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Treatment of diabetic retinopathy with ocular delivery of metformin

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Abstract:
Apart from its anti-diabetic properties, metformin has been shown to reduce inflammation. Therefore, topical metformin may be a useful treatment approach for controlling diabetic ocular inflammation. In order to accomplish this and tackle the problems of regulated release and ocular retention, an in situ gel containing metformin was created. Gellan gum, hypromellose, and sodium hyaluronate were used to make the formulations. Viscosity, mucoadhesion, and gelling time/capacity were all monitored in order to optimize the composition.

I. Introduction

Diabetes puts one at risk for a host of physiological conditions. A higher sugar content causes the cells' homeostasis to change, leading to degeneration and a decrease in the cells' capacity to control inflammation. Despite being a protected organ, the eye's equilibrium is negatively impacted by the elevated sugar level. Diabetes has been linked to an increase in the reninangiotensin system (RAS), vascular endothelial growth factor (VEGF), advanced glycation end products (AGES), polyol and protein kinase C (PKC) pathway activity, and oxidative damage. The over-regulation of these mutually reliant metabolic pathways is a contributing factor to long-term inflammation and various eye conditions (diabetic retinopathy).[1]

Because metformin (MET) is polar and can pass across the ocular barrier through cationic transporters produced on it, it may be useful for repurposing against ocular inflammation linked to diabetes. Through several mechanisms of action, it can lessen inflammation in addition to reducing the glucose level. Repurposing metformin (MET) against diabetes-related ocular inflammation may be beneficial because it is polar and can cross the ocular barrier via cationic transporters generated on it. It can lower the level of glucose and also reduce inflammation through a number of different methods of action. Through a pleiotropic mechanism that preserves mitochondrial integrity and lowers inflammation, stress, and proliferation, it is known to protect cells." Additionally, it is known to sustain the equilibrium of cellular metabolism that is essential to cellular homeostasis and to activate the AMP-activated protein kinase (AMPK) pathway.[1,6] MET has been demonstrated to prevent open-angle glaucoma (OAG) and lessen inflammation and angiogenesis in retinal vascular hyperplasia, which is consistent with these mechanisms of action. In addition to its anti-diabetic effects, metformin is also known to reduce inflammation. Therefore, topical metformin may be used as a treatment approach to control diabetic ocular inflammation. An in situ gel of metformin was created to accomplish this and deal with the problems of regulated release and ocular retention. Gellan gum, hypromellose, and sodium hyaluronate were used to create the formulations. By tracking viscosity, mucoadhesion, and gelling time/capacity, the composition was optimized. The ideal formulation was determined to be MF5.[4] It demonstrated compatibility on both a chemical and physiological level. It was determined to be stable and sterile. Metformin was released continuously in MF5 for 8 hours, which best fit zero-order kinetics. Additionally, it was discovered that the release mode closely resembled the Korsmeyer-Peppas model.[1]

Clinical studies that show diabetic patients utilizing oral MET had comparatively decreased occurrences of ocular disease further demonstrate the usefulness of MET for ocular problems. On the other hand, ocular inflammation or a similar condition might not be sufficiently managed by the usual MET dose range used to treat diabetes.

Pathophysiology of Diabetic Retinopathy:

One of the main consequences of diabetes mellitus (DM), which continues to be the most common cause of vision loss in people of working age, is diabetic retinopathy (DR).Due to its effects on retinal blood vessels, diabetic retinopathy (DR) is the most common cause of vision loss in individuals with diabetes as well as the primary cause of visual impairment and blindness in adults

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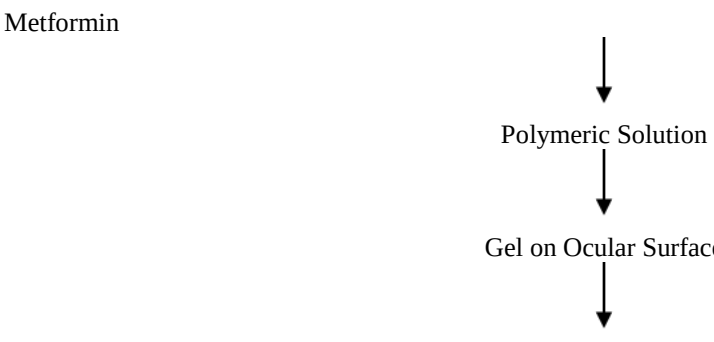
of working age. Diabetic Retinopathy (DR) is a Neurodegenerative Retinal Disease that is associated with significant costs. Its global incidence is rising due to both the exponential spread of diabetes and improved life expectancy. Clinical signs of vascular anomalies in the retina are used to diagnose diabetic retinopathy (DR). Non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) are the two stages of DR that are separated clinically.[2] Diabetic macular edema is the most frequent cause of vision loss in DR patients (DME). The hallmark of DME is the thickening or enlargement of the macula as a result of intra- and sub-retinal fluid buildup brought on by the disintegration of the blood-retinal barrier.[7]

It has long been known that DR is a microvascular condition. It is thought that hyperglycemia is a key factor in the pathophysiology of retinal microvascular injury. The accumulation of advanced glycation end products (AGEs), the polyol route, the protein kinase C (PKC) pathway, and the hexosamine pathway are among the metabolic processes that have been linked to hyperglycemia-induced vascular injury.[8,9]Hyperglycemia, Retinal Microvasculopathy, Inflammation, and Retinal Neurodegeneration are other conditions associated with DR. In glaucoma, diabetic retinopathy, and hypertensive retinopathy, retinal ischemia/reperfusion (I/R) injury is a common pathological process that causes cellular damage.

Recent Applications:

The FDA has approved metformin as a first-line treatment for type 2 diabetes in individuals who are overweight or obese and who are at high risk of developing cardiovascular problems. Metformin enhances fibrinolytic action by decreasing plasminogen activator inhibitor 1. Furthermore, metformin prevents inflammation-mediated angiogenesis in a mouse model and in humans, possibly as a result of plasminogen activator inhibitor 1's effects on thrombospondin activation.[5]Nonetheless, there have been contradictory reports about how metformin affects vascularization; this appears to be due to variations in the experimental paradigm and time course at analysis. Metformin has been shown to lessen the severity of diabetic retinopathy (DR) and to delay its progression. Still unknown, though, are the underlying mechanisms.Compared to traditional eye drops, in situ ophthalmic gels can offer superior medication retention and prolonged release. This could guarantee better efficacy and less discharge. As a result, the release of MET should be sustained by the in situ gel.It was decided that MF5 was the best formulation. It demonstrated compatibility on a chemical and physiological level. It turned out to be stable and sterile. Additionally, it was discovered that the release mode resembled the Korsmeyer-Peppas model.[1] Its potential for sustained activity was supported by an ex vivo permeation study. It demonstrated a noteworthy decrease in ocular inflammation that was on par with the usual medication. MF5 has the potential to be a safe substitute for steroids in the treatment of ocular inflammation.[4]

Nevertheless, metformin markedly reduced the severity of diabetic retinal necrosis, possibly by reducing the amount of new blood vessels seen in the retina. To ensure ocular bioavailability, MET is expected to permeate over the ophthalmic barrier due to its greater permeability through cationic transporters. These elements might influence how well MET reduces ocular inflammation.[3] In light of these factors, the current study was conducted to create an appropriate in situ MET gel.



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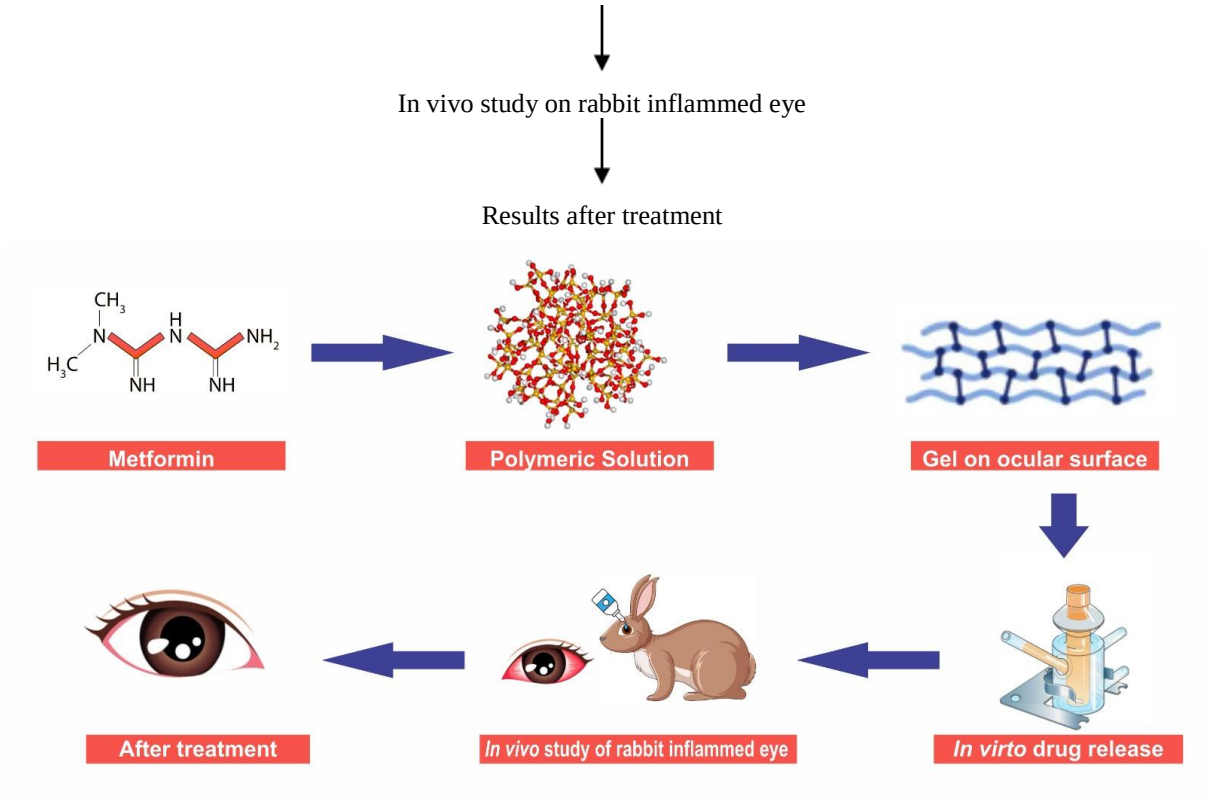

Figure 1In Vivo Study of Rabbit Inflammed Eye

Advantages:

- They impart accuracy and uniformity in dosing rate. Pulsed dosing of conventional systems can be avoided.
- Sustained and controlled release of drugs can be achieved.
- By increasing corneal contact time, they cause enhancement in the ocular bioavailability of drugs and it is achieved by effective adherence of the drug to the corneal surface.[3]
- For the prevention of loss of ocular tissues, targeting within the ocular globe is to be done.
- They bypass the protective ophthalmic barriers, such as drainage, lacrimation and conjunctival absorption.
- They also improve patient's compliance, offer comfort and enhance therapeutic drug performance.
- They provide better housing of delivery systems.

Disadvantages:

- Termination of the dosage form is not possible during an emergency.
- Interference with vision.
- Faces difficulty in placement and removal of the dosage form.

II. Conclusion:

The current review identifies a unique regulatory mechanism in metformin-mediated defense against diabetic retinopathy. The potential of MET for ocular application is supported by the current study. The MF5 in situ gel demonstrated enhanced efficacy in reducing initial ocular inflammation and adjustment of crucial parameters for sustained release, bolstered by extended bleeding. Created using components that have been approved, MF5 exhibits promising results as a secure substitute for steroids in the treatment of ocular inflammation. This may stimulate additional research to apply it to other ocular conditions.

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