Influence of skin permeation enhancers on the transdermal delivery of palonosetron: An in vitro evaluation

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ARTICLE INFO

Article history:
Received 21 July 2017
Received in revised form 30 October 2017
Accepted 12 December 2017
Available online 21 December 2017

Keywords:
Palonosetron
Transdermal
Adhesive
Enhancers
Release

ABSTRACT

It is proposed that the low skin permeation potential of palonosetron could be enhanced by the inclusion of chemical permeation enhancers. The objective of this study is to evaluate the influence of various chemical enhancers on the transdermal permeation of palonosetron. Different drugs in adhesive transdermal patches (F1–F5) were prepared using five pressure sensitive adhesives; Duro-Tak 87–4098, Duro-Tak 87–2074, Duro-Tak 87–900A, Duro-Tak 87–9301 and Duro-Tak 87–2287. Patches prepared using Duro-Tak 87–9301 (F5) was further combined with four well-known chemical enhancers. The influence of permeation enhancers (propylene glycol, diethylene glycol monoethyl ether, Tween 80 and oleic acid) on the transdermal flux was evaluated ex vivo. Release of the drug from fabricated patches was carried out for a period of 6 h. Greater amount of drug (12% w/w) was incorporated in the patches prepared using Duro-Tak 87–9301 (F5). Incorporation of skin permeation enhancers significantly (P < 0.001) improves the transdermal flux of palonosetron. Among the permeation enhancers, propylene glycol (5% w/w) shows highest permeation (53.12 ± 5.62 µg/cm²/h), which is ~4 folds higher than control. Biphasic drug release was noticed in the prepared patches and the rate of release was relatively high with patch F7. This study reveals that the optimized transdermal system with propylene glycol as permeation enhancers can provide effective therapeutic level of palonosetron.

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INTRODUCTION

Cancer is one of the most life threatening and demoralizing diseases known to affect human worldwide. Chemotherapy plays a vital role in advancing patient outcomes in oncology and is a mainstay of therapy for most patients suffering from cancer. The cancer chemotherapy management protocols are cytotoxic in nature and cause intolerable and painful adverse effects. Chemotherapy-induced nausea and vomiting (CINV) remains a major side-effect despite the vast array of novel antiemetic medicines, with delayed effects being observed usually (Rao and Faso, 2012). Unfortunately, nausea and vomiting generally affect the patient’s quality of life, which in turn cause difficulty in performing the day-to-day activities (Perwitasari et al., 2012). In addition, there are instances wherein patients even decline to pursue possibly useful treatment regimens because of treatment associated nausea and vomiting. On the other hand, uncontrolled CINV necessitates rescue medication and most likely end up with emergency admission, which increases the cost burden of medical care (Turini et al., 2015). The introduction of safe and selective type three 5-hydroxytryptamine (5-HT3) receptor antagonists, which also possess greater therapeutic index, is considered as a breakthrough in the pharmacotherapy of CINV (Billio et al., 2013). Progress in this field has produced new therapeutic 5-HT3 receptor antagonists and one among them is palonosetron, which is 30–100 times more effective and owns long half-life (Aapro, 2007). Hence, recent guidelines for the treatment of CINV recognize the importance of palonosetron and recommend its use preceding cancer chemotherapy (Affronti and Bubalo, 2014). However, this drug is currently administered by intravenous route, which is invasive as well as possess less patient compliance (Moon et al., 2014). Thus an alternative route for this drug in CINV could be significantly beneficial to the patient population.

Transdermal delivery systems have been developed to surmount the typical issues associated with the conventional formulations including oral and parenteral (Paudel et al., 2010).
This drug delivery system is a non-invasive approach, which provides sustained and steady delivery of actives through the skin membrane and into the systemic circulation (Tanner and Marks, 2008). Transdermal drug delivery system offers a tailored pharmacokinetic profile in respect of specified nature of active pharmaceutical compound. There are quite a few approved transdermal systems, typically for the adults, and most of these systems are effective and deliver molecules without much hindrance from the skin (Pastore et al., 2015). The adaptability and versatility of the transdermal drug delivery approach could be due to the technology being suitable for a wide range of pharmaceutical applications and/or pharmaceutical compounds. Drug in adhesive transdermal patches prepared with pressure sensitive adhesives has demonstrated its potential as an effective system for the delivery of therapeutic agents (Niharka et al., 2017). Indeed, these adhesives provide adequate adhesion of patch to the skin as well as allow the drug/enhancer to be incorporated directly into it. In addition, they also contribute in the delivery, transport and stability of the product, which makes it the most significant component in transdermal systems (Lobo et al., 2016).

Palonosetron possesses distinct properties, such as molecular weight (≈332 g/mol), melting point (≈240 °C), dose (0.5 mg), aqueous solubility (≈1 mg/ml) and partition coefficient (log P≈2.7), which seems to be ideal for transdermal delivery (Benet et al., 2011). Indeed, development of a controlled release transdermal delivery system of palonosetron could be advantageous in all three major group of CINV such as acute, delayed and anticipatory emesis (Seol et al., 2016). Attempts have already been made to develop transdermal delivery system of palonosetron, although resulted with moderate efficacy (Liu et al., 2016). Recently, another study assessed the feasibility of transdermal application of palonosetron and observed that the intrinsic permeability is extremely low (Kamil et al., 2016). In this context, chemical permeation enhancers are widely used to improve the skin delivery of such BCS class III drugs (Chen et al., 2014). Thus in the current study, four well-known skin chemical permeation enhancers (propylene glycol, diethylene glycol monoethyl ether, Tween 80 and oleic acid), which are potent and safe are selected (Chen et al., 2014). Different mechanisms have been proposed in the literature for these enhancers; propylene glycol (solvates α-keratin thus reducing drug/tissue binding), diethylene glycol monoethyl ether (improves hydration and/or solubility of drug in skin) Tween 80 (modifies the fluidity of stratum corneum) and oleic acid (selective perturbation the intercellular lipid bilayers) (Lane, 2013; Thong et al., 2007). Thus the objective of the present investigation is to evaluate the effect of these well-known skin permeation enhancing agents on the transdermal delivery of palonosetron.

### Materials and methods

#### Materials

Palonosetron hydrochloride, propylene glycol, diethylene glycol monoethyl ether, Tween 80® and oleic acid (Sigma Aldrich, St. Louis, MO) were purchased commercially. Polyester release liner (Scotchpak® 1022) and polyethylene monolayer backing membrane (CoTran™ 9720) were supplied by 3M, St. Paul, USA. Duro-Tak 87-4098, Duro-Tak 87-2074, Duro-Tak 87-900A, Duro-Tak 87-9301. Duro-Tak 87-2287 were procured from the National Starch and Chemical Company, Bridgewater, NJ, USA. Other chemicals/ reagents were purchased from local suppliers.

#### Analytical method

Estimation of palonosetron was carried out using reverse phase high performance liquid chromatography (HPLC) method with diode array detector (Agilent, 1200 series, Germany). Separation of compound by chromatography was achieved on zorbax C18 column (150 mm × 4.6 mm i.d, 5 μm) with mobile phase consisting of acetonitrile and 0.1% formic acid (30:70 v/v). The mobile phase was pumped at the rate of 1.2 ml/min and 20 μl samples were injected (Bourdon et al., 2014). The column oven temperature was kept at 25 °C and the elute was detected at 240 nm. The retention time (tR) was found to be 6.14 min. The calibration curves (peak area vs. concentration) were constructed in the range of 0.1–12 μg/ml with excellent correlation (r² > 0.998). The concentration of analyte in the samples was determined using regression equations.

#### Fabrication of transdermal patch

Solvent evaporation method was followed to fabricate the drug in adhesive transdermal system of palonosetron (Nair et al., 2016). Five pressure sensitive adhesives selected to formulate transdermal patches (F1–F5) and the components used are summarized in Table 1. Briefly, the weighed amount of drug (Table 1) was dissolved in ethyl alcohol and added to the pressure sensitive adhesives with continuous stirring using high speed mechanical stirrer (Remi Elektrotechnik Limited, Thane, India). The mixing was continued until a homogenous clear layer was observed which indicates the drug is completely and uniformly dispersed in the adhesive. The adhesive mixture was then spread over the polyester release liner (Scotchpak® 1022, 3 M, St. Paul, USA) at a thickness of ≈350 μm. The patch was allowed to dry at room temperature for 6 h, and the bubbles were removed. The air dried patches are further kept in oven at 40 °C for 2 h to eliminate the organic solvents. Then the patches were punched out and fixed over the backing membrane (CoTran™ 9720, 3 M, St. Paul, USA) (Nair et al., 2014). To prepare patches with enhancers (F6–F9), the respective

<table>
<thead>
<tr>
<th>Code No.</th>
<th>Drug concentration</th>
<th>Adhesives</th>
<th>Enhancers (% w/w)</th>
<th>Release liner</th>
<th>Backing membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.0% w/w</td>
<td>Duro-Tak 87-4098</td>
<td>–</td>
<td>Scotchpak® 1022</td>
<td>CoTran™ 9720</td>
</tr>
<tr>
<td>F2</td>
<td>7.5% w/w</td>
<td>Duro-Tak 87-2074</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F3</td>
<td>10% w/w</td>
<td>Duro-Tak 87-900A</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F4</td>
<td>6.5% w/w</td>
<td>Duro-Tak 87-2287</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F5</td>
<td>12% w/w</td>
<td>Duro-Tak 87-9301</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F6</td>
<td>12% w/w</td>
<td>Duro-Tak 87-9301</td>
<td>Oleic acid</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F7</td>
<td></td>
<td>–</td>
<td>Propylene glycol</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F8</td>
<td></td>
<td>–</td>
<td>Diethylene glycol monoethyl ether</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F9</td>
<td></td>
<td>–</td>
<td>Tween 80</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
enhancers are added (required quantity) to the adhesive along with drug in the beginning and followed similar procedure as above.

The initial process in preparing an adhesive transdermal patch is to find an appropriate pressure sensitive adhesive. Five adhesives (Duro-Tak 87–4098, Duro-Tak 87–2074, Duro-Tak 87–900A, Duro-Tak 87–9301, Duro-Tak 87–2287) were selected to prepare transdermal systems (F1–F5), then the palonosetron solubility in these adhesives were measured. In addition, the effect of various skin permeation agents (propylene glycol, diethylene glycol monoethyl ether, Tween 80 and oleic acid) on the transdermal permeation of palonosetron was assessed (F6–F9).

Drug content

The quantification of palonosetron in prepared patches was determined by precisely weighing a small piece of drug in adhesive patch and placing it in the water. The patch along with the water was sonicated for 1 h and further centrifuged (10,000 rpm for 5 min). The amount of drug in the patch was estimated after filtering water through a syringe filter (0.2 μm, Millipore Corporation, Bedford, MA, USA) and analyzed by HPLC.

Skin preparation

The skin membrane was prepared from Wistar rats after a cautious epilation of skin and subsequent removal of subdermal tissue, while all other layers (stratum corneum, epidermis, and dermis) remain intact (IAEC/SSP/16/PR-124). The prepared samples were washed carefully with isotonic saline solution and preserved at −20 °C in aluminum foil. Prior to the permeation studies, skin membrane was thawed and membrane resistance was measured to ensure the resistance of >20 kΩ cm², which was proved to be suitable in our earlier studies (Nair et al., 2016).

In vitro permeation studies

The transport of palonosetron through the skin membrane was assessed for 12 h using vertical Franz diffusion cell. The skin membrane with particular integrity was fixed in the middle of upper and low chambers of the diffusion cell, such that the dermis side faces receiver fluid. The receiver compartment was filled with phosphate-buffered saline (PBS, pH 7.4) and the area available for drug permeation was 0.64 cm². Similarly, the upper chamber was filled with PBS (1 ml) and equilibrates for 1 h (Anroop et al., 2009). Following equilibration, the fluids in the donor and receptor chambers were taken out and then receiver chamber was filled with new PBS media. In the upper chamber, a small circular patch (punched out with biopsy punch – 0.6 cm²) was positioned by applying slight pressure with finger to adhere the system to the skin. The receptor media was stirred and the temperature was maintained at 37 ± 0.5 °C. Experiment was performed for 12 h and samples were collected at predetermined time intervals (1, 2, 4, 6, 8 and 12 h) and replaced with fresh media to compensate the loss of sample withdrawn.

Drug release studies

Release of the drug from fabricated patches was evaluated using a Franz diffusion cell (Logan Instruments Ltd., Somerset, NJ). A cellulose dialysis membrane having molecular weight cut off 12,000 (2.4 nm porosity; Himedia Labs Ltd., Mumbai, India) was soaked in water for 24 h and clamped between two chambers of the Franz cell. The effective surface area for all the experiments was 0.64 cm². The receiver chamber was filled with PBS (pH 7.4). Further, ~1 ml of buffer was placed in the donor chamber and the membrane was equilibrated for 1 h by continuously stirring the receiver chamber at 600 rpm at 37 ± 0.5 °C. Later, both of the fluids were discarded and a patch area of 0.6 cm² was fixed on the membrane and occluded with paraffin to prevent evaporation of solvent. The receptor compartment was filled with fresh buffer solution (5 ml). Release experiment was carried for a span of 6 h. Samples were withdrawn at regular intervals, filtered (0.2 μm, Millex syringe filter) and analyzed by the HPLC.

Data analysis

The total amount of drug permeated per unit area at every time point was plotted against the time (for every trial) and the slope of the straight line is determined as flux. This flux values were further divided with the donor drug level to estimate the permeability coefficient (Anroop et al., 2005). Enhancement factor was calculated as the ratio of flux value was observed with patches contain enhancers to flux values of control. All values are mean ± SD (n = 6) unless stated. P < 0.05 was considered as the level of significance and data analysis was performed using GraphPad Prism (USA).

Results and discussion

Drug in adhesive systems are widely preferred transdermal delivery of pharmaceutical actives. The main constituents in such system are adhesive, backing membrane and a release liner. The prospective of chemical skin permeation enhancers in improving the transdermal transport of pharmaceutical actives is widely demonstrated. The optimization of transdermal system is usually carried out for appropriate adhesive, quantity of drug incorporation, as well as the skin permeation agents. Therefore, the present investigation assessed the influence of all the three factors while optimizing transdermal patches of palonosetron. In the first stage we developed five transdermal patches (F1–F5) using different pressure sensitive adhesives with maximum possible drug being incorporated. Then the influence of various chemical permeation enhancers was screened. Preliminary study was initiated to assess the feasibility of fabricating transdermal patch of palonosetron using various pressure sensitive adhesives (Duro-Taks). Five pressure sensitive adhesives (Duro-Tak 87–4098, Duro-Tak 87–2074, Duro-Tak 87–900A, Duro-Tak 87–9301 and Duro-Tak 87–2287) were selected based on the literature to formulate patches (F1–F5) and the drug solubility in these adhesives were determined.

It is well known that the maximum thermodynamic activity can be achieved when the drug concentration in the matrix is at its high. Hence the maximum solubility of palonosetron in each pressure sensitive adhesives was determined by adding excess quantity of drug (1–20% w/w). The components were mixed and the patches were prepared by evaporating solvent at room temperature. Then the patches were frequently checked for crystallization using optical microscope. The saturation solubility of drug in adhesive patch was determined when there is no crystallization in patches during storage of three months. It was noticed that the saturation solubility of palonosetron changes with the pressure sensitive adhesives and was 12% (w/w), 10% (w/w), 7.5% (w/w), 7% (w/w) and 6.5% (w/w) of drug with Duro-Tak 87–9301, Duro-Tak 87–900A, Duro-Tak 87–2074, Duro-Tak 87–4098 and Duro-Tak 87–2287, respectively. However, a slightly higher concentration above the saturation solubility of the drug (observed in this study) with these adhesives produced crystallization within a week or before. The observed difference in the solubility of palonosetron with selected adhesives could be attributed to their chemical composition.

The formulation constituents of the prepared patches are summarized in Table 1. As seen from Table 1 that the amount of
drug incorporated in patches (F1–F5) accounts to their saturation solubility. It is also noticed that all the formulations exhibited ideal organoleptic and physicochemical characteristics. Further, the drug content in prepared films are found to be high and comparable (92–96%), which indicates consistency of drug in the films and suggest that the content uniformity is not influenced by the pressure sensitive adhesives used. The evaluation of the prepared patches was carried out by assessing the permeation of drug across the rat skin membrane. The profiles of palonosetron permeated from various patches (F1–F5) are depicted in Fig. 1. It is evident from Fig. 1 that the drug permeation profiles of palonosetron from various patches are distinct, although the trend resembles typical transdermal permeation. As anticipated, the palonosetron permeation rises with increase in the donor drug concentration due to the differences in drug solubility. In addition, transdermal permeation might have influenced by the rate of drug release from the patch. The flux values decreases as; Duro-Tak 87-9301 > Duro-Tak 87-900A > Duro-Tak 87-2074 > Duro-Tak 87-4098 > Duro-Tak 87-2287. This observation is in agreement with several earlier studies wherein the higher drug concentration leads to greater drug permeation (Nair et al., 2009; Paudel et al., 2010). It is also noticed that the calculated flux value of patch F5 was significantly higher ($P < 0.01$) than other patches (F1–F4) (Table 2). Further, a short lag time of 2 h was observed in patches prepared using Duro-Tak 87-4098, Duro-Tak 87-2074 and Duro-Tak 87-2287. Calculated permeability coefficient values of different patches (F1–F5) are summarized in Table 2. From the above observations, it is likely that the composition of the pressure sensitive adhesives influenced the palonosetron transdermal flux. Based on permeation data, Duro-Tak 87-9301 was selected for the next phase of the study.

The data observed in the first phase of the study suggests that the transdermal permeation of palonosetron is definitely low to deliver therapeutically relevant concentration of drug. In this framework, it is recognized that the incorporation of certain chemical skin permeation agents, which disturbs the skin membranes and reduce the hindrance, are capable to improve the drug transport across the skin (Nair et al., 2011). Moreover, there are several studies which demonstrate the role of chemical skin permeation enhancers when incorporated along with drug in adhesive transdermal systems (Liu and Fang, 2015; Nair et al., 2012; Ravula et al., 2016). Hence, in this phase of the study, the selected chemical agents were included in the transdermal patch F5 (fabricated using Duro-Tak 87-9301 adhesive, contain 12% (w/w) of palonosetron) to enhance the percutaneous permeation of palonosetron. The concentration of enhancers (5% w/w) was selected based on the literature wherein it was reported that these agents are safe for human use (Lane, 2013). Fig. 2 compares the permeation profile of palonosetron in presence of different chemical agents aimed for improving the permeation. It is apparent from Fig. 2 that the amount of palonosetron permeated through the rat skin from patches with various permeation enhancers is significantly high, even though the rate of drug permeation is dissimilar. Certainly, the palonosetron permeation was significantly improved with the inclusion of chemical enhancers. Among the permeation enhancers tested, the enhancement ratio decreased as; propylene glycol > diethylene glycol monoethyl ether > Tween 80 > oleic acid, compared to the control. Greater drug permeation was noticed in patches contain propylene glycol (53.12 ± 5.62 μg/cm²/h; $P < 0.0001$), which accounts four times more than the amount recorded with patch F5 (without any enhancers). Interestingly, the flux values of palonosetron observed in the current study is significantly higher (~2.6 folds) than the value reported in the literature (Liu et al., 2016). This discrepancy is most likely due to the variation in the skin membrane (rat versus rabbit) as well as the drug concentrations (12% w/w versus 8% w/w) in the prepared patches. The total quantity of palonosetron transported in 12 h was 637.02 ± 47.98 μg/cm², 457.89 ± 47.04 μg/cm², 405.72 ± 37.72 μg/cm² and 290.82 ± 23.03 μg/cm² when treated with propylene glycol, diethylene glycol monoethyl ether, Tween 80 and oleic acid, respectively. The higher permeability coefficient of palonosetron observed ($K_p = \sim 4.42 \times 10^{-3}$) when treated with propylene glycol is the highest value observed among various treatments assessed in the current study, under similar experimental conditions. The improvement in flux values by these enhancers could be linked to their diverse mechanisms as reported earlier (Lane, 2013; Nair, 2016; Nair et al., 2010), though it was not examined during the current investigation. Interestingly, propylene glycol is also reported to inhibit the crystal growth of palonosetron and is widely used in various pharmaceutical formulations (Kumria et al., 2016; US Patent, 2009). However, the measured enhancement in

![Fig. 1. Comparison of the amount of palonosetron permeated at different time intervals across the rat skin membrane from patches prepared with different pressure sensitive adhesives. All values are mean ± SD (n = 6).](image-url)
palonosetron flux values with other chemical agents like diethylene glycol monoethyl ether, Tween 80 and oleic acid were ~2.54, ~2.25 and ~1.61 folds, respectively in comparison to patches without enhancer.

The drug permeation into and through the biological membrane is influenced by various factors including the rate and extend of release of actives from the prepared systems. However, the release of drug from the matrix is guided by the drug properties as well as polymer characteristics, primarily the solubility of drug in the matrix (Nair et al., 2007). Thus in the final phase of the study, drug release studies were carried out for a period of 6 h using optimized formulation and the observed percentage drug release is

<table>
<thead>
<tr>
<th>Code No.</th>
<th>Flux (µg/cm²/h) (± SD)</th>
<th>Permeability coefficient (cm/h) (Kp × 10⁻⁴)</th>
<th>Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>10.23 ± 2.51</td>
<td>1.46 ± 0.24</td>
<td>–</td>
</tr>
<tr>
<td>F2</td>
<td>11.07 ± 2.18</td>
<td>1.47 ± 0.35</td>
<td>–</td>
</tr>
<tr>
<td>F3</td>
<td>13.02 ± 3.02</td>
<td>1.30 ± 0.23</td>
<td>–</td>
</tr>
<tr>
<td>F4</td>
<td>8.31 ± 1.95</td>
<td>1.27 ± 0.37</td>
<td>–</td>
</tr>
<tr>
<td>F5</td>
<td>15.01 ± 3.12</td>
<td>1.25 ± 0.28</td>
<td>–</td>
</tr>
<tr>
<td>F6</td>
<td>24.23 ± 4.82</td>
<td>2.02 ± 0.19</td>
<td>1.61</td>
</tr>
<tr>
<td>F7</td>
<td>53.12 ± 5.62</td>
<td>4.42 ± 0.38</td>
<td>3.56</td>
</tr>
<tr>
<td>F8</td>
<td>38.15 ± 7.64</td>
<td>3.18 ± 0.45</td>
<td>2.54</td>
</tr>
<tr>
<td>F9</td>
<td>33.81 ± 3.63</td>
<td>2.82 ± 0.17</td>
<td>2.25</td>
</tr>
</tbody>
</table>

Fig. 2. Comparison of the amount of palonosetron permeated at different time intervals across the rat skin membrane from patches with different permeation enhancers. All values are mean ± SD (n = 6).

Fig. 3. Comparison of the percentage of palonosetron released at different time intervals across the cellulose dialysis membrane (2.4 nm porosity) from patches with different permeation enhancers. All values are mean ± SD (n = 6).
depicted in Fig. 3. The duration of the study was fixed for 6 h as the drug release was almost complete during this period. It is apparent from Fig. 3 that release profiles of palonosetron from the patches with different enhancers (F6–F9) and control (F5) are slightly different. The rate of release was relatively higher with patch containing propylene glycol (F7) which was followed by diethylene glycol monoethyl ether (F8). From Fig. 3 it is also evident that the release was rapid in the initial period (2 h; F7 ~90%, F8 ~69%, F9 ~58% and F6 ~51%), suggesting a biphasic release pattern. In addition, the release of drug from all patches exhibited first order kinetics when assessed with different mathematical models (zero-order, first-order, Hixson–Crowell, Higuchi, and Korsmeyer–Peppas) (Nair et al., 2007). The rapid release observed from the prepared patches substantiated our choice of formulation composition for palonosetron to provide effective delivery. Moreover, this prompt release could be helpful in providing higher drug transport in the skin surface which in turn can lead to rapid transport of drug molecules. In case of formulations F7–F9, followed by the rapid release, there was a slow phase and the drug release was almost complete in 6 h. The complete release of drugs seen in the current study (varies between 4 and 6 h) could be beneficial in prolonging the transdermal therapy, considering the patch is in close contact with the skin surface for a long application period.

Comparing the release data with the permeation study, one can easily corroborate that the difference in flux values observed is probably due to the high drug release rate from the patch contain propylene glycol. Therefore, it is presumed that the higher release of drug may be caused by propylene glycol owing to its potential to improve the solubility of palonosetron inside the patch system.

Conclusion

The present study is aimed to improve the transdermal permeation of palonosetron using different chemical permeation enhancers. Preliminary studies indicated that the drug solubility varied with pressure sensitive adhesives tested and the highest enhancers. Preliminary studies indicated that the drug solubility is probably due to the high drug release rate from the patch/C24 F9/C24 with different enhancers (F6 from Fig. 3 that release prodrug release was almost complete during this period. It is apparent that the difference in

CD006272.145.


http://dx.doi.org/10.1002/14651858.CD006272.pub3 Art. No.: CD006272.


