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Controlled transdermal iontophoresis for poly-pharmacotherapy: Simultaneous delivery of granisetron, metoclopramide and dexamethasone sodium phosphate *in vitro* and *in vivo*

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ABSTRACT

Iontophoresis has been used to deliver small molecules, peptides and proteins into and across the skin. In principle, it provides a controlled, non-invasive method for poly-pharmacotherapy since it is possible to formulate and to deliver multiple therapeutic agents simultaneously from the anodal and cathodal compartments. The objective of this proof-of-principle study was to investigate the simultaneous anodal iontophoretic delivery of granisetron (GST) and metoclopramide (MCL) and cathodal iontophoresis of dexamethasone sodium phosphate (DEX-P). In addition to validating the hypothesis, these are medications that are routinely used in combination to treat chemotherapy-induced emesis. Two preliminary *in vitro* studies using porcine skin were performed: Study 1 — effect of formulation composition on anodal co-iontophoresis of GST and MCL and Study 2 — combined anodal iontophoresis of GST (10 mM) and MCL (110 mM) and cathodal iontophoresis of DEX-P (40 mM). The results from Study 1 demonstrated the dependence of GST/MCL transport on the respective drug concentrations when co-iontophoresed at 0.3 mA·cm^{-2}. Although they possess similar physicochemical properties, MCL seemed to be a more efficient charge carrier ($J_{MCL} = 0.0591 * C_{MCL}$ *vs* $J_{GST} = 0.0414 * C_{GST}$). In Study 2, MCL permeation was markedly superior to that of GST (2324.83 ± 307.85 and 209.83 ± 24.84 μg·cm^{-2}, respectively); this was consistent with the difference in their relative concentrations; DEX-P permeation was 336.94 ± 71.91 μg·cm^{-2}. The *in vivo* studies in Wistar rats (10 mM GST, 110 mM MCL and 40 mM DEX-P (0.5 mA·cm^{-2} for 5 h with Ag/AgCl electrodes and salt bridges) demonstrated that significant drug levels were achieved rapidly for each drug. This was most noticeable for dexamethasone (DEX) where relatively constant plasma levels were obtained from the 1 to 5 h time-points; DEX-P was not detected in the plasma since it was completely hydrolyzed to the active metabolite. The calculated input rates *in vivo* (k_{01}) for GST, MCL and DEX were 0.45 ± 0.05, 3.29 ± 0.48 and 1.97 ± 0.38 μg·cm^{-2}·min^{-1}, respectively. The study confirmed that iontophoresis provided a controlled method for the simultaneous administration of multiple therapeutic agents and that it could be of use for poly-pharmacotherapy in general and more specifically that it was able to deliver different drugs used in the treatment of chemotherapy-induced emesis.

1. Introduction

One of the principal advantages afforded by iontophoresis is its ability to control drug delivery kinetics (Kalia et al., 2004). To-date, it has shown itself as a technique that is ideally suited for the delivery of polar and ionized, hydrosoluble species, including small molecules (*e.g.* Cázares-Delgadillo et al., 2010a, 2010b, 2010c), peptides (*e.g.* Schuetz et al., 2005a, 2005b) and proteins (*e.g.* Cázares-Delgadillo et al., 2007; Dubey and Kalia, 2010; Dubey et al., 2011) into and across the skin. These studies routinely involve the iontophoretic delivery of a single ionized species, although a neutral molecule may be included as a marker for electroosmotic transport (Padula et al., 2005; Schuetz et al., 2005a). Given that iontophoretic transport depends on the directed movement of ions, it was hypothesized that it should be possible to deliver multiple ions simultaneously. For example, if two or more positively charged drugs were present in the anodal compartment, then under the influence of an applied potential difference, they would both electromigrate away from the anode and into the skin. They would compete to carry current and the fraction of the total iontophoretic current carried by each ion would be reflected by the transport number. This co-iontophoresis could be of significant interest in treating diseases and conditions where there are different therapeutic targets.

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With this in mind, it was thought to be of interest to see whether the technique could be used for the simultaneous delivery of different therapeutic agents as required in the treatment of delayed chemotherapy-induced nausea and vomiting (CINV).

Treatment of CINV represents a considerable challenge due to its complex etiology. The emetic center consists of a nucleus of cells located in the medulla and it controls the complex series of physiological events required for emesis (Davis and Walsh, 2000). It receives signals from the chemoreceptor trigger zone (CTZ), the cortex, the vestibular apparatus and the gastrointestinal (GI) tract. Vomiting occurs when the emetic center sends impulses to the salivation center, abdominal muscles, respiratory center and cranial nerves. The CTZ and GI tract are the principal sources of afferent input to the emetic center in acute-chemotherapy induced vomiting. On the other hand, the cerebral cortex may stimulate the emetic center during delayed (or anticipatory) vomiting. The CTZ, which lies outside the blood–brain barrier, and so responds to stimuli in the blood or in the cerebrospinal fluid, contains receptors for dopamine (D_2), serotonin (5-HT_3), acetylcholine (nicotinic ACHr) and opioids, which are all emetogenic.

Although the first-generation 5-HT_3 receptor antagonists have shown substantial efficacy, almost 50% of patients continue to suffer both acute and delayed emesis despite prophylactic treatment with these agents, (Hesketh, 2000; Hickok et al., 2003; Grunberg et al., 2004). A number of clinical trials have demonstrated the superiority and safety profile of combined therapy with dexamethasone and a 5-HT_3 antagonist (IGAR, 1999; The Italian Group for Antiemetic Research, 2000; Saito et al., 2009; Simpson et al., 2000) over monotherapy with a 5-HT_3 antagonist alone (Leslie and Gan, 2006). American Society of Clinical Oncology (ASCO) guidelines have also recommended the combination of metoclopramide (D_2 receptor antagonist) and dexamethasone as the antiemetic regimen of choice for the prevention of cisplatin-induced delayed emesis (Kris et al., 2006). In light of the multiplicity of receptors that feed information to the emetic center, it is not surprising that there are a number of different therapeutic targets.

At present, these poly-pharmacotherapies are administered either orally or *via* the intravenous route. Obviously, the latter requires trained personnel and rigorous device care and in particular is not adapted to the treatment of delayed emesis which occurs more than 24 h after chemotherapy. Oral administration is clearly simpler but not ideal for patients with emesis and systemic bioavailability in these patients can be severely reduced. We have previously investigated the iontophoretic delivery of three antiemetics (Fig. 1): granisetron hydrochloride (GST) (Cázares-Delgadillo et al., 2010a), metoclopramide hydrochloride (MCL) (Cázares-Delgadillo et al., 2010b) and dexamethasone disodium phosphate (DEX-P) (Cázares-Delgadillo et al., 2010c) separately *in vitro* and *in vivo*. Transdermal delivery achieved using iontophoresis was higher than that observed with other transdermal methodologies. Given the pharmacokinetics of the three drugs in humans (Sweetman, 2003), it was estimated that transdermal iontophoresis would be able to deliver therapeutic amounts of each drug using reasonably sized patches.

The objective of this work was to investigate the co-iontophoretic delivery of GST, MCL and DEX-P, *i.e.* simultaneous transdermal administration of the three antiemetics and at the same time to demonstrate more generally that iontophoresis could be used as a means to provide controlled transdermal poly-pharmacotherapy. Although passive transdermal patches that contain two different drugs, *e.g.*, estradiol and norethindrone acetate (CombiPatch®) are available, there is no competition between the molecules to be delivered. In contrast, during iontophoresis, two charged molecules to be delivered from the same electrode compartment will compete to carry the ionic current (Kalia et al., 2004).

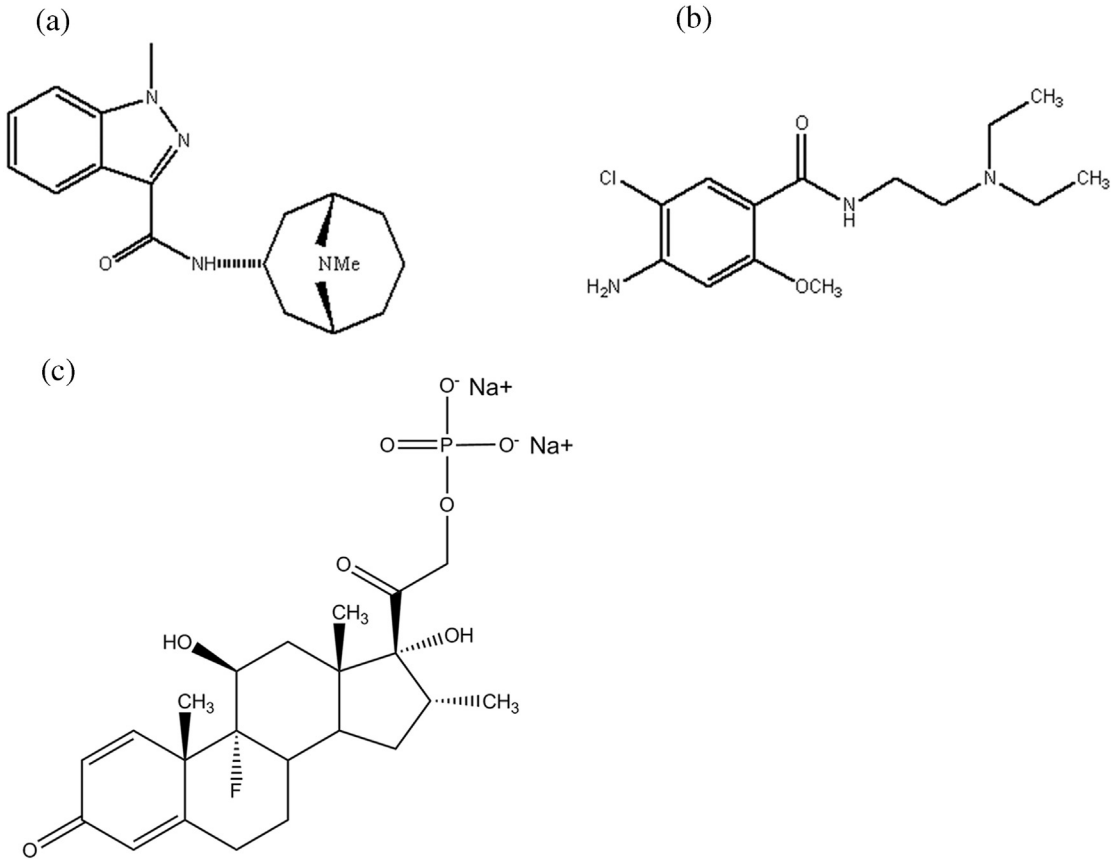

Fig. 1. Chemical structure of (a) granisetron (GST), (b) metoclopramide (MCL) and (c) dexamethasone sodium phosphate (DEX-P).