

Challenges and potentials of developing domperidone into the transdermal delivery

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Submitted: 17-04-2022

Revised: 11-05-2022

Accepted: 27-05-2022

ABSTRACT

Oral domperidone is widely prescribed in nausea treatment. The low bioavailability of oral domperidone makes a patient take the drug more frequently, even though some patients have difficulty swallowing the drug when suffering nausea. Recently, the drug formulation development for transdermal delivery systems is expected to increase in the future. Practical and increase patient comfortable is the notable advantages of using transdermal dosage form. Domperidone is currently being studied into various pharmaceutical dosage forms with the transdermal route. This present article provides summaries of the challenges also the current formulation development of domperidone which shows the potential of domperidone in transdermal delivery.

Keywords: domperidone; drug delivery; formulation; transdermal

INTRODUCTION

Domperidone, a dopamine antagonist, is one of the drugs widely prescribed to treat nausea and vomiting. Domperidone had been reported could ameliorate functional dyspepsia symptoms and infant nausea and vomiting (Wang *et al.*, 2011). Domperidone is a compound that is poorly soluble in water (1 mg/mL) and its oral bioavailability is only in the range of 15-17%. This low oral bioavailability is due to its low solubility, extensive first-pass effect, and the efflux by transporters located in the small intestine (Athukuri and Neerati, 2017; Zayed *et al.*, 2020). Domperidone is an active substrate of CYP3A4 and the active efflux transporter P-glycoprotein (P-gp), which causes extensive metabolism (Templeton *et al.*, 2016).

Formulation scientists frequently consider transdermal delivery to avoid the extensive first-pass effect, even though some challenges must be evaluated. Currently, domperidone is available in oral dosage forms such as tablets and suppository forms. Patients who suffer nausea and vomiting may have difficulty swallowing if given the drug in oral form. These dosage forms are difficult to administer to patients with acute nausea and diarrhea (Kashiwagura *et al.*, 2021). Thus, those

explanations support that the transdermal dosage form is an alternative route that can help overcome the weakness of domperidone in oral administration.

Skin is the largest organ of the human body that can be the primary target for delivering drugs into the body (Haque and Talukder, 2018). In the transdermal delivery system, the drug penetrates through the skin and enters the systemic circulation avoiding the first-pass effect. Compared with drug given orally and parenterally, transdermal delivery gives convenience and reduces the frequency of drug administration (Kalluri and Banga, 2011). This route delivers the drugs less or non-invasively, ease on application, and comfort patients, especially pediatric patients (Delgado-Charro and Guy, 2014; Ramadan *et al.*, 2021). The transdermal delivery system is also interesting to be chosen as it can minimize and avoid the limitations of oral and parenteral drug delivery such as "peak" and "valley" phenomena which indicate fluctuations in plasma drug levels and do not provide a sustained effect (Mudshinge *et al.*, 2011). The transdermal route maintains drug levels for a long time. The drug profile is steady-state, reduces the incidence of side effects related to peak drug levels, and

ensures that the drug is above the minimum therapeutic concentration. The development of transdermal delivery is expected to increase in the future and lead to modern techniques to overcome problems related to skin barrier properties. This delivery system is sure to be clinically highly needed in the next few years (Alexander *et al.*, 2012).

Challenges in Transdermal Delivery

The main challenge in drug delivery into the skin is the stratum corneum, the outermost layer of the epidermis, which serves as the skin's main barrier. Researchers have developed several techniques to overcome the barrier properties of the skin, which include both physical and chemical techniques. The most common and easy technique is to use special excipients into the formulation called chemical penetration enhancers which result in either binding to the drug molecules themselves or making changes to the structure of the stratum corneum, thus allowing the drug molecules to penetrate the stratum corneum (Haque and Talukder, 2018).

Due to the skin's natural protective properties against the foreign materials, only a small amount of drug can be delivered systemically with appropriate rate achieves therapeutic range concentrations. The physicochemical properties of the drug, which are ideal for the delivery system through the skin are moderate lipophilicity and low molecular weight (Paudel *et al.*, 2010). In general, compounds that are ideal candidates for transdermal delivery are compounds that have a low dose that tends to be below 20 mg/day, a half-life of fewer than 10 hours, a low molecular weight that is below 500 Da, and a partition coefficient between -1 and 3 (Akhtar *et al.*, 2020). Skin irritation also becomes a challenge regarding transdermal formulations. Based on some reports, it is predicted that the pKa value of the drugs between 5 and 8 provides minimal skin irritation (Paudel *et al.*, 2010).

Domperidone has a low dose (10 mg), weak base (pKa=7,89), low molecular weight (BM= 425,9), extensive first-pass effect, and lipophilicity value of the drug is log P 3,90. This compound is commonly used for long-term treatment and is also dosed repeatedly (Palem *et al.*, 2011; Patil *et al.*, 2016). These parameters make domperidone suitable as a drug candidate to be developed into transdermal formulations.

Currently Formula Development of Domperidone in Transdermal Drug Delivery System

Transdermal delivery of domperidone is an attractive option for future research. Several studies were carried out to develop domperidone formulations into transdermal dosage forms (Table I). The dosage forms studied included patches, films, niosomes, nanoemulsions, and creams.

In table I, several studies have used chemical enhancers in the formulation of domperidone patch preparations. The use of eucalyptus oil, d-limonene, oleic acid, isopropyl alcohol, and menthol affects increasing drug absorption in the skin. These compounds can reduce skin integrity, change the structure of the stratum corneum, and reversibly disrupt the intercellular lipids of the stratum corneum to increase the diffusivity of the drug (Herman and Herman, 2015; Vasudevan and Rajan, 2012).

One parameter to see the drug's ability to penetrate the membrane/skin is the flux value. Flux is the amount of drug across the membrane per area per unit time (Akram *et al.*, 2018).

In the study of Akhter *et al.* (2008), they developed domperidone nanoemulsion for transdermal delivery. Nanoemulsion is a nano sized-emulsion in which two immiscible liquids are mixed to form a single phase with the help of an emulsifying agent (surfactant and co-surfactant). It is thermodynamically stable, unlike the emulsion. The droplet size of nanoemulsion is approximately in the range of 20–200 nm (Jaiswal *et al.*, 2015). Based on the research, the results showed that the developed nanoemulsion had a flux value was $169,32 \pm 8,33 \mu\text{g/hr/cm}^2$. In an *in vivo* study, the maximum domperidone concentration in plasma of oral suspension was $45,0 \pm 3,3 \text{ ng/ml}$ at $0,5 \pm 0,1$ hour; meanwhile transdermal nanoemulsion was $30,7 \pm 2,1 \text{ ng/ml}$ at $4,0 \pm 0,5$ hour. The nanoemulsion preparation provided a relative bioavailability value of 3,5 times higher than the oral suspension of domperidone. In addition, the effective plasma concentration of the drug can be maintained for 16 hours after administration (Akhter *et al.*, 2008).

Some of the reports enlist in Table 1 showed that the domperidone was developed into the transdermal patch. The transdermal patch refers to a medicated patch that can deliver drugs through the skin into the bloodstream at a predetermined rate. A

Table I. Various formulations of domperidone with a transdermal delivery system

Drug	Dosage Form	Optimum/Chosen Formula	References
Domperidone	Cream	N-methyl-2-pyrrolidone (NMP) and urepearl cream (base cream)	(Kashiwagura <i>et al.</i> , 2021)
Domperidone Maleate	Patch type matrix	HPMC E15 (polymer), Eucalyptus oil (5% v/w) as a chemical enhancer	(Shirisha <i>et al.</i> , 2017)
Domperidone	Niosome	Span 60 (surfactant) and aloe gel (vehicle)	(Saritha <i>et al.</i> , 2015)
Domperidone	Nanoemulsion	Oleic acid (4% w/w), polysorbate 20 (10% w/w), diethylene glycol monoethyl ether (20% w/w), and water (64% w/w)	(Akhter <i>et al.</i> , 2008)
Domperidone	Patch type matrix	HPMC and Sodium CMC (polymer)	(Prabhu <i>et al.</i> , 2011)
Domperidone hydrochloride	Patch type matrix	Eudragit RL and Eudragit RS (8:2)	(Latha <i>et al.</i> , 2011)
Domperidone	Transdermal film	Xanthan gum and Sodium alginate	(Rajesh and Siddaramaiah, 2009)
Domperidone	Transdermal film	HPMC and Eudragit RS100 (7:3)	(Anisree <i>et al.</i> , 2012)
Domperidone	Patch type matrix	HPMC and Eudragit RL100 (polymer) Oleic acid and isopropyl alcohol as a chemical enhancer	(Pawestri <i>et al.</i> , 2021)
Domperidone	Patch type matrix	HPMC E15 and Eudragit RL100 D-limonene (12% v/v) as a chemical enhancer	(Madishetti <i>et al.</i> , 2010)
Domperidone maleate	Patch type matrix	Polyvinylpyrrolidone (PVP) and Ethylcellulose (polymer) Menthol 0.1% w/w as a chemical enhancer	(Khan <i>et al.</i> , 2012)

transdermal patch comprises several layers: a backing layer, a drug reservoir, an adhesive, and a liner (Roy, 2011). Madishetti *et al.* (2010) developed the domperidone formula in a patch-type matrix using a combination of hydrophilic (HPMC) and hydrophobic (Eudragit RL100) polymers and using d-limonene as a chemical enhancer. Based on this study, the in vitro drug release (dialysis membrane) was approximately 90,7% for 24 hours. Meanwhile, the in vitro drug permeation was 6806,64 µg for 24 hours. The flux was 86,02 µg /hr/cm² (Madishetti *et al.*, 2010).

Shirisha *et al.* (2017) also developed domperidone maleate into transdermal patch type matrix using HPMC E15 as a polymer and Eucalyptus oil (5% v/w) as a chemical enhancer. The in vitro cumulative number of drug release was 1832,16±6014 µg/ cm². The in vitro cumulative number of permeation was 650,36±29,6µg/cm² for 10 hours. The flux was 20,462 µg/ hr/cm² (Shirisha *et al.*, 2017).

In the study of Saritha *et al.* (2015), domperidone was formulated into niosome. Niosomes are composed of the hydration of a combination of non-ionic surfactants and

cholesterol, which will form a bilayer structure so that they can trap hydrophilic, hydrophobic, and amphiphilic compounds. Niosomes can diffuse through the stratum corneum and adhere to the surface of skin cells, causing a high thermodynamic activity gradient of the drug on the surface of the stratum corneum, thereby promoting drug penetration through the skin (Alkilani *et al.*, 2015; Hariyanti *et al.*, 2019). The in vitro cumulative number of permeation was $1954,9 \pm 78,4 \mu\text{g}/\text{cm}^2$ for 24 hours. The flux value in this study was $67,4 \mu\text{g}/\text{hr}/\text{cm}^2$.

Meanwhile, the research of Kashiwagura *et al.* (2021), who formulated domperidone into the cream, showed that the flux value was $0,21 \pm 0,07 \mu\text{g}/\text{hr}/\text{cm}^2$. In the in vivo absorption studies, the maximum concentration of the drug in plasma was $1,68 \pm 0,45 \text{ ng}/\text{mL}$ for 24 hours.

However, on those developed domperidone transdermal formulation studies, currently in vivo evaluations was limited performed, whereas it becomes an important step to discover if the target effective minimum concentrations of the drug in the plasma are achieved or provided prolonged-release after administration of the developed formulation (Ruela *et al.*, 2016). Therefore, besides preclinical studies for understanding the skin absorption of the drug, clinical evaluation is also necessary to find out the bioavailability, safety, and efficacy, also cost-effectiveness manner (Ramadon *et al.*, 2021). Based on those studies, it is shown that the nanoemulsion system for domperidone can be a promising preparation for transdermal delivery for long-term treatment.

CONCLUSION

Domperidone has physicochemical properties whose potential developed into the transdermal dosage form. The studies enlist the importance and advantages of this route. Various pharmaceutical formulation developments aimed at transdermal delivery such as patch, niosome, film, nanoemulsion, and cream were reported. The ability of domperidone to pass the membrane through in vitro and preclinical studies becomes a good initiation for the development of domperidone into a promising transdermal delivery. However, further research is necessary conducted such as clinical evaluation for ensuring the bioavailability, safety, and efficacy

also considering the cost-effectiveness for this route delivery.

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