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Evaluation of Pentravan®, Pentravan® Plus, Phytobase®, Lipovan® and Pluronic Lecithin Organogel for the transdermal administration of antiemetic drugs to treat chemotherapy-induced nausea and vomiting at the hospital

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ABSTRACT

The objective of this study was to evaluate five commercial ready-to-use transdermal vehicles (Phytobase®, Lipovan®, Pentravan®, Pentravan® Plus and Pluronic Lecithin Organogel (PLO)), for the compounding of three antiemetic drugs (ondansetron, dexamethasone and aprepitant) and their administration in combination to treat chemotherapy-induced nausea and vomiting (CINV) at the hospital. Drugs were individually formulated in these vehicles and in mixture in Pentravan® Plus using different penetration enhancers. Quality control of the forms has demonstrated that formulation process was mastered and convenient for the hospital (time required: 20 min). Diffusion experiments through synthetic membranes and pig ear epidermis performed using Franz-type diffusion cells, have shown that the release and permeation process were greater for ondansetron than for dexamethasone and aprepitant, with a release step not limiting. As permeation of aprepitant was too low, it was discarded of the study. When ondansetron and dexamethasone were compounded in combination in Pentravan® Plus, the most efficient vehicle, a permeation decrease was observed. Finally, the use of tween 20 instead of EtOH as chemical enhancer has led to 2-fold factor increase in the flux of dexamethasone, resulting in fluxes convenient for transdermal administration of ondansetron to a child, but insufficient for an adult and for dexamethasone.

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) are common adverse effects associated with cancer treatment. Several medical society guidelines recommend the simultaneous administration of ondansetron, dexamethasone and aprepitant (Fig. 1) as they targeted different therapeutic receptors and synergistic effect has been observed in the treatment of CINV (Schwartz et al., 2012; Durand et al., 2009; Roila et al., 2010; Ettinger et al., 2012). Despite oral route is recommended for the administration of this antiemetic treatment, it is clearly not convenient, especially for populations like the elderlies or new-borns. Besides, ondansetron suffers from low oral bioavailability about 60% due to its extensive first-pass metabolism and low biological half life (3–5 h) depending on the subjects (Simpson and Hicks, 1996). The other alternative, *i.e.* the intra-venous route, results in an important discomfort for the patient, especially for children. To improve the patient quality of life, the development of a transdermal formulation containing these three antiemetic drugs is expected by clinicians.

However, the penetration of drugs across the skin and their percutaneous delivery are limited by the barrier function of the organized structure of *stratum corneum* (SC). It is admitted that neutral drugs with a molecular weight lower than 500 Da and a logP (octanol/water) value between 1 and 3 are suitable for

Abbreviations: Apt, aprepitant; Dex, dexamethasone; MAPE, mean absolute percentage error; Ond, ondansetron; Pent, Pentravan®; Pent+, Pentravan® Plus; Phyt, Phytobase®; Lipo, Lipovan®; PLO, Pluronic Lecithin Organogel.

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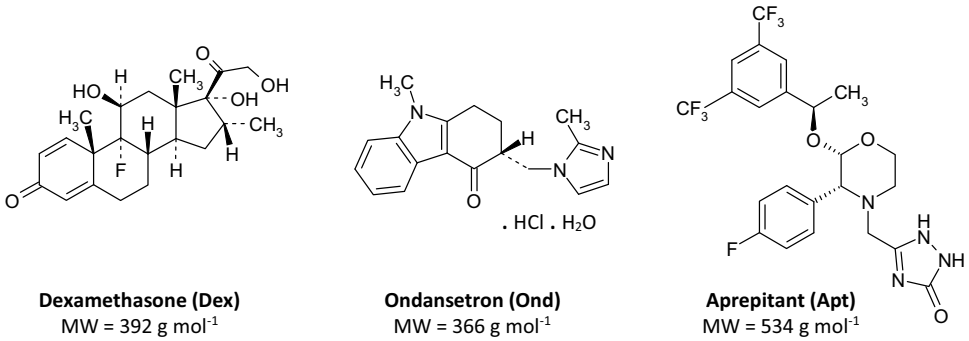

Fig. 1. Chemical structures, molecular weight (MW), pKa and log P values of antiemetics investigated.

permeation across the SC to reach the systemic circulation. However, some studies have shown that molecules that do not match all these criteria are able to cross this barrier (Idrees et al., 2014; Gannu et al., 2010; Jung et al., 2015). Indeed, some hydrophobic compounds, cationic at the SC pH, are commercialized as transdermal patches: Durogesic® (fentanyl: logP = 4.05); Kentara® (oxybutinine: logP = 4.02); Neupro® (rotigotine: logP = 4.58) and Butrans® (buprenorphine: logP = 4.98).

To date, there is only one commercial drug transdermal delivery based on granisetron for the therapeutic management of CINV (Sancuso®) (Howell et al., 2009). However, the physico-chemical properties of setrons are in favor of their percutaneous administration. Therefore, several studies report the development of microemulsions (Malakar et al., 2012; Al Abood et al., 2013), patchs (Krishnaiah et al., 2009; Swain et al., 2010; Rajabalaya et al., 2012), hydrogels (Obata et al., 2010; Patel et al., 2015) and a semi-solid preparation (Gwak et al., 2004) for the transdermal delivery of ondansetron using passive diffusion. Likewise, dexamethasone has been incoporated in a patch (Mukherjee et al., 2005), an hydrogel (Lopez et al., 2000), a microemulsion (Chandra et al., 2009) and a pluronic lecithin organogel (Willis-Goulet et al., 2003) for its transdermal delivery. Concerning aprepitant, no paper dealing with transdermal formulation has yet been reported.

Results of permeation were very promising, especially for ondansetron. Indeed, the bioavailability of ondansetron determined from microemulsion gel resulted in a 6-fold increase in comparison to oral conventional syrup and 10 times with reference to the conventional gel (Al Abood et al., 2013). Likewise, microemulsion-based hydrogel permits the transdermal delivery of dexamethasone with a high permeability constant (Chandra et al., 2009).

However, all these transdermal delivery systems require the development of complex vehicles able to solubilize, to release and to permeate the drug through the skin while maintaining skin hydration and limiting its irritation. Enhancers are generally added to the formulation to promote the transdermal drug delivery. While isopropyl alcohol was particularly suitable to improve the transdermal delivery of ondansetron formulated in hydrogel (Obata et al., 2010), the addition of hydroxypropyl-β-cyclodextrin to an hydrophilic vehicle is necessary to permeate dexamethasone through the skin (Lopez et al., 2000). Gwak et al. have shown, after numerous assays, the synergistic effect of diethylene glycol monoethyl ether combined with ethanol for the transcutaneous permeation of ondansetron (Gwak et al., 2004). Neutral surfactants are effective permeation enhancers both for passive diffusion as well as for formulation subjected to iontophoresis, resulting in a cumulative amount of ondansetron of 93 and 336 $\mu g\,cm^{-2}$ after 24 h, respectively (Silva et al., 2012).

As shown previously, the development of new transdermal formulation is tedious and time-consuming because the choice of enhancers, their content, the drug loading and the matrix type determine the efficiency of the formulation to permeate the drug through the skin. The aim of this work was to develop a transdermal formulation containing aprepitant, ondansetron and dexamethasone for hospital use. Taking into account the hospital constraints, this compounding has to be easy to make by the pharmacist, *i.e.* using simple formulation process, low costs and easily available matrixes. Last few years, organogels and hydrophilic liposomal or phytosomal creams have emerged on the transdermic market. Among them five vehicles (Phytobase®, Lipovan®, Pentravan®, Pentravan® Plus and Pluronic Lecithin Organogel (PLO)) have been highlighted by the Fagron's company as potential transdermal drug delivery systems. These five vehicles are colloidal systems with a hydrophilic external phase. PLO, Pentravan® and Pentravan® plus are composed of the same phase (lipoil®), which is constituted of synthetic lecithin and isopropyl palmitate. This mixture is associated either to a F127-pluronic gel, to constitute the PLO that contains cylindrical micelles entrapped in the three dimension network of the organogel, or to an aqueous phase (water) to compose the pentravan® and the Pentravan® plus that are liposomal cream. While Pentravan® and Pentravan® plus are ready to use transdermal vehicles, the PLO has to be prepared extemporaneously by mixing the lipoil to the F127-pluronic gel. Regarding Lipovan®, this vehicle is enriched in liposome and in phosphatidylcholine compared to the other vehicles. The composition of Phytobase® is meaningful different from the liposomal vehicles because of the presence of phytosomes.

Only few works have evaluated the efficiency of these vehicles for transdermal applications. Polonini et al. have shown the ability of pentravan® to release steroid hormones (Polonini et al., 2014a, 2014b). Testosterone and ketoprofen have been individually formulated in Pentravan® and PLO: the superiority of Pentravan® with respect to PLO has been demonstrated for the permeation of these drugs through the skin (Lehman and Raney, 2012). Only one study describes the use of Phytobase® for the release study of green tea (Campos Alves et al., 2014). To our knowledge, no paper deals with the interest of Lipovan® and pentravan® plus for transdermal drug delivery.

The goal of this study was to identify a vehicle among Fagron's products cited previously, to compound simultaneously aprepitant, ondansetron and dexamethasone, able to release them easily and to drive them through the skin. Hence, these five vehicles were evaluated for the transdermal delivery of these drugs. In a first