and stop chemotherapy-induced nausea and vomiting (CINV), it is also after radiation therapy-induced nausea and vomiting [6–8].

antagonist receptor [1–5]. It is a primary drug utilized to treat, prohibit and overcome the side effects associated with IV and/or oral dosage forms. Subsequently, it is very eligible to develop another delivery system to subsequently in vitro and ex vivo studies [9]. Whereas it is especially suitable for cancer patients who suffer from frequent episodes of vomiting and nausea and thus they cannot keep the oral dosage form and intravenous chemotherapy formerly worn out their veins.

Chromatographic and biopharmaceutical studies of drug products are useful tools to investigate the relationship between physicochemical properties of the drug and the pharmacological effect produced [10]. Measurement of drug concentration in biological fluids, such as blood or urine following drug administration is considered a direct and efficient method for the determination of systemic drug bioavailability [11]. However, quantitative measurement of drug concentration in biological fluids is not always available or, in other instances, lacks sufficient accuracy. In this case, the pharmacological effect of the drug can be used as an indirect measure of drug bioavailability [12].

Nausea and vomiting associated with the administration of chemotherapeutic drugs are attributed to the activation of serotonin type 3 receptors existing in the gastrointestinal tracts and/or central nervous system [13–16] due to cellular damage to the intestinal mucosa [17]. Cisplatin, a common chemotherapy drug, has many hurtful side effects such as the stimulation of nausea, vomiting, anorexia and general malaise [18]. Cisplatin was classified as the highest emetic risk group as it causes acute and delayed vomiting [19, 20]. So, selective 5-HT3 receptor antagonists are very efficient in prohibiting nausea and emesis in animals [21, 22] and cancer patients [23, 24].

To evaluate the antiemetic efficacy, different animal models including ferrets, dogs, and monkeys have been utilized [25]. However, generally, rodents such as mice and rats do not show vomiting behaviors, in comparison to the emesis-prone animals such as ferrets and dogs. Instead, mice and rats eat non-nutritive materials such as kaolin, so-called pica as a phenomenon of vomiting reflex, following treatment with poisons or under rotating situation [26–30]. It was proposed that increased pica is an illness-response behavior of the rat, similar to vomiting in other species and humans [26], which can be utilized as a readily-quantifiable behavioral assay of deleterious drug effects [27].

Thus, the main adjective of this study was to estimate a comparative bioavailability study of ondansetron gel formulation in rabbits and healthy human volunteers using intravenous ondansetron, as a reference standard applying UPLC as the analytical tool for assessing the drug concentration in plasma. Further, the investigation is extended to evaluate the potential effect of ondansetron from gel formulation for the prohibition of different phases of emesis encouraged by exposure to antineoplastic drugs such as cisplatin by determination of body weight loss, water and food intake employing kaolin-pica model in rats.

ABSTRACT

Objective: This study was undertaken to determine the bioavailability of ondansetron gel in experimental animals and humans applying UPLC as an analytical tool and evaluation of the antiemetic effect of ondansetron gel in cisplatin-induced emesis in rats.

Methods: Ondansetron gel (F13: sodium alginate 7% w/w) was used, marketed I. V. ondansetron (Zofran) * was chosen as reference. The bioavailability study in rabbits was selected as a parallel design using nine healthy rabbits divided into three groups whereas, bioavailability study in humans was an open-label, wherein 6 healthy subjects administered ondansetron gel. The potential effect of ondansetron gel was evaluated for the prevention of different phases of emesis motivated by exposure to antineoplastic drugs (cisplatin) by determination of body weight loss, water and food intake applying kaolin-pica model in rats using seventy-two rats divided into six groups.

Results: Ondansetron gel (0.5%) showed detectable plasma concentration 22.83±2.17 ng/ml after 0.5 h and 419.55±2.17 ng/ml after 1-h post-treatment in rabbits and human respectively and concentration was maintained above-reported minimum effective concentration for more than 2.5 h for rabbits and 7 h for humans compared to 1.75 h after I. V. administration.

The ondansetron gel significantly reduces all phases of cisplatin-induced emesis and a decrease in body weight, water, and food consumption was significantly attenuated.

Conclusion: Based on the high efficacy of gel on emesis induced by cisplatin, and its high bioavailability, transdermal ondansetron gel could be a promising convenient system to prevent nausea and vomiting following administration of antineoplastic drugs.

Keywords: Ondansetron, Transdermal gel, Bioavailability, UPLC, Cisplatin-induced emesis in rats

INTRODUCTION

Ondansetron is a selective 5-HT3 (5-hydroxytryptamin, or serotonin) antagonist receptor [1–5]. It is a primary drug utilized to treat, prohibit and stop chemotherapy-induced nausea and vomiting (CINV), it is also efficient in prevailing postoperative nausea and vomiting (PONV) and after radiation therapy-induced nausea and vomiting [6–8]. Ondansetron is taken 1–3 times daily, and it is available commercially as an oral and disintegrable tablet, solution, and injection [8]. Intravenous (IV) route has quick effects, but it confers a local pain and for its short half-life, ondansetron requires recurrent administrations. Also, oral administration has many disadvantages as it not desirable in nausea and vomiting, difficulties occurred in the gastrointestinal tract during absorption due to enzymes, food-drug interactions, etc. [6]. Subsequently, it is very eligible to develop another delivery system to overcome the side effects associated with IV and/or oral dosage forms. So, ondansetron transdermal gel was formulated and evaluated from previous in vitro and ex vivo studies [9]. Whereas it is especially suitable for cancer patients who suffer from frequent episodes of vomiting and nausea and thus they cannot keep the oral dosage form and intravenous chemotherapy formerly worn out their veins.

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Original Article

BIOAVAILABILITY STUDY OF ONDANSETRON GEL IN RABBITS AND HUMAN VOLUNTEERS APPLING UPLC AS ANALYTICAL TOOL AND EVALUATION OF THE ANTIEMETIC EFFECT OF ONDANSETRON GEL IN CISPLATIN-INDUCED EMESIS IN RATS

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MATERIALS AND METHODS

Materials

Ondansetron was kindly provided by (Adwia Co., Cairo, Egypt), K$_3$EDTA ampoules (Voma med., Italy), Zofran® l. v. injection 8 mg/4 ml (Glaçox Smithkline S. A. E, El-Salam City, Egypt), HPLC grade of Acetonitrile and methanol (Sigma Chemical Co., St. Louis, Mo, USA). Cisplatin®, I. v. vial 10 mg/10 ml (Mylan France), Sodium alginate (The General Chemical and Pharmaceutical Co., Ltd., England). Standard rat chow pellets. Kaolin of pharmaceutical grade (Clay, naturally hydrated aluminum silicate) was purchased from (El-Gomhouria Co., Egypt). Acacia (gum Arabic) (ISO-CHEM, Egypt). All chemicals and reagents were used of analytical grade.

Methods

Preparation of ondansetron gel (F13)

The gel was prepared by dissolving an accurately weighed 0.5 gram of ondansetron powder in a mixture of 5 grams polyethylene glycol 400 and 1.5 grams polysylvyn pyrrolidone and 50 ml of distilled water using a magnetic stirrer. The remaining amount of distilled water required to prepare 100 g of the gel was added to the specified amounts of the gelling polymer sodium alginate (7% w/v) and 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 stirrer [9].

Transdermal bioavailability study of ondansetron gel in experimental animals (rabbits) and human volunteers applying UPLC as the analytical tool

Experimental design

a. Bioavailability studies in rabbits

Ondansetron sodium alginate gel (7%/w/w) (F13) was selected for this study which showed a greater extent of permeation than other gels [9]. Marketed I. V. ondansetron (Zofran)® was chosen as the reference standard.

A parallel design study was selected using nine healthy New Zealand rabbits weighing 1.75-2 kg (Animal house of faculty of Medicine, Assiut University-Egypt). Rabbits were fasted 12 h before the administration of the drug but had free access to water [31] and were housed at room temperature. Food was not allowed after drug administration [32]. The study protocol was approved and carried out according to the animal ethics guidelines of the Ethical Review Board of Faculty of Pharmacy, Assiut University Assiut, Egypt No. 17300082.

Rabbits were divided randomly into three groups; each group consisted of three rabbits, and classified as:

1. The first group received marketed ondansetron injection Zofran® (8 mg/4 ml, Glaçox) for each rabbit using direct I. V. administration in the vein of an ear.
2. The second group received the gel formulation of a dose equal to 8 mg using 0.5 % ondansetron gel).
3. The third group received the gel formulation of a dose equal to 16 mg using 1 % ondansetron gel).

The gel formulation was applied on an area of 4x4 cm of rabbit’s dorsal skin which shaved a day before the experiments. Blood samples were collected from the marginal ear vein at time intervals 0, 0,25, 0,5, 0,75, 1, 1,5, 2, 2,5, 3 and 4 h. The acclimation condition of animals was good before and after the experimental procedure.

b. Bioavailability studies in healthy volunteers

This study was designed to estimate the pharmacokinetic parameters of ondansetron gel formulation. The fundamental objective was to determine the bioavailability of ondansetron after a single application of the gel (8 mg using 0.5% ondansetron gel and 16 mg using 1% ondansetron gel) behind the ear for 7 h. Secondary objectives included determination of local tolerance, safety, and tolerability of the gel. An open-label design study was selected, wherein 6 healthy subjects (3 males and 3 females) were administered ondansetron gel. The study protocol was approved by the Research Ethics Committee at the Faculty of Medicine, Assiut University Assiut, Egypt No. 17300082.

The volunteers were in good health as determined by a physician, with a weight of more than 50 kg and a body mass index (BMI) of 26–31 kg/m2 and they were aged 21-36 y who were non-smoker for 3 mo. No medical history, physical examination, blood pressure and pulse rate findings at baseline were considered clinically relevant. All subjects were ready and eligible to participate in the study and provided written informed approval.

Exclusion criteria were: hypersensitivity to similar drugs or transdermal systems, taking any medication within 2 w of study period, participation in another study within 30 d before receiving study medication, clinically significant symptoms in the 3 mo pre-study, probably need treatment during the study period, presence of situations known to intervene with any drug pharmacokinetics, any skin conditions at site of application that may block evaluations, a history of headaches or subject unlikely to comply with protocol like uncooperative attitude [33, 34].

Volunteers were instructed not to take any other medication through the study period. Also, they were advised to avert taking baths, exposure to sun or use any cream or oil at application sites of the gel [34].

Blood sampling

Serial blood samples of (1-2 ml) were withdrawn before gel application and at several time intervals, into a 5-ml screw-capped centrifuge tube with K$_3$EDTA as antiocoagulant [35]. Drug-free blood samples were taken from each group before the initiation of the treatment. Samples were centrifuged (using Bench-top centrifuge, model 3-30K, Sigma, Germany) at 4500 rpm at 4 °C for 15 min [36]. The clear supernatant (separated plasma) was taken away and transferred into a new screw-capped centrifuge tube and stored at -20 °C until being analyzed [36, 37].

Extraction and analysis of blood samples

The extraction of ondansetron from plasma samples was carried out. First, to precipitate proteins a 200 μl of acetonitrile were added to 200 μl of plasma, then the mixture was vortexed (Vortex Mixer, model Fine Vortex, Fine PCR®, Korea) for 2 min and centrifuged at 10,000 rpm at 4 °C for 20 min and 5 μl of supernatant was filtered then injected directly into the UPLC apparatus (Acquity™ UPLC, Model CHA, Serial # B 15CHA 4326, C18 column of 1.7 μm particle size and 2X100 mm inner diameter, PDA-e Detector, Empower-2 software, Singapore) with Ultraviolet spectrophotometer (Jenway 6305 Single Beam spectrophotometer, U. K) for analysis [1]. The UPLC analysis was performed on a reversed-phase UPLC system using a mobile phase of methanol (70 % v/v) containing ultrapure distilled water, with a 0.24 ml/min flow rate at 304 nm using UV detector [38, 27, 39].

Calibration curve of ondansetron in plasma

The standard calibration curve of ondansetron in plasma was constructed utilizing drug-seven plasma spiked with standard ondansetron solutions to get a concentration range from 20-1000 ng/ml. The spiked plasma was then undergoing the same extraction procedure as the samples. Triplicate running was done for each standard sample to assess the reproducibility of the detector at each concentration. Unknown concentrations of ondansetron were calculated from this calibration curve which was obtained by plotting various known ondansetron concentrations versus the corresponding peak areas.

Recovery of ondansetron from plasma samples

Recovery of ondansetron from plasma samples was determined by replicate analysis of plasma samples containing known amounts of the drug. As in the standard preparation, the samples were spiked to the blood and it was extracted, collected in vials and injected into the UPLC system. The amount of the drug to be added was calculated as well as the amount found was calculated [39].
Pharmacokinetic analysis of data
After measuring the ondansetron concentration in plasma, the pharmacokinetic parameters were investigated by analyzing the plasma concentration-time data according to the method of residuals. The maximum plasma concentration \( C_{\text{max}} \) and time to reach \( C_{\text{max}} \) \( (T_{\text{max}}) \) were gained directly from the data. Absorption rate constant \( (K_r) \), absorption half-life \( (T_{1/2a}) \), elimination rate constant \( (K_e) \), elimination half-life \( (T_{1/2e}) \) and area under the ondansetron plasma concentration versus time curve \( (AUIC) \) were computed according to conventional algorithms using the log plasma concentration vs. time curve [40]. The elimination half-life \( (T_{1/2e}) \) was computed by dividing 0.693 with \( K_e \) [40].

Common adverse effects assessment
Adverse effects were observed by the inspectors (local or systemic) as well as volunteers were asked to record any things that happened during the study.

Local dermal tolerance evaluation
Local tolerance was estimated by the inspectors employing a scoring system, clinical examination, and registering the appearance of adverse effects. The irritation scoring system was as follows: 0 = no evidence of irritation, 1 = minimal erythema, hardly sensible, 2 = specified erythema, easily visible, minimum edema, or minimal papular reaction, 3 = erythema and papules, 4 = specified edema, 5 = erythema, edema, and papules, 6 =vesicular eruption and 7 = powerful reaction at site of application.

Also, volunteer was asked about the potential manifestation of pruritus and burning/stinging feelings, and if recorded, the intensity of this reaction was classified from 0 to 3 as follows: 0 = none, 1 = mild: some feelings of pruritus/burning, intermittent, without consequence on daily activity, 2 = moderate: moderate feelings of pruritus/burning, persistent, with some intervention with daily activity and 3 = severe: strong pruritus/burning feelings, persistent, interfering with daily activity, and/or demanding gel elimination, and/or impairing sleep [33].

Study of the antiemetic effect of ondansetron gel in cisplatin-induced emesis in rats
Experimental animals
Seventy-two female Albino Wister rats, weighing 160–190 g (Animal house of faculty of Medicine, Assiut University-Egypt), adopted to the laboratory environments for 3 d before experiments. They were kept under normal conditions of an appropriate humidity and temperature and 12 h of light/dark cycle.

All rats were pliable to free access to kaolin, standard rat chow pellets, and water. The standard rat chow and kaolin pellets were mixed with 1 g of acacia at ratio 50:1 with distilled water to form a dense paste. Then, the paste was extruded through a syringe onto wire mesh samples. (R2 = 0.9998, slope = 42.313, intercept = -0.659) serve as a practical tool for the analysis of ondansetron in plasma conditions con

The standard calibration curve of ondansetron in human plasma is plotted in (fig. 1a) A straight line was obtained with an excellent correlation coefficient (R2 = 0.9998), which reflects good linearity of the relationship over the investigated concentration range [50-1000 ng/ml]. The retention times obtained for ondansetron in the mobile phase and rabbit plasma was around 0.93 and 1.512 min, respectively comparing to 8-9 min of reported retention time [39]. These chromatography conditions confirm the accuracy and reliability of this assay method to serve as a practical tool for the analysis of ondansetron in plasma samples. (R2 = 0.9998, slope = 42.313, intercept = 0.659)

The standard calibration curve of ondansetron in human plasma is plotted in (fig. 1b) A straight line was obtained with an excellent correlation coefficient (R2 = 0.9993), which reflects good linearity of the relationship over the investigated concentration range [20-800 ng/ml]. The retention times obtained for ondansetron in human plasma were around 1.55 min.

Recovery from plasma samples
The chromatograms show sharp and identifiable peaks. Moreover, the ondansetron peaks showed high resolution without interference

The rats were given individually cisplatin intraperitoneal. The dosage of cisplatin was selected to induce dose-limiting emesis (acute and delayed) as 10 mg/kg dose to encourage acute emesis, which peaked after 2 h, while 5 mg/kg dose induced a biphasic profile of emesis; the acute phase began 10 h after cisplatin administration, peaked after 12 h and a nadir was attained after 24 h. The delayed stage was more strong and prolonged than the acute phase and attained a peak 48th post cisplatin before gradually decreasing in severity during the next 24 h until 72 h post cisplatin, at which time a small amount of emesis continued [20, 44].

One gram of ondansetron gel 0.5 % was dermally applied on an area of 2 x 3 cm of rat dorsal skin which shaved in the adaptation days before the experiment to animals 12 h before exposure to cisplatin and repeated every 12 h. Rats were returned to cages for the estimation of daily kaolin, water, and feed intake and body weight changes during the next experiment time.

Kaolin, normal feed and water containers were removed each day at the same time and any spillage of them was collected and weighed using Digital balance (Precisa, Switzerland) to the nearest 0.01 g. Food hoppers were then refilled and weighed. The volume of the bottle of water was also determined and refilled by fresh tap water. The quantity consumed within every 24 h was evaluated by matching the weights with the former weights. The following equation was applied to determine the ultimate weight value:

\[ \text{Ultimate weight value (day n) = weight (day n)-weight (day n+1)} \ [45] \]
with the endogenous plasma components. The average recovery of ondansetron from spiked plasma samples ranged from 99.4 to 100.7 %, which reflects good efficiency of the extraction procedure as shown in (fig. 2.)

Bioavailability studies in rabbits

Based on previous results obtained from ex vivo permeation studies, the suitable formulation that selected was ondansetron gel (F13; 7%w/w sodium alginate) [9]. In this study, the selected formula with different concentrations exhibited a slower, but higher extent of permeation in four hours than the I. V. application. During the study, it was observed that no remarkable signs of any irritation or redness at application sites.

The UPLC method used for the determination of the concentrations of ondansetron permeated from skin to the systemic circulation was sufficiently precise and convenient for the analysis.

![UPLC calibration curve of ondansetron in (a) rabbit's plasma and (b) human's plasma](image1)

**Fig. 1:** UPLC calibration curve of ondansetron in (a) rabbit's plasma and (b) human's plasma

![UPLC chromatograms of blank plasma (rabbits and human) spiked with ondansetron at concentration 400 ng/ml](image2)

**Fig. 2:** UPLC chromatograms of blank plasma (rabbits and human) spiked with ondansetron at concentration 400 ng/ml
From the calibration curve, the plasma drug concentrations were determined for each rabbit and the mean plasma drug concentrations were calculated, with a standard deviation for each treatment group, and the drug concentration-time profiles were plotted. The mean plasma concentration-time profiles of ondansetron following gel application of the selected formulation with different concentrations and IV injection of ondansetron was shown in (fig. 3a, b). It could be seen that; the transdermal ondansetron (0.5%) gel formula showed plasma detectable concentration of (22.83±2.17 ng/ml) after 1/4 h post-treatment and the concentration was maintained nearer the reported minimum effective concentration (MEC) of ondansetron that it is 30 ng/ml [46] for more than 2.5 h. While the transdermal ondansetron (1%) gel formula showed a plasma detectable concentration of (212±38.432 ng/ml) after 1/4 h post-treatment and the concentration still detectable for 4 h.

The plasma drug concentration of transdermal gel formula which contains 0.5% ondansetron increased progressively to reach maximum concentration $C_{\text{max}}$ of (116.66±14.418 ng/ml) at $T_{\text{max}}$ of (1.5 h), then decreasing to (13.66±2.08 ng/ml) at 4 h after transdermal administration. While, the plasma drug concentration of transdermal gel formula which contains 1% ondansetron increased progressively to reach maximum concentration $C_{\text{max}}$ of (373±43.92 ng/ml) at $T_{\text{max}}$ of (1.5 h), and then decreasing to (26.33±5.508 ng/ml) at 4 h after transdermal administration.

The plasma profile of ondansetron after I. V. administration in the rabbits shows the $C_{\text{max}}$: 311.03±20.518 ng/ml just after injection. The plasma concentration decreased to reach (15.74±5.44 ng/ml) at 2 h after injection. The pharmacokinetic parameters of ondansetron were assessed and listed in tables 1-3.

**Bioavailability studies in healthy volunteers**

Using the calibration curve, the plasma drug concentrations were determined for each volunteer and the mean plasma drug concentrations were calculated, with a standard deviation for each treatment group, and the drug concentration-time profiles were plotted. The plasma drug concentrations of ondansetron were represented in (fig. 4) It could be seen that; the transdermal gel containing 0.5% ondansetron showed a plasma detectable concentration of (419.5±2.17 ng/ml) after 1 h post-treatment and the concentration was maintained above the reported minimum effective concentration (MEC) for ondansetron that it is 30 ng/ml [46] for more than 7 h.

![Graph](attachment:image.png)

**Fig. 3:** Mean plasma concentration-time profile of ondansetron after administration of gel formula (F13) of (a) 8 mg dose (b) 16 mg dose as compared to the marketed I. V. injection

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**Table 1: Pharmacokinetics parameters (a) of ondansetron I. V. administration of Zofran® and the gel formula F13 to rabbits (8 mg/dose)**

| Pharmacokinetics parameter (a) | Marketed I. V. ondansetron (8 mg/dose) | Transdermal gel F13 (8 mg/dose) | P value | Significance of the difference (c) |
|-------------------------------|----------------------------------------|---------------------------------|---------|-----------------------------------|
| C_{max} (ng/ml)               | 311.037±20.518                         | 117.168±6.603                   | 0.001   | ***                               |
| T_{max} (h)                   | 0                                      | 1.5                             | 0.001   | ***                               |
| K_{a} (h^{-1})                | ----                                   | 1.844±0.019                     | ----    |        |
| t_{1/2a} (h)                  | ----                                   | 0.376±0.004                     | ----    |        |
| K_{el} (h^{-1})               | 1.255±0.079                            | 1.176±0.221                     | 0.05    | NS                               |
| t_{1/2e} (h)                  | 0.553±0.035                            | 0.605±0.152                     | 0.05    | NS                               |
| AUC <= (µg. h/ml)             | 0.303±0.039                            | 0.22±0.022                      | 0.05    | NS                               |
| AUMC <= (µg. h/ml)            | 0.249±0.048                            | 0.413±0.099                     | 0.05    | NS                               |
| MRT <= (h)                   | 0.816±0.055                            | 1.78±0.152                      | 0.001   | ***                               |
| Clr (L/h)                     | 26.686±3.303                           | 36.529±3.615                    | <0.05   | *                                |
| V_{d} (liter)                 | 21.217±1.409                           | 31.725±3.83                     | <0.01   | **                               |
| F (%)                         | ----                                   | 73.01±5.124                     | ----    |        |

*mean±SD (n = 3). C_{max}: maximum plasma concentration, T_{max}: time to reach C_{max}, K_{a}: absorption rate constant, t_{1/2a}: absorption half-life, K_{el}: elimination rate constant, t_{1/2e} elimination half-life, AUC: area under the ondansetron plasma concentration versus time curve, AUMC: area under the moment vs. time curve, MRT: mean residence time, Cl: clearance, V_{d}: volume of distribution, F: fraction absorbed (bioavailability). highly significant *** p 0.001, moderate significant ** p 0.01, mild significant * p 0.05, non-significant NS p>0.05.

**Table 2: Pharmacokinetics parameters (a) of ondansetron I. V. administration of Zofran® and the gel formula F13 to rabbits (16 mg/dose)**

| Pharmacokinetics parameter (a) | Marketed I. V. ondansetron (16 mg/dose) | Transdermal gel F13 (16 mg/dose) | P-value | Significance of the difference (c) |
|-------------------------------|-----------------------------------------|---------------------------------|---------|-----------------------------------|
| C_{max} (ng/ml)               | 311.037±20.518                         | 360.33±24.168                   | <0.05   | *                                |
| T_{max} (h)                   | 0                                      | 1.5                             | 0.001   | ***                               |
| K_{a} (h^{-1})                | ----                                   | 2.02±0.049                      | ----    |        |
| t_{1/2a} (h)                  | ----                                   | 0.34±0.008                      | ----    |        |
| K_{el} (h^{-1})               | 1.255±0.079                            | 1.065±0.068                     | 0.05    | *                                |
| t_{1/2e} (h)                  | 0.553±0.035                            | 0.657±0.05                      | 0.05    | *                                |
| AUC <= (µg. h/ml)             | 0.303±0.039                            | 0.721±0.044                     | 0.001   | ***                               |
| AUMC <= (µg. h/ml)            | 0.249±0.048                            | 1.09±0.109                      | 0.001   | ***                               |
| MRT <= (h)                   | 0.816±0.055                            | 1.50±0.051                      | 0.001   | ***                               |
| Clr (L/h)                     | 26.686±3.303                           | 22.32±1.2                      | >0.05   | NS                               |
| V_{d} (liter)                 | 21.217±1.409                           | 20.989±0.286                    | >0.05   | NS                               |
| F (%)                         | ----                                   | 26.39±16.091                    | ----    |        |

*mean±SD (n = 3). C_{max}: maximum plasma concentration, T_{max}: time to reach C_{max}, K_{a}: absorption rate constant, t_{1/2a}: absorption half-life, K_{el}: elimination rate constant, t_{1/2e} elimination half-life, AUC: area under the ondansetron plasma concentration versus time curve, AUMC: area under the moment vs. time curve, MRT: mean residence time, Cl: clearance, V_{d}: volume of distribution, F: fraction absorbed (bioavailability). highly significant *** p 0.001, moderate significant ** p 0.01, mild significant * p 0.05, non-significant NS p>0.05.
Each pharmacokinetic value was compared between men and women. Women consistently had significantly higher mean residence time (MRT) and elimination half time than men and the drug remained in higher value in women at 7 h post-application than men. While there is no significant differences were detected between genders in AUC for ondansetron gel.

Maximal plasma concentrations of ondansetron were attained after 3 h. of application of an average of 617.22 ng/ml. The plasma drug concentration of ondansetron (0.5%) gel increased progressively to reach maximum concentration Cmax of (690.67±57.75 ng/ml) at Tmax of (3 h) for men and Cmax of (546.92±70 ng/ml) at Tmax of (3.5 h) for women, then decreasing to (61.3±14 ng/ml and 178.75±22.5 ng/ml) at 7 h after transdermal administration for men and women, respectively as presented in table 4.

In general, the dermal evaluation showed that ondansetron gel was fully tolerated and a total rating of skin irritation was very low. In the plurality of assessments, Grade 0 (none) was observed. Common adverse effects were headache, back pain and dizziness for all volunteers and one subject suffer from the metallic taste. There are no serious adverse effects were considered treatment-related.

Linearizing the ondansetron plasma concentration data using semi-log graph scale

By plotting the intravenous plasma concentration data onto the semi-log graph scale, we can obtain a straight line which indicates the elimination phase and the drug occupies one compartment pharmacokinetics (40) as shown in fig. 5a. While in case of extravascular dose (transdermal gel) the two processes of absorption and elimination occur in parallel and at late times in graphs, absorption may be complete and we see virtually clear elimination phase (47) as shown in fig. 5b, c, and d

### Table 3: Pharmacokinetics parameters of ondansetron gel formula F13 with different doses (8 and 16 mg) to rabbits

| Pharmacokinetics parameter | Transdermal gel F 13 (8 mg dose) | Transdermal gel F 13 (16 mg dose) | P value | Significance of the difference |
|----------------------------|----------------------------------|----------------------------------|---------|-------------------------------|
| Cmax (ng/ml)               | 117.16±84.603                   | 360.8±24.17                     | 0.001   | ***                           |
| Tmax (h)                   | 1.5                              | 1.5                              | >0.05   | Ns                            |
| K1 (h⁻¹)                   | 1.84±0.019                      | 2.02±0.049                      | <0.01   | **                            |
| t1/2a (h)                  | 0.37±0.004                      | 0.34±0.008                      | <0.01   | **                            |
| K1 (h⁻¹)                   | 1.17±0.22                        | 1.065±0.069                     | <0.05   | *                             |
| t1/2c (h)                  | 0.657±0.05                      | 0.657±0.05                      | <0.05   | *                             |
| AUC (ng·h/ml)              | 0.22±0.022                      | 0.721±0.044                     | 0.001   | ***                           |
| AUMC (μg·h/ml)             | 0.41±0.099                      | 1.069±0.109                     | 0.01    | *                             |
| MRT (h)                    | 1.78±0.152                      | 1.503±0.751                     | <0.01   | **                            |
| Ct (L/h)                   | 36.5±29.365                     | 22.3±2.32                      | 0.01    | *                             |
| Vd (L)                     | 31.7±25.383                     | 20.9±0.29                      | <0.01   | **                            |
| F (%)                      | 73.01±5.124                     | 261.9±16.1                     |        | ---                           |

*mean±SD (n = 3), Cmax: maximum plasma concentration, Tmax: time to reach Cmax, K1: absorption rate constant, t1/2c: absorption half-life, K1: elimination rate constant, t1/2a: elimination half-life, AUC: area under the ondansetron plasma concentration versus time curve, AUMC: area under the moment vs. time curve, MRT: mean residence time, Cl: clearance, Vd: volume of distribution, F: fraction absorbed (bioavailability).

### Table 4: Pharmacokinetics parameters of ondansetron gel administrated to women and men

| Pharmacokinetics parameter | Transdermal gel male | Transdermal gel female | P-value | Significance of the difference |
|----------------------------|----------------------|------------------------|---------|-------------------------------|
| Cmax (ng/ml)               | 690.27±0.065         | 522.65±0.098           | >0.05   | Ns                            |
| Tmax (h)                   | 3                   | 3.5                    | >0.05   | Ns                            |
| K1 (h⁻¹)                   | 0.89±0.050           | 0.70±0.043             | <0.01   | **                            |
| t1/2a (h)                  | 0.779±0.043          | 0.994±0.061            | <0.01   | **                            |
| K1 (h⁻¹)                   | 0.955±0.091          | 0.357±0.148            | 0.05    | *                             |
| AUC (ng·h/ml)              | 3.33±0.468           | 3.17±0.071             | >0.05   | Ns                            |
| AUMC (μg·h/ml)             | 11.65±1.93           | 15.6±3.184             | >0.05   | Ns                            |
| MRT (h)                    | 3.48±0.099           | 4.95±2.113             | >0.05   | Ns                            |
| Ct (L/h)                   | 2.80±0.96            | 2.70±1.55              | >0.05   | Ns                            |
| Vd (L)                     | 5.60±0.956           | 6.47±1.55              | >0.05   | Ns                            |

*mean±SD (n = 3), Cmax: maximum plasma concentration, Tmax: time to reach Cmax, K1: absorption rate constant, t1/2c: absorption half-life, K1: elimination rate constant, t1/2a: elimination half-life, AUC: area under the ondansetron plasma concentration versus time curve, AUMC: area under the moment vs. time curve, MRT: mean residence time, Cl: clearance, Vd: volume of distribution, F: fraction absorbed (bioavailability).

### The antiemetic effect of ondansetron gel in cisplatin-induced emesis in rats

American Society of Clinical Oncology guidelines classified cisplatin as the highest emetic risk group as it causes acute and delayed vomiting [19]. Acute vomiting mainly occurs within a few hours to several hours next to cisplatin administration and usually resolves within the first 24 h. Delayed vomiting develops after 24 h next to cisplatin administration and continues for 6-7 d [20].

Signs and mortality rates detected due to cisplatin injection in rats and the effect of ondansetron gel

All groups received cisplatin of 5 mg/kg dose suffered from most common side effects caused by it as general drowsiness, fatigue, loss of appetite and low locomotor activity like horizontal movement, mobility, and rearing during first 24 h after injection [46]. This result is in agreement with Malik et al. [49] who reported the influence of cisplatin on locomotor activity on rats after administration of 6 mg/kg cisplatin on day 2 post-injection compared to control group. They suggested that the lowering in locomotor activity might be a primary influence of cisplatin [50] or secondary to “nausea” or visceral malaise; the decrease in food intake might be attributed to nausea or to a reduction in locomotor activity.

From day 3-5 the feces of the cisplatin group was constipated grey in color compared with the control group, and on day 5 the feces became black and soft and convert to dark watery diarrhea in late
days before the death of rats. Also, the rats suffering from nosebleeds and red spots on the skin of the head, neck and lower parts of legs due to reducing the number of platelets, alopecia, dry skin and dehydration. Also, there are muscle weakness and paralysis leading to death within 24 h.

About 25% of rats receiving cisplatin without ondansetron gel died at day 5 of experiment and 100% of this group died at day 7 of the experiment, while another group which receiving cisplatin and ondansetron gel began to die at day 6 and 50% of rats still alive up to day 15 of the experiment.

Also, the previous signs also observed in the groups receiving cisplatin of 10 mg/kg dose but more aggressive and accelerated after day 3 of the experiment and all rats died on days 4 and 5. While, the blank group receiving ondansetron gel did not show any specific signs like irritation, redness, drowsiness or fatigue and preserves the same activity comparing to the control group.

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**Fig. 5:** Semi-log plot of ondansetron plasma concentration against time curve following administration of (a) marketed I. V. injection, (b) transdermal administration of 8 mg dose in rabbits, (c) transdermal administration of 16 mg dose in rabbits and (d) transdermal administration of 8 mg dose in humans.
Effect of ondansetron on cisplatin-induced body weight loss

Cisplatin produced hypophagia and weight loss in all rats but these symptoms of illness were less severe in rats which had been administrated ondansetron gel than those did not have [51].

The results show that the body weight loss was increased in a dose-dependent manner, as the higher cisplatin tested dose (10 mg/kg); rats show more weight loss compared to smaller dose and these results are in good harmony with data obtained by Cabezos et al. [52].

The two groups receiving cisplatin injection induce significant loss of animal’s body weight of about 13.43 and 18 % for 5 and 10 mg/kg doses, respectively at day 5 of an experiment comparing to 7.89 and 14.75 % for groups receiving ondansetron gel (p< 0.05).

Also, the groups receive 5 mg/kg cisplatin induces significant loss of animal’s body weight of about 13.43 and 18 % for 5 and 10 mg/kg doses, respectively at day 5 of an experiment comparing to 7.89 and 14.75 % for groups receiving ondansetron gel (p< 0.05).

### Table 5: Effect of ondansetron gel formulation (F13) on body weight change (grams) of rats administered cisplatin (5 mg/kg, i. p.)

| Days | Control | Control+ondansetron gel | Cisplatin (5 mg/kg) I. P. | Cisplatin (5 mg/kg) I. P. +ondansetron gel |
|------|---------|-------------------------|---------------------------|---------------------------------------------|
| 0    | 186.4 ±1.66 | 185.10±1.15 | 183.67±3.79 | 184.95±2.92 |
| 1    | 181.33±1.24 | 179.69±1.15 | 180.4 8±1.50 | 184.09±3.82 |
| 2    | 179.52±1.16 | 181.42±1.67 | 176.33±1.15 | 180.10±3.02 |
| 3    | 180.84±2.16 | 180.71±1.86 | 170.02±2.11 | 180.21±3.11 |
| 4    | 181.22±2.64 | 178.57±3.50 | 167.63±0.55 | 176.09±2.85 |
| 5    | 182.32±1.82 | 182.43±1.68 | 159.08±1.81 | 170.34±2.41 |
| 6    | 183.50±2.29 | 180.08±2.13 | 157.42±4.88 | 164.74±2.69 |
| 7    | 181.59±4.13 | 180.59±2.90 | 151.77±2.92 | 165.29±2.36 |
| 8    | 185.33±2.52 | 182.09±2.14 | 158.74±4.03 | 162.50±1.32 |
| 9    | 184.23±2.25 | 184.93±2.03 | 157.42±4.03 | 161.30±3.93 |

For<0.05, #P<0.01, #P<0.001 vs. control group, P<0.05, **P<0.01, ***P<0.001 vs. cisplatin group.

### Table 6: Effect of ondansetron gel formulation (F13) on body weight change (grams) of rats administered cisplatin (10 mg/kg, i. p.)

| Days | Control | Cisplatin (10 mg/kg) I. P. | Cisplatin (10 mg/kg) I. P. +ondansetron gel |
|------|---------|---------------------------|---------------------------------------------|
| 0    | 186.42±1.66 | 184.18±4.06 | 184.98±1.36 |
| 1    | 181.33±1.24 | 176.2 6±3.33 | 179.07±2.07 |
| 2    | 179.52±1.16 | 164.44±5.09 | 169.34±1.12 |
| 3    | 180.84±2.16 | 158.74±4.03 | 165.24±0.96 |
| 4    | 181.22±2.64 | 153.78±2.86 | 163.90±1.33 |
| 5    | 182.32±1.82 | 151.02±3.02 | 157.68±1.71 |

For<0.05, #P<0.01, #P<0.001 vs. control group, P<0.05, **P<0.01, ***P<0.001 vs. cisplatin group.

![Graph a](image1.png)  
**a-After administration of cisplatin (5 mg/kg, i. p.)**

![Graph b](image2.png)  
**b-After administration of cisplatin (10 mg/kg, i. p.)**
Effect of ondansetron on the nutrition profile of cisplatin treating rats

Water consumption

After adaptation period, control rats consume daily amount of 23.46±5 ml of water and intraperitoneal administration of cisplatin (5 mg/kg) make a significant decrease in daily water consumption to average 11.8±7.8 ml except at day 2 and 3 the results show increasing in water consumption due to the nephrotoxicity which is a current side effect of cisplatin treatment [53] and increased water intake has been noted in several studies [51].

These results are in good consent with De Jonghe et al. [51] who found that kaolin consumption ameliorates cisplatin-induced reductions in food but not water intake. This might be explained by the different mechanisms that underlie food and water transit and absorption in the gut. While the daily water amount consumed by rats significantly elevated to about 21.17±4.7 by using ondansetron gel comparing with cisplatin only (p < 0.05) as shown in fig. 7a and table 7.

Intraperitoneal administration of cisplatin of a dose (10 mg/kg) make a significant decrease in daily water consumption to average 7±11.5 ml in nearly all days and the using of ondansetron gel significantly elevate the volume of water consumed by rats to 11.6±8.7 (p <0.05) as elucidated in (fig. 7b) and table 8 and this result is in agreement with Liu et al. [44] who reported that the using dose of cisplatin more than 5 mg/kg cause increase in gastric contents as well as decreased food and water intake at 48 h post-cisplatin treatment. Further support by the studies of Bradner and Schurig [54] and Olver et al. [55] in mice showing a dose-related decrease in water intake due to an increase in the weight of gastric contents measured at 24 or 48 h after cisplatin. This effect was obtained with other cytotoxic anticancer drugs in mice and rats [56].

Table 7: Effect of ondansetron gel formulation (F13) on the change of water consumption (ml) induced by cisplatin (5 mg/kg, i. p.)

| Days | Control (ml) | Control + ondansetron gel (ml) | Cisplatin (5 mg/kg) I. P. (ml) | Cisplatin (5 mg/kg) I. P. + ondansetron gel (ml) |
|------|-------------|-------------------------------|-------------------------------|--------------------------------------------------|
| 0    | 26.7±2.75   | 28.4±2.27                     | 27.50±2.50                    | 26.0±2.00                                         |
| 1    | 30.5±2.63   | 35.0±7.00                     | 15.50±1.50                    | 20.0±2.00                                         |
| 2    | 22.7±2.25   | 31.4±2.65                     | 27.0±3.50                     | 21.0±2.00                                         |
| 3    | 25.2±2.50   | 29.9±1.00                     | 26.3±3.51                     | 23.5±0.02                                         |
| 4    | 27.7±2.88   | 28.5±6.50                     | 9.3±3.25                      | 25.1±1.76                                         |
| 5    | 25.7±1.75   | 34.4±2.95                     | 4.6±2.00                      | 16.6±2.02                                         |
| 6    | 20.3±1.53   | 29.4±4.51                     | 5.5±2.18                      | 18.6±2.52                                         |
| 7    | 14.3±1.53   | 28.6±5.56                     | 4.0±0.50                      | 29.0±3.00                                         |
| 8    | 21.1±1.76   | 30.7±1.11                     | Died                          | 17.0±2.00                                         |
| 9    | 20.0±2.00   | 29.6±4.73                     | Died                          | 15.0±2.50                                         |

*P<0.05, **P<0.01, ***P<0.001 vs. control group, P<0.05, **P<0.01, ***P<0.001 vs. cisplatin group.
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a-cisplatin (5 mg/kg, i. p.)

b-cisplatin (10 mg/kg, i. p.)

Fig. 7: Effect of ondansetron gel formulation (F13) and (a) cisplatin (5 mg/kg, i. p.) and (b) cisplatin (10 mg/kg, i. p.) on water consumption (ml) in rats

Table 8: Effect of ondansetron gel formulation (F13) on the change of water consumption (ml) induced by cisplatin (10 mg/kg, i. p.)

| Days | Control | Cisplatin (10 mg/kg) I. P. | Cisplatin (10 mg/kg) I. P. + ondansetron gel |
|------|---------|-----------------------------|----------------------------------------------|
| 0    | 30.00 ± 3.50 | 31.50 ± 2.50                | 30.00 ± 3.50                                |
| 1    | 26.75 ± 2.75  | 31.50 ± 2.50                | 31.50 ± 2.50                                |
| 2    | 30.50 ± 2.63  | 31.50 ± 2.50                | 31.50 ± 2.50                                |
| 3    | 22.75 ± 2.25  | 31.50 ± 2.50                | 31.50 ± 2.50                                |
| 4    | 25.25 ± 2.50  | 31.50 ± 2.50                | 31.50 ± 2.50                                |
| 5    | 27.75 ± 2.88  | 31.50 ± 2.50                | 31.50 ± 2.50                                |

\*P<0.05, \#P<0.01, \%P<0.001 vs. control group, \#P<0.05, \#\#P<0.01, \#\#\#P<0.001 vs. cisplatin group.

Food consumption

Tables 9-10 and (fig. 8a, b) showed that after injection of cisplatin, normal feed consumption in the cisplatin groups significantly decreased when compared with the control group after 24 h of injection (P<0.01). Moreover, this decrease was reduced by ondansetron administration after the third day of injection (P<0.05) in the case of 5 mg/kg cisplatin dose. Similarly, in case of 10 mg/kg cisplatin dose, there is slight attenuation of food intake by using ondansetron gel comparing with cisplatin group and these results are in harmony with data obtained by Cabezos et al. [52] who reports that administration of cisplatin prompted a significant decrease in food ingestion in the 24 h instantly after administration due to severe anorexia.

Kaolin consumption

In case of 5 mg/kg dose of cisplatin, there is a significant increase in kaolin consumption during first 48 h after injection and the changes in of kaolin intake were remarkably recovered on day 3, although the body weight loss was still preserved as demonstrated in table 11 and (fig. 9a).

Further administration of cisplatin did not change the kaolin consumption and still maintained at the normal level. This explains the change of quality of rats feces during the experiment period as cisplatin produces gastric stasis and diarrhea [49, 57, 58] and clay possesses toxin-binding properties [59, 60] as an anti-diarrhea drug [61]. Thus, kaolin consumption could limit the side effects of cisplatin on the GI tract, lessening the severity of distress experienced by the animal. Pre-treatment with the ondansetron gel significantly reduced the cisplatin-induced increase in kaolin consumption to the normal levels.

While in the case of 10 mg/kg dose of cisplatin the level of kaolin was increased significantly on day 4 (P<0.001) comparing to both control and ondansetron group as elucidated in table 12 and (fig. 9b). Delayed access of rats to kaolin may be one of the reasons for
rapid death due to increasing the severity of illness symptoms like weight loss and hypophagia. These data suggest that kaolin consumption following cisplatin not only indicates sickness but also plays a therapeutic role by diminishing the degree of malaise experienced by the rat and/or enhancing the rate of recovery as reported by Riezzo G, et al. [58].

Effect of ondansetron gel alone on rats

There is no significant difference in changing in body weight and water, food, and kaolin consumption comparing with the control group as shown in (fig. 6a, 7a, 8a, and 9a) and tables 5, 7, 9 and 11. Also, there were no important signs and side effects reported by this group.

### Table 9: Effect of ondansetron gel formulation (F13) on the change of food consumption (grams) induced by cisplatin (5 mg/kg, i. p.)

| Days | Control | Control+ondansetron gel | Cisplatin (5 mg/kg) I. P. | Cisplatin (5 mg/kg) I. P. +ondansetron gel |
|------|---------|-------------------------|---------------------------|---------------------------------|
| 0    | 15.99±1.97 | 13.6±0.03               | 15.92±2.98                | 13.04±1.56                      |
| 1    | 15.15±1.12 | 18.35±7.66              | 4.14±0.68                 | 5.5±0.59                        |
| 2    | 13.07±2.89 | 14.8±5.5               | 1.90±1.01                 | 3.4±0.43                        |
| 3    | 10.98±3.92 | 8.18±4.17               | 1.42±1.32                 | 3.4±0.41                        |
| 4    | 12.66±1.85 | 8.32±0.91              | 0.36±0.25                 | 4.63±0.61                       |
| 5    | 12.33±0.70 | 10.11±0.10             | 0.24±0.02                 | 3.8±0.35                       |
| 6    | 13.42±0.14 | 10.7±1.12              | 0.01±0.01                 | 3.78±0.48                       |
| 7    | 10.16±0.62 | 11.5±1.39              | 0.18±0.28                 | 4.55±0.55                       |
| 8    | 12.40±0.24 | 12.6±0.35              | Died                      | 4.5±0.55                        |
| 9    | 14.21±2.08 | 12.3±1.53              | Died                      | 4.0±0.50                        |

*P<0.05, **P<0.01, ***P<0.001 vs. control group, "P<0.05, ""P<0.01, """"P<0.001 vs. cisplatin group.
Table 10: Effect of ondansetron gel formulation (F13) on the change of food consumption (grams) induced by cisplatin (10 mg/kg, i. p.)

| Days | Control | Cisplatin (10 mg/kg) I. P. | Cisplatin (10 mg/kg) I. P. +ondansetron gel |
|------|---------|----------------------------|---------------------------------------------|
| 0    | 15.99±1.97 | 15.40±2.94 | 14.21±1.21 |
| 1    | 15.15±3.12 | 5.85±0.93 | 9.40±0.96 |
| 2    | 13.07±2.89 | 2.09±0.21 | 6.45±0.48 |
| 3    | 10.98±3.92 | 0.07±0.12 | 1.78±0.20 |
| 4    | 12.66±1.85 | 0.3±0.58 | 2.03±0.95 |
| 5    | 12.33±0.70 | 0.5±0.50 | 3.60±0.96 |

aP<0.05, bP<0.01, c P<0.001 vs. control group., *P<0.05, **P<0.01, ***P<0.001 vs. cisplatin group.

![Fig. 9: Effect of ondansetron gel formulation (F13) and (a) cisplatin (5 mg/kg, i. p.) and (b) cisplatin (10 mg/kg, i. p.) on the Kaolin consumption (grams) in rats](image)

Table 11: Effect of ondansetron gel formulation (F13) on the change of Kaolin consumption (grams) induced by cisplatin (5 mg/kg, i. p.)

| Days | Control | Control+ondansetron gel | Cisplatin (5 mg/kg) I. P. | Cisplatin (5 mg/kg) I. P. +ondansetron gel |
|------|---------|-------------------------|--------------------------|---------------------------------------------|
| 0    | 0.25±0.02 | 0.08±0.08 | 0.21±0.06 | 0.24±0.07 |
| 1    | 0.28±0.12 | 0.18±0.01 | 1.59±0.40 | 0.01±0.02*** |
| 2    | 0.25±0.05 | 0.20±0.02 | 0.97±0.35 | 0.02±0.03*** |
| 3    | 0.27±0.02 | 0.29±0.04 | 0.11±0.10 | 0.03±0.03 |
| 4    | 0.15±0.15 | 0.20±0.02 | 0.13±0.12 | 0.29±0.12 |
| 5    | 0.21±0.11 | 0.22±0.02 | 0.22±0.03 | 0.18±0.03 |
| 6    | 0.24±0.10 | 0.34±0.04 | 0.20±0.09 | 0.24±0.04 |
| 7    | 0.17±0.15 | 0.14±0.13 | 0.20±0.10 | 0.20±0.04 |
| 8    | 0.10±0.05 | 0.14±0.01 | Died      | 0.04±0.05 |
| 9    | 0.24±0.10 | 0.26±0.10 | Died      | 0.18±0.03 |

aP<0.05, bP<0.01, c P<0.001 vs. control group., *P<0.05, **P<0.01, ***P<0.001 vs. cisplatin group.
CONCLUSION
Based on the high efficacy of transdermal ondansetron gel (7%w/w sodium alginate) on the emesis induced by antineoplastic drugs and long-term efficiency, as well as a high bioavailability, the transdermal ondansetron gel could be a promising convenient system to relieve, prohibit or stop nausea and vomiting in patients taking chemotherapy or radiotherapy.

AUTHORS CONTRIBUTIONS
El sayed A Ibrahim designed the work, Mai M. Rasheedy carries out the laboratory work with guidance from Dina Fathallah and Mona M. El-Mahdy, Dina Fathallah wrote the article. All authors critically revised and approved the work for publication.

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Table 12: Effect of ondansetron gel formulation (F13) on the change of Kaolin consumption (grams) induced by cisplatin (10 mg/kg, i. p.)

| Days | Control | Cisplatin (10 mg/kg) L. P. | Cisplatin (10 mg/kg) L. P. +ondansetron gel |
|------|---------|---------------------------|--------------------------------------------|
| 0    | 0.2±0.05 | 0.23±0.06                 | 0.35±0.08                                 |
| 1    | 0.28±0.17 | 0.19±0.05                 | 0.29±0.03                                 |
| 2    | 0.25±0.05 | 0.30±0.09                 | 0.33±0.08                                 |
| 3    | 0.27±0.02 | 0.63±0.55                 | 0.14±0.06                                 |
| 4    | 0.18±0.19 | 1.82±0.33                 | 0.28±0.7**                                |
| 5    | 0.21±0.21 | 1.96±0.44**               | 0.36±0.6**                                |

*P<0.05, **P<0.01, ***P<0.001 vs. control group, "P<0.05, ""P<0.01, """"P<0.001 vs. cisplatin group.
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