم دراسة نفاذية الدواء من الصياغات الهلامية المحضرة خلال غشاء سيلوفاني عياري جلد الفأر المنزوع الشعر.

وقد أظهرت النتائج هذه الدراسة أن هلام (١٦٪ هيدروكسي بروبيل سليلوز / ٠,٥٪ أندانسترون) والمحتوي على مزيج البيروليدون عديد الفينيل والجليكول عديد الإيثيلين (٤٠٠:١,٥٪) أعطى أعلى معدل نفاذية للأندانسترون خلال غشاء سيلوفاني عياري بعد ست ساعات، كما وجد أيضاً أن معدل نفاذية الأندانسترون من الصياغات الهلامية المحضرة يقل بزيادة تركيزات البوليمر.

كما أثبتت الدراسة أن معدل نفاذية الأندانسترون خلال جلد الفأر المنزوع الشعر من صياغات الهلام المحضرة ب٧٪ ألجينات الصوديوم المحتوي على مزيج البيروليدون عديد الفينيل والجليكول عديد الإيثيلين (٤٠٠:١,٥٪) و ١٦٪ هيدروكسي بروبيل سليلوز والمحتوي على مزيج البيروليدون عديد الفينيل والجليكول عديد الإيثيلين (٤٠٠:١,٥٪) أبدت أعلى من باقي الصياغات، بينما معدل نفاذية الأندانسترون من صياغات الهلام المحضرة ب٢٪ هيدروكسي بروبيل ميثيل سليلوز كان الأقل.

كما أظهرت النتائج أن مزيج البيروليدون عديد الفينيل والجليكول عديد الإيثيلين (٤٠٠:١,٥٪) أعطى أعلى معدل نفاذية للدواء، حيث أن هذا المزيج يعتبر كأفضل مذيّب مساعد للأندانسترون.