Mohammed Ali Mutar et al /J. Pharm. Sci. & Res. Vol. 10(3), 2018, 562-574

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Injectable Glucose-Responsive Hydrogels as Insulin Delivery Systems for Diabetes Treatment Based on Boronic Acid−Glucose Complexation

Prof. Dr. [1] Mohammed Ali Mutar & [2]Makarim Ali Anad

[1] Department of Chemical Engineering, College of Engineering, University of AL-Qadisiyah, Iraq
[2]Department of Chemistry, College of Education, University of Al-Qadisiyah, Iraq

Abstract :

Diabetes is one of the most common chronic diseases in the world and its incidence is on the rise. Maintenance of continuous normoglycaemic conditions is the key goal for the management of both type 1 and type 2 diabetes in patients. In this study, different types of glucose-responsive polymers have been synthesized by polymerization of different monomers(Methyl acrylamide, Methyl acrylic acid, and1-vinyl2-pyrolidone) with 4-vinyl phenyl boronic acid (4-VPBA) by free radical polymerization in the presence of ethylene glycol dimethacrylate (EGDMA) and 1,6-Hexanediol diacrylate (HDODA) as a crosslinking agents and Potassium Peroxodisulfate, Sodium metabisulfite as an initiators. which has been used for glucose sensing due to its ability to form complexes with diols at different pH values and at different sugar concentrations. PBA-moiety has the ability to reverse crosslinks with glucose-diols and form the most stable boronate ester complexes. The prepared polymers were confirmed by using the FTIR and 1HNMR techniques. The Thermal stability of all polymers were also studied using the TGA and DSC techniques. In addition to the use of polymers in glucose sensing has been exploited to control the level of sugar and reduce the concentrations of high through the loading of insulin on these polymers as the large area of polymers improve the possibility of loading insulin. The release of insulin in vitro at physiological pH , different concentrations of glucose and different times were also studied. The results show the gradual release of insulin, preceded by the sudden release of insulin due to the presence of large amounts of the diols of sugar particles, as well as high release rate of high concentrations of glucose which decreases when glucose concentration decreases .The effectiveness of these polymers has also been studied on the laboratory rats , the results showed that the polymers have an evident effect in reducing the blood glucose levels in rats , as well as to avoid the problem of higher loading glucose caused by the treatment process insulin which is usually what happens as a result of the overdose in addition to reducing the number of periodic tests to monitor the level of sugar in the blood.

Keywords: 4-vinyl phenyl boronic acid, copolymerization, glucose sensitivity, physiological pH, load, control, drug release, Vitro, Vivo.

INTRODUCTION

The development of glucose-responsive controlled insulin delivery systems has attracted much attention due to its potential application in maintaining normal blood glucose levels, one of the key goals of the treatment of Type 1 diabetes [1]. Blood glucose levels in diabetics exhibit large swings throughout the day. However, current widely used devices, such as test strips and glucose meters, give only discrete time information about blood glucose level, possibly missing fluctuations involving sudden increase or decrease in glucose level [2,3]. Recently commercialized enzyme based sensors such as Medtronic CGMS® GoldTM and Dexcom® G4 Platinum can offer continuous information, but they can be problematic due to instability of the enzyme, fouling under physiological conditions, and inflammation and infection that result from breaching the skin with a needle electrode [4]. While improved enzyme based sensors that minimize some of these issues are under development [5], parallel investigation of nonenzymatic sensing modalities is of continued interest. Hydrogels have been broadly used for biomedical applications, including drug delivery and tissue engineering[6-8]. Injectable hydrogels that flow under modest pressure and exhibit self-healing recovery following cessation of pressure offer many advantages for medical applications. Specifically, injectable implantation can be self-administered and is minimally invasive, leading to improved patient compliance[9] . In addition, a number of injectable hydrogels have been evaluated preclinical or in early stage clinical trials, including hydrogels for cancer therapy and bone repair[10]. In order to prepare injectable hydrogels, a variety of cross-linking mechanisms have been leveraged, including in situ covalent cross-linking as well as physical cross-linking that include salt bridges, peptide interactions, molecular recognition motifs,and/or van der Waals forces [11-13]. Preparing hydrogels with crosslinks that can respond to a specific biologic stimulus, such as elevation of blood glucose levels in diabetes, could further expand the utility of this class of material in preparing new therapies. Early efforts to prepare glucose-responsive materials for insulin delivery evaluated the complexation of a glycosylated insulin derivative with the lectin concanavalin A (Con A), a natural carbohydrate binding protein [14-16]. The competitive binding to Con A of glucose and glycosylated insulin regulates the breakdown of the complex, leading to glucose-responsive insulin release [17-19]. However, possible immunogenicity of Con A, as well as a requirement for a special modified insulin derivative, would prove limiting to the translation of this approach[20]. Another method to prepare glucose-responsive materials utilizes the enzymatic actuation, leveraging the catalytic conversion of glucose into gluconic acid by glucose oxidase. The drop in pH that arises through this conversion can be used to trigger hydrogel swelling, leading to the release of encapsulated insulin [21-22]. This method has been widely used in a number of insulin delivery systems, including injectable networks[23-25]. However, this strategy also has risks associated with enzyme immunogenicity along with toxicity of the hydrogen peroxide by product produced in the conversion. Phenylboronic acids (PBAs) are Lewis acids that can bind reversibly to cis-1,2 or cis-1,3 diols, including glucose, to form a stable five-membered ring complex [26]. In 1959, Lorand and Edwards reported the first quantitative study describing the complexation of boronic acids and polyols[27]. Extensive studies since this time have investigated the binding affinity of boronic acids with different diols including fructose, glucose, and other sugars[26,28,29] . On the basis of previous work in the preparation of glucose responsive polymeric hydrogels from PBA−diol complexation[30] .We endeavored to design a hydrogel leveraging crosslinking between PBA and glucose-like diols that could be injectable (i.e., self-healing) . In this system, polymers containing multiple PBA groups would cross-link through interaction with multiple glucose units installed within the same polymer to form a stable hydrogel network. This PBA−glucose complexation is reversible, enabling the preparation of an injectable self-healing hydrogel as verified through rheological measurements. Herein, we report a hydrogel cross-