Improving Transdermal Drug Delivery Using Gellan Gum Hydrogels and Temperature Responsive Nanospheres

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Statement of Purpose: Transdermal delivery of nonsteroidal anti-inflammatory drugs (NSAIDs) to treat joint pain associated with osteoarthritis minimizes the adverse systemic effects and organ damage of oral medications [1]. However, delivering drugs through the skin is difficult due to the barrier properties of skin. To overcome skin transport barriers, chemical penetration enhancers embedded into a hydrogel containing the drug of interest are used [2]. The use of gellan gum as a hydrogel offers several advantages including biocompatibility, tunable mechanical properties, and an active chemical reaction group [3]. In the present work, hydrogels containing diclofenac and penetration enhancers in combination with temperature-responsive nanospheres have been developed to improve transdermal transport of diclofenac (Fig 1A). **Methods:** *Diclofenac transport kinetics:* Diclofenac transport kinetics were measured in a custom-made diffusion cell using a synthetic human skin equivalent membrane (Strat-M®, Millipore, MA). Briefly, a 25 mm diameter Strat-M membrane was secured into a 24 mm internal diameter transwell insert (Millipore, MA). A diclofenac formulation is applied on top of a membrane and drug transport is measured by sampling the receiver chamber. A glass coverslip was placed on top of the drug formulation to eliminate evaporation of formulation components (Fig 1A). Drug transport was quantified by measuring diclofenac concentration in the receiver chamber using High Performance Liquid Chromatography-Liquid Chromatography-Mass Spectrometry (LC MS/MS). *Hydrogel formation:* Gellan gum is dispersed in water and heated to 75°C to dissolve the polymer. Chemical penetration enhancers including dimethyl sulfoxide (DMSO) and isopropyl alcohol at different concentrations are added to the mixture as well as diclofenac sodium at 1.5% W/V. After incorporation of all the components, the gels are cast into a mold, 24 mm diameter discs are cut from the mold and loaded on top of the StratM membrane. For the semi-solid hydrogel, gellan gum, drug and penetration enhancers are combined and emulsification is carried out using a homogenizer. Nanospheres are made as previously described [4] and loaded with diclofenac. **Results:** Increasing DMSO and isopropyl alcohol concentration increases diclofenac transport (Fig 1C & 1D). When diclofenac transport from the gellan gum solid hydrogel was compared to transport using currently available topical diclofenac gel and solution formulations, diclofenac transport is increased 397% and 163% as compared to the gel and solution formulations (data not shown). Incorporation of temperature responsive nanospheres loaded with diclofenac into the hydrogel increases the release of diclofenac from the hydrogels at 32°C (average skin temperature), but not at 22°C (Data not shown). **Conclusions:** In the present work we have developed hydrogel formulations that improves diclofenac transport compared to currently available topical diclofenac gel and solution formulations. Incorporation of diclofenac loaded temperature responsive nanospheres in the hydrogel extends the release time of diclofenac from the hydrogel at skin temperature. The combined use of novel responsive nanomaterials represents an improved approach for controlled delivery of transdermal pharmaceutical preparations.

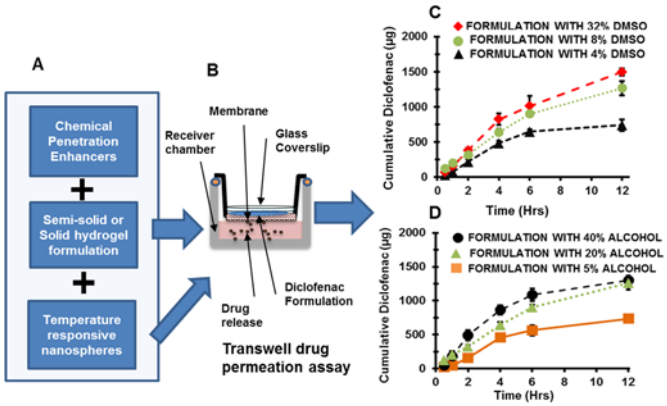

Figure 1: Experimental approach and results: A) Transdermal formulations are made by combining penetration enhancers and temperature responsive nanospheres into either a semi solid hydrogel emulsion or a solid hydrogel patch. B) Transwell diffusion cell schematic. Cumulative diclofenac transport as a function of C) DMSO or D) isopropyl alcohol concentration in a semisolid gel formulation. Data are mean±SD (n=3). Where errors bars are not visible, they are smaller than the symbol.

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