Microemulsions for Topical Delivery of Water Soluable Drugs

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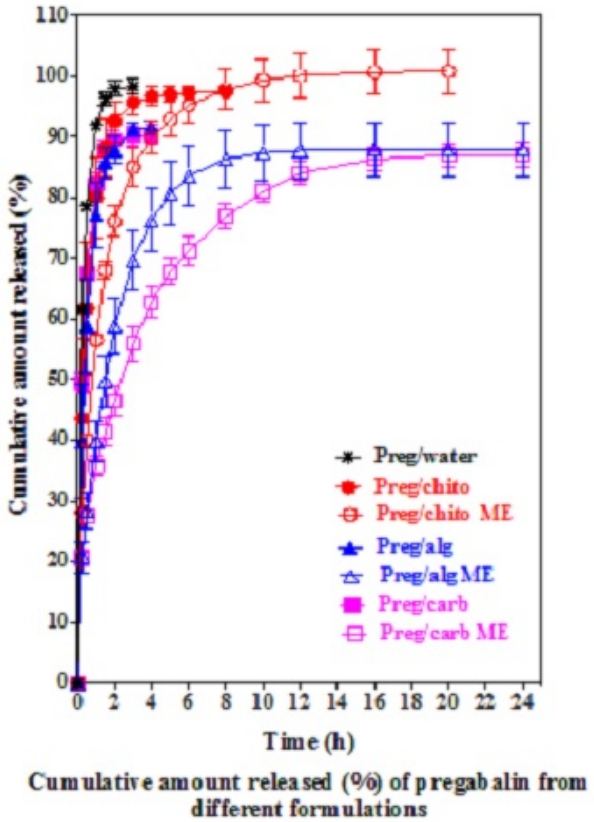
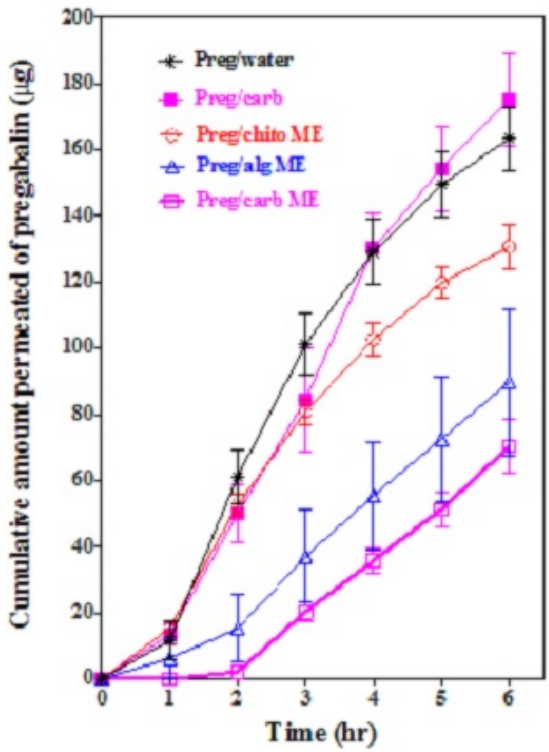
Technology description

The Problem:
Elevated intraocular pressure (IOP) is the most significant risk factor that contributes to visual field loss in primary open angle glaucoma (POAG). Despite glaucoma prevalence and its impact on society, current medications do not address the underlying pathophysiologies that cause elevated IOP, nor do they address genetic variations related to IOP modulation. Moreover, because of their short half-life and low corneal residence time, current medications require multiple daily topical applications, which are associated with poor patient compliance. Thus, an improved formulation is needed to improve patient compliance while at the same time maintaining and enhancing efficacy in lowering IOP.
The Technology Solution:
Researchers at the University of Tennessee have developed novel extended release topical bioadhesive microemulsion (ME) formulations to deliver pregabalin (preg) and that will allow for once daily dosing and better patient compliance. Through systems genetics investigations using the large BXD family of recombinant inbred mice as a genetic reference panel, they identified Cacna2d1 as a novel modulator of IOP. They discovered and confirmed that pregabalin is a specific modulator of CACNA2D1 that can lower IOP, and its IOP lowering effect is dependent upon the haplotype of Cacna2d1. They constructed multilayered w/o/w microemulsions with different polymers including alginate, chitosan, and carbopol; and loaded these microemulsions with pregabalin. They have characterized these formulations, showing drug release profiles, corneal permeability, formulation safety, formulation efficacy, and other characteristics. The release profiles (Fig. 1) show that all control formulations exhibited fast release behaviors that released 100% of the drug content within 3-8h. On the other hand, the tested MEs exhibited sustained release behaviors that last for up to 24h. Figure 2 shows that the ME-free formulation (Preg/water and Preg/ carbopol) possessed a higher permeation rate than the formulation containing ME. This is because of the natural ability of the drug to rapidly permeate through the cornea. This behavior is contrary to the required sustained release behavior. On the other hand, all formulations containing ME possessed a lower permeation rate. This is due to the special engineering of the ME, as the drug is located in the innermost aqueous layer of the multilayered ME. To be released, the drug must pass through two interfaces the inner w/o interface and the outer o/w interface after which it has to diffuse through the viscous hydrogel to be ready for permeation through the cornea. This behavior is ideal to support the sustained release of the formulation. In comparing the ME

formulations, it was found that the formulation that contained carbopol possessed the lowest permeation rate among all tested formulations. This experiment confirmed the in vitro release data that carbopol ME can perfectly sustain pregabalin release to be suitable for once daily application. Figure 3 shows the IOP profile of Dutch belted (DB) rabbits after a single application of different ME formulations. It is clear from the figure that the maximum IOP-reduction and the most extended effect was achieved with the carbopol ME, which may be due to the carbopol in situ gelling property at the physiological pH. The IOP did not return to baseline until after about 34h. Figure 4 compares both carbopol formulations (gel and ME) in order to show the effect of ME on the duration of the drug effect. Overall, these data provide evidence that 1) pregabalin is an effective IOP lowering drug, and that 2) its lowering effects are enhanced and sustained by the ME formulations. These data provide evidence of a potential new therapy for glaucoma that is both effective and sustained; thereby providing a feasible once daily dosing that would likely improve patient compliance.



Cumulative amount released (%) of pregabalin from different formulations



Advantages

Novel sustained release formulation for treatment of glaucoma
ME is compatible with other hydrophilic drugs
Therapy based on systems genetics approach
Once daily dosing formulation

Institution

University of Tennessee

Inventors

Mohamed Moustafa
Postdoctoral Fellow
Ophthalmology
Monica Jablonski
Associate Professor
Ophthalmology