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Transdermal delivery of naloxone: skin permeation, pharmacokinetic, irritancy and stability studies

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Abstract

The current investigation aims to evaluate ex vivo, in vivo performance, stability and irritancy potential of a transdermal formulation of naloxone (NLX) developed at our laboratory at different concentrations (10, 20 and 30 mg/g of gel) in a transdermal reservoir patch. Ex vivo permeation studies were performed by employing porcine and rat skins. In vivo performance was assessed in Sprague–Dawley rats by single and multiple application of the patch. Further stability of the formulation was established for 3 months at accelerated stability conditions as per ICH guidelines. Amongst the barriers used the rat skin was found to be more permeable than the porcine epidermis and the flux across each barrier increased with increasing thermodynamic activity of drug in the gel. Based on ex vivo data, the surface area (SA) of the patch was predicted to be 39.6 cm^2 in order to achieve therapeutic blood levels. Upon single dose administration, the steady-state levels were maintained from 4–48 h, which proves the clear advantage of transdermal delivery system over the current mode of administration, i.e., intravenous (i.v.) bolus which is effective upto a maximum of 1.5 h. Upon multiple dose administration, the sustained steady state for 12 h, even after patch removal proves the formation of drug depot in the skin. The formulations were found to be stable with respect to NLX assay and penetration enhancer efficacy upto 3 months under accelerated stability conditions. The alteration of penetration barrier function, as evidenced by increased trans epidermal water loss (TEWL) was not accompanied by any significant amount of skin irritation measured using laser doppler velocimetry (LDV). The developed transdermal delivery system of NLX is efficacious, stable and safe upon single and multiple dose applications each lasting for 48 h.

Keywords: Naloxone; Transdermal delivery; Stability; Laser doppler velocimetry (LDV); Trans epidermal water loss (TEWL); Pharmacokinetics

1. Introduction

Drug abuse involves non-therapeutic use of drugs resulting in physical, mental and social harm to an individual. Morphine is the most frequently abused drug (Gutstein and Akil, 2001). Tolerance develops from its

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chronic use and thus user has to increase dose to get euphoric effect. In US, around three million people are opioid dependent among which about 9,80,000 are long term users (Raisch et al., 2002). Naloxone (NLX), is a non-specific, competitive opioid antagonist and is used to reverse opioid induced CNS and respiratory depression. NLX shows a short biological half life (64 min) (Ngai et al., 1976), following its intravenous (i.v.) administration. Owing to extensive first pass metabolism leading to poor bioavailability of about 2%, peroral route is not effective for its delivery. NLX shows a very short duration of therapeutic effect thus requires frequent administration by i.v. or intramuscular (i.m.) routes which are invasive (Gourlay and Coulthard, 1983). Transdermal drug delivery (TDD), being non-invasive offers an improved approach to administration of drugs by maintaining a therapeutic concentration of drug in plasma over a prolonged duration extending to several days (Cleary, 1993). Development of a TDDS will thus circumvent the current delivery problems associated with NLX. Feasibility of transdermal delivery of NLX was demonstrated across excised rat skin by Jaiswal et al. (1999) and human skin by Aungst et al. (1986). Panchagnula et al. (2001) have also studied the effect of water, ethanol (EtOH), propylene glycol (PG) and their binary combination for selection of a suitable solvent system of NLX transdermal delivery. In continuation of that, we have developed and optimized a gel formulation of NLX containing 5% oleic acid as penetration enhancer (Panchagnula and Khandavilli, 2004; Khandavilli and Panchagnula, 2002), which can be effectively incorporated in a transdermal patch for its delivery across skin. In the present study, a TDDS for NLX was fabricated in which the gel formulation containing different concentrations of NLX was incorporated. Ex vivo studies were performed on either gel or using the prototype patch to evaluate permeation profile of NLX across excised rat skin and porcine epidermis. Further, in vivo studies using a prototype reservoir patch were performed for NLX at three concentrations (10, 20 and 30 mg/g). Pharmacokinetic evaluation of the patch at single dose (10 mg/g) was also assessed by its multiple application at different sites on skin. Further, the irritancy potential of gel formulation was assessed in vivo in Sprague–Dawley rats by histopathology, laser doppler velocimetry (LDV) and trans epidermal water loss (TEWL) measurements. The stability of the formulation with respect to drug content and penetration enhancer efficacy was established by accelerated stability testing for 3 months.

2. Materials and methods

2.1. Materials

NLX and Klucel-HF (hydroxypropylcellulose (HPC)) were gift samples from Mallinckrodt, USA and Signet Chemicals, India, respectively. ^{3}HNLX (specific activity 52 Ci/mmol) was procured from Amersham Pharmacia biotech, UK. EtOH was supplied by Merck, Germany, and PG, sodium azide and oleic acid by Sigma Chemicals, USA.

2.2. Analytical method

All skin/membrane permeation samples were analyzed by radiotracer method using liquid scintillation counting (Wallac 1409, Finland). It is specific to NLX and free from interference from skin proteins and plasma components (Sznitowska, 1991). ^{3}HNLX (radiochemical purity 97.8%) (Amersham Pharmacia Biotech, UK) was used as tracer molecule. A series of blank samples were always run to account for background activity. Further, a RP-HPLC method was developed and validated for the analysis of NLX in stability samples. The method was found to be specific, sensitive, rugged and reproducible in the sample matrix (Panchagnula et al., 2004).

2.3. Preparation of formulation

All experiments were performed using NLX gel, prepared at different concentrations (10, 20 and 30 mg/g of gel). Gels were prepared based on a previously optimized formulation (Panchagnula et al., 2001, 2004; Panchagnula and Khandavilli, 2004; Jaiswal et al., 1999; Khandavilli and Panchagnula, 2002), containing hydroxypropylcellulose, EtOH, PG and oleic acid. Polymer in the formulation was added after uniform mixing of all other components including radioactive tracer (2 μCi/g for ex vivo and 5 μCi/g for in vivo studies) and then subjected to further mixing for two more hours. Gels prepared were centrifuged to remove any entrapped air bubbles and stored at 2–8 °C overnight for complete swelling of polymer.