TOPICAL OCULAR AND OTIC DUAL PHASE DRUG DELIVERY SYSTEM APPLICATION

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INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide and therefore significantly affects the quality of life of those affected, leading to a need for improved treatment options. Current treatments include oral medication and eye drops, both of which must be administered multiple times a day for the rest of the patient’s life. In addition to the frequent dosing regimen, the eye drop administration is complicated, deterring patients from strict compliance. Furthermore, drug delivery efficiency is low with adherence of less than 50%.

Beyond ocular diseases, similar problems exist in drug delivery for treatment of otic diseases. One third of children experience six or more cases of acute otitis media (AOM) or middle ear infection before the age of seven. Treatment is often poor due to low compliance with the frequent dosing needed. Additionally, ear drops have low efficiency due to tympanic membrane permeability of approximately 10%.

The proposed solution to the aforementioned issues with current treatments is a reverse thermoresponsive hydrogel matrix containing drug-loaded microspheres (MS). The hydrogel’s liquid precursor forms a pliable, non-degradable gel at body temperature allowing for retention in the target area. The hydrogel then releases the drug at a consistent rate through the degradation of the poly(lactic-co-glycolic acid) (PLGA) is microspheres.

OBJECTIVE

In order to properly deliver the mixture of hydrogel and MS, a consistent volume of the highly viscous impregnated gel must be mixed immediately before application to prevent MS degradation. Lastly, the applicator must be disposable and sterile to comply with strict FDA sterilization requirements. Due to the unique challenges presented by the viscosity, degradability, and sanitization of the MS-loaded hydrogel, my research objective is to develop a novel dual-phase applicator for continued research into the efficacy of the hydrogel matrix.

HYPOTHESIS/SUCCESS CRITERIA

I believe an applicator can be designed such that eighty percent or higher of materials loaded can be recovered during application of the hydrogel matrix. The excreted mixture must be fully homogenized as validated by SEM imaging.

METHOD

Microspheres were fabricated by dissolving PLGA (MW 24-38 kDa, viscosity 0.32-0.44 dl/g, Sigma Aldrich, St Louis, MO) in dichloromethane. To this solution, aqueous brimonidine tartrate solution was added (Santa Cruz Biotechnologies, Santa Cruz, CA). This suspension was then sonicated and homogenized in 2% poly(vinyl alcohol) (PVA) (Polysciences, Warrington, PA) at 7000 rpm (Silverson L4RT-A). The emulsion was then mixed with a 1% PVA solution for 3h to allow residual DCM to evaporate. The microspheres were then washed via centrifugation with deionized (DI) water prior to lyophilization for 24-48 hours (Virtis Benchtop K Freeze Dryer, Gardiner, NY). Dry microspheres were stored at -20°C until use.

Reverse thermoresponsive hydrogels were prepared by combining n-isopropylacrylamide (NIPAAm) (Fisher Scientific, Waltham, MA), poly(ethylene glycol) (MW ~200kDa, Sigma Aldrich, St Louis, MO), 100mg/mL ammonium persulfate (APS) solution, and DI water. The APS solution was made by dissolving 100mg dry APS in 1mL DI water. Polymerization was achieved by refrigerating overnight. The resulting gel was washed five times in DI water heated to 37°C.

Modeling of the applicator was completed using SolidWorks 2014 (Dassault Systèmes SOLIDWORKS Corp.) Prototype creation was completed using the Viper SLA System (3D Systems®) in combination with Somos® Water Shed XC 11122 as the plastic building material. Blister packs were molded in the SLA (stereolithography) printed pieces using Impregum™ F Polyether Impression Material. (3M®) Future molding will be completed using a heated press and medical grade silicone. Upon the creation of the molded piece, the septum will be machined down from plastic barstock using a Baileigh® laithe.

Blister packs are loaded with 100µL of gel and 50mg of MS. The septum was inserted into the groove within the blister pack and the gel was then injected using an 18-gauge hypodermic needle under the septum. Once complete, the MS are poured into the top portion of the blister pack and the compression lid and ring are secured. Each polyether pack was then voided onto a weigh boat using the assembled syringe. Post-ejection mass of the weigh boat then was used to determine percent recovery. In order to ensure homogeneity of the dispensed MS impregnated hydrogel, scanning electron microscopy (SEM) images were taken using samples of the mixture dried at 37°C. Each sample imaged was said to be homogenous if large clumps of embedded MS were not found. Further homogeneity testing will consist of measuring the absorbance of the impregnated gel in multiple sections of the sample using a spectrophotometer.
RESULTS
The applicator can be split into three main components; the blister back, the main body, and the plunger. Blister packs are disposable vessels for the separated gel and MS that will be sent to patients yearly. Consequently, the shelf life of the sealed blister pack must be over a year. Additional design considerations include size, ability to homogenize the gel and MS, and drug recovery rate.

Both side-loading and bottom-loading designs were made for the main body of the syringe. Design inputs for the main body were sizing, ease of cleaning, ease of achieved blister pack compression, and ergonomics. Both designs must be assembled, used, and cleaned efficiently for the applicator to become a valid replacement for the ease of a completely disposable daily eye drop. Lastly, the syringe plunger was originally designed as one solid piece shown in Figure 1. In order to optimize the gel recovery rate from the blister pack, a threaded 18-gauge needle tipped plunger was created to perforate the back side of the blister pack, allowing for easier compression and increased recovery rate.

The original blister pack design was tested for homogeneity of MS and gel, and recovery rate. SEM imaging of the dispensed mixture should show homogeneity in all tests. Additionally, the prototype recovery rate was measured at 62%, meaning that an average of 38% of the gel was left within the blister pack after application. In order to achieve consistent application, design changes such as creating an easier perforation surface for the needle tipped plunger, tapered walls for greater recovery rates and easier removal from the mold, reduction of wall thickness for less resistance to application and greater compressibility resulting in increased recover rates were implemented. Additionally, the inner volume and surface area of the blister pack was manipulated to maximize application yield. Testing completed after design change implementation yielded showed increased gel recovery rate, homogeneity, and ease of use.

DISCUSSION
Future models of the applicator aim to further increase recovery rate and ergonomics while not compromising the homogeneity of the dispensed mixture. By switching the molding material from the quickly degrading polyether material to silicone, we expect to accomplish these goals. In conjunction with a heat press, silicone is a very versatile molding material. Each mold will include bellows allowing the blister pack to compress much further, in turn increasing the recovery rate. Furthermore, the heat press will minimize the air bubbles and other material defects that plagued the polyether material. This allows for thinning of the walls, resulting in less resistance to application and easier mixing.

Further retention testing will be improved through post-ejection dissection of the blister packs in order to further determine which features of the molded pieces are retaining the most gel. Additionally, remnants within the blister pack will be removed and analyzed for homogeneity using SEM imaging. The results will allow for a deeper knowledge of how various features within the blister pack effect homogeneity.

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REFERENCES