Screening of Polymeric Gels As A Means Of Controlling Local Skin Delivery

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Introduction: Skin Cancer is the most common cancer by which people are afflicted. While most forms of skin cancer have high survival rates if they are caught early, both Squamous Cell Carcinoma and Melanoma can metastasize and are very difficult to treat once this happens. Matrix Metallopeptidases (MMPs), Normally involved in cell growth, movement, and death, can become overactive in patients with cancer. While research suggested that MMP inhibitors could be used to treat many forms of cancer, clinical trials in late stage cancer patients showed that this was not the case. While they were not useful in shrinking late stage tumors, they were effective in preventing growth and metastasis of existing tumors. For this reason, they may be especially useful in the treatment of skin cancers as they may prevent metastasis. While MMP inhibitors can be delivered systemically, whether orally, or intravenously, systemic delivery can give rise to severe unwanted off-target side effects. As such, localized delivery is preferable. By incorporating MMP inhibitors into polymer gels, the drug can be administered topically and its distribution within the skin and into the systemic circulation may be controlled. Formulations may therefore be customized to alter the depth which the drug is delivered.

Materials and Methods: Screening of a wide range of polymers was performed. Polymer gels A, B, C, D, J, and K were created by dissolving the solid polymer in water using a stir bar at room temperature. Polymers E,F,G, and H were formulated by adding the polymer to water chilled to 5 degrees Celsius, mixed in an ice bath until dissolved, then stored in a fridge overnight. Polymer I was heated as it mixed, and then put in the fridge to chill. After all of the polymers were formulated to contain a model MMP Inhibitor, they were individually applied to human skin recovered from a 60 year old female using the high throughput skin permeation screening method developed by Martins *et. al*. The permeation study was allowed to run for 24 hours, at which point the samples were removed and the concentration of the drug that crossed the skin was quantified using High Performance Liquid Chromatography with a Waters 1525 Binary HPLC Pump, Waters 717plus Autosampler, A Waters 2487 Dual λ Absorbance Detector, and a Waters, Symmetry C18 3.5um (Part No. WAT200632) Column.

Results and Discussion: HPLC analysis showed that all of the tested formulations were able to permeate across the skin as shown in Figure 1 though at varying degrees. The permeation of Polymers A, D, and J1 were higher than the other polymers by a statistically significant margin. Further, the differences between Polymers J1 and J2, as well as L1 and L2, which were both binary combinations of polymers that were gelled with different concentrations of a cross linking agent, were statistically significant.

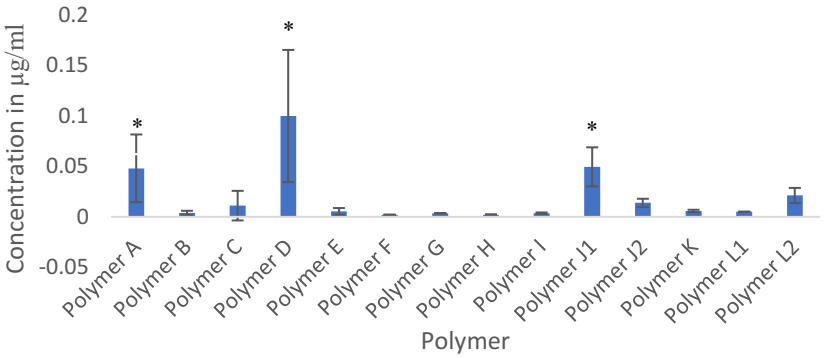

Figure 1. Concentrations of tested Polymer that permeated across the skin

Conclusions: Polymeric gels are shown to be a viable method of delivering MMP inhibitors topically. Due the permeation enhancing effects of different polymers and the effects of various concentrations of cross-linking agents, Formulations could be customized to penetrate the entire tumor, without entering the blood stream and causing systemic effects.

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References: Martins PP, Estrada AD, Smyth HD. *International journal of pharmaceutics.* 2019 Jun 30;565:557-68.