Background:

Transdermal administration of drug molecules is considered to have numerous clinical benefits, such as avoiding the liver first pass effect, improvement in patient compliance, and a reduction in adverse effects. The skin’s outermost layer, the stratum corneum, has excellent barrier properties that limit drug delivery into and through the skin. Nevertheless, the outstanding advantages of the administration of drugs by the dermal route have motivated intensive research activity in this area. As a result of this activity, various methods and strategies have emerged to overcome the skin barrier and to improve drug transport into the skin and into the blood circulation. Some methods are based on chemical enhancers and various vehicle formulations. Other methods rely on physical techniques, such as microneedle technologies, iontophoresis. In addition, various combinations of enhancing methods have been tested and some of them have indeed resulted in improved skin penetrations.

Therefore, in the present study, it was set out to demonstrate the potential advantages of iontophoretic delivery of some analgesic drugs from proniosomal gel to skin.

Naproxen proniosomal delivery:

Proniosomal formulae were prepared with coacervation-phase separation method. Eight different surfactants were evaluated, namely S 20, S40, S60, S80, T 20, T 40, T 60 and T 80. Effect of different amount of drug, surfactant, lecithin and cholesterol was studied. Proniosomal gel was mixed with HPMC gel and evaluated for EE, vesicle size, zeta potential, microscopy (optical and TEM), DSC, in-vitro release, ex-vivo permeation across goat skin, rate of hydration (spontaneity), stability studies (at refrigerated and room temperature), in-vivo (assessment of anti-inflammatory effect and antinociceptive activity). Among the different surfactant studied, formulation with S 60 showed good EE (98.34%), minimum vesicle size (180.4 nm), highest enhancement fold (5.2), good physical stability and in-vivo effect compared to market product.
Naproxen iontophoretic delivery:
- Cationic proniosomal formulation (S60) was prepared. Anodal iontophoresis study was performed using silver/silver chloride electrode. Formulation was evaluated for EE, vesicle size, zeta potential, \textit{in-vitro} release with iontophoresis, \textit{ex-vivo} permeation with iontophoresis. The characteristics of the applied electric current, such as density, frequency, and on/off interval ratio were observed. The results showed 1.45 fold enhancement with 0.5 mA/cm$^2$ current density, 2000 Hz frequency and 1:1 on/off interval ratio.
- Overall, compared to HPMC gel naproxen permeation was enhanced 5.2 fold with proniosomal gel, 1.9 fold with iontophoresis and 7.6 fold with combined effect of proniosome and iontophoresis.

Lornoxicam proniosomal delivery:
- Eight different surfactant were evaluated, namely S 20, S40, S60, S80, T 20, T 40, T 60 and T 80. Effect of different amount of drug, surfactant, lecithin and cholesterol was studied using four-factor three-level Box–Behnken design. Proniosomal gel was mixed with HPMC gel and evaluated for EE, vesicle size, zeta potential, microscopy (optical and TEM), DSC, \textit{in-vitro} release, \textit{ex-vivo} permeation across goat skin, rate of hydration (spontaneity), stability studies (at refrigerated and room temperature), \textit{in-vivo} (assessment of anti-inflammatory effect and antinociceptive activity). Among the different surfactant studied, formulation with S 60 showed good EE (98.18%). So, that formulation was selected for design. From the result of design the optimized batch (F 19) showed good EE (92.33%), optimum vesicle size (485.0 nm), highest enhancement fold (6.3), good physical stability and \textit{in-vivo} effect compared to market product.

Lornoxicam iontophoretic delivery:
- Cationic proniosomal formulation (S60) was prepared. Anodal iontophoresis study was performed using silver/silver chloride electrode. Formulation was evaluated for EE, vesicle size, zeta potential, \textit{in-vitro} release with iontophoresis, \textit{ex-vivo} permeation with iontophoresis. The characteristics of the applied electric
current, such as density, frequency, and on/off interval ratio were observed. The results showed 1.67 fold enhancement with 0.5 mA/cm$^2$ current density, 2000 Hz frequency and 1:1 on/off interval ratio.

Overall, compared to HPMC gel lornoxicam permeation was enhanced 6.3 fold with proniosomal gel, 2 fold with iontophoresis and 10.51 fold with combined effect of proniosome and iontophoresis.

Tramadol HCl proniosomal delivery:

Eight different surfactant were evaluated, namely S 20, S40, S60, S80, T 20, T 40, T 60 and T 80. Effect of different amount of drug was studied. Proniosomal gel was mixed with HPMC gel and evaluated for EE, vesicle size, zeta potential, microscopy (optical and TEM), DSC, in-vitro release, ex-vivo permeation across goat skin, rate of hydration (spontaneity), stability studies (at refrigerated and room temperature), in-vivo (assessment of anti-inflammatory effect and antinociceptive activity). Among the different surfactant studied, formulation with S 80 showed good EE (97.09 %), minimum vesicle size (121.7 nm), highest enhancement fold (5.81), good physical stability and in-vivo effect compared to market product.

Tramadol HCl iontophoretic delivery:

Cationic proniosomal formulation (S80) was prepared. 2% w/v tramadol HCl solution was prepared with distilled water. Anodal iontophoresis study was performed using silver/silver chloride electrode. Formulation was evaluated for EE, vesicle size, zeta potential, in-vitro release with iontophoresis, ex-vivo permeation with iontophoresis for solution and proniosomal gel. The characteristics of the applied electric current, such as density, type, frequency, and on/off interval ratio were observed. The results showed 2.22 fold enhancement in solution and 1.64 fold enhancement in proniosomal gel with 0.5 mA/cm$^2$ current density, 2.5 KHz frequency and DC.

Overall, compared to solution, tramadol HCl permeation was enhanced 2.52 fold with proniosomal gel, 2.21 fold with iontophoresis and 4.13 fold with combined effect of proniosome and iontophoresis.