Analysis of various types of nanoparticles for diabetes management: which is the best?

Análisis de los diversos tipos de nanopartículas para el manejo de la diabetes mellitus: Cuál es la mejor?

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Recibido: 06/10/2022 Aceptado: 09/15/2022 Publicado:11/10/2022 DOI: http://doi.org/10.5281/zenodo.7844055

RESUMEN

Nanotechnology has proven incredibly useful, especially in the delivery systems of several drugs. In recent decades, interest in this topic has grown substantially due to the unique properties of nanomaterials (NM), which results in a great variety of applications that can significantly improve patients' quality of life. Implementation of nanoparticles (NP) has allowed various molecules to overcome almost any physical or chemical barrier, providing patients a friendlier alternative to receive drugs like insulin through novel routes, such as orally. These alternatives offer several benefits, including increased treatment adherence and tolerability. Significant advances have been made in the interest of achieving viable alternatives to administer insulin orally. Most of these advances are due to the implementation of nanotechnology to a variable extent. A large amount of evidence supports the implementation of different drug delivery systems like liposomes, niosomes and metallic NP, and most of this evidence has given encouraging results indistinctly of the nature of the molecule. This review aims to evaluate the safety and efficacy profile of different NP concerning diabetes and the delivery of insulin.

Keywords: Nanotechnology, nanoparticles, drug delivery, insulin, diabetes.

ABSTRACT

La nanotecnología ha demostrado ser de gran utilidad, especialmente en los sistemas de administración de varios medicamentos. En las últimas décadas, el interés por este tema ha crecido sustancialmente debido a las propiedades únicas de los nanomateriales, lo que se traduce en una gran variedad de aplicaciones que pueden mejorar significativamente la calidad de vida de los pacientes. La implementación de nanopartículas (NP) ha permitido que varias moléculas superen casi cualquier barrera física o química, brindando a los pacientes una alternativa más amigable para recibir medicamentos como la insulina a través de vías novedosas, como la vía oral. Estas alternativas ofrecen varios beneficios, incluido el aumento de la adherencia al tratamiento y la tolerabilidad. Se han realizado importantes avances en el interés de lograr alternativas viables para administrar insulina por vía oral. La mayoría de estos avances se deben a la implementación de la nanotecnología en una medida variable. Una gran cantidad de evidencia respalda la implementación de diferentes sistemas de administración de fármacos como liposomas, niosomas y NP metálicas, la mayoría de esta evidencia ha brindado resultados alentadores independientemente de la naturaleza de la molécula. Esta revisión tiene como objetivo evaluar el perfil de seguridad y eficacia de diferentes NP en relación con la diabetes y la administración de insulina.

Palabras clave: nanotecnología, nanopartículas, administración de fármacos, insulina, diabetes.

INTRODUCTION

Nanotechnology is a term used to describe the manipulation of matter at an atomic scale while considering unique quantum mechanics. Therefore, nanotechnology requires the design, production, and characterization of nanoscale materials and their application in different areas to achieve novel advances[1]. In the past few decades, interest in this topic has grown substantially due to the unique properties of nanomaterials (NM), which results in a great variety of applications that can significantly improve patients' quality of life[2]. The point where medicine and nanotechnology merge is known as nanomedicine, a branch of medicine that applies the fundamentals of nanotechnology to the prevention and treatment of various diseases[3].

The range of applications of nanomedicine encompasses prevention, diagnosis, drug delivery and tissue repair. Nanotechnology has been successfully used in several disorders, such as cancer, Parkinson's disease, tuberculosis, and diabetes mellitus (DM)[4]. Regarding the latter, nanotechnology has proven incredibly useful, especially in the delivery systems of several drugs[5]. Some macromolecules used to treat DM, such as insulin and glucagon-like peptide 1 agonists (GLP-1a), have to be administered subcutaneously because of the harsh environment of the gastrointestinal (GI) tract; moreover, parenteral drug administration can be painful, resulting in poor patient compliance[6]. However, the implementation of nanoparticles (NP) allows these molecules to overcome almost any physical or chemical barrier, providing patients a friendlier alternative to receive their drugs[7].

There is growing evidence about various NP implemented in the treatment of DM. To date, the most employed NP for drug delivery are liposomes, niosomes, metallic NP, nanospheres, polymeric micelles, and chitosan NP, all of which have unique properties[8]. These have been implemented with many antidiabetic drugs, resulting in heterogeneous findings[9]. This review aims to evaluate the safety and efficacy profile of different NP concerning DM and the delivery of insulin.

Nanoparticles in the transport of insulin and GLP-1 AGONISTS

Oral administration is, by far, the most common route of drug administration and the one with the highest rate of adherence compared to other routesb[10]. However, the GI tract imposes anatomical and chemical barriers, halting the absorption of almost every molecule interacting with it. The stomach's low pH, the presence of peptidases and the selective permeability of the enterocytes are some of the mechanisms that oppose the oral absorption of the drugs[11,12]. For that reason, big and complex molecules are most frequently administered parenterally, which is the case for insulin and GLP-1a. However, parenteral administration has many drawbacks, such as pain, risk of infection and low patient compliance[13].

Many attempts have been made to create an oral carrier able to deliver insulin efficiently. Furthermore, oral administration of insulin better mimics the normal insulin pathway in the body, thus, providing better glucose homeostasis[14]. Oral administration allows for high portal insulin concentration with no sustained peripheral hyperinsulinemia, which is associated with neuropathy and retinopathy[15]. The implementation of nanotechnology has allowed scientists to overcome all of the chemical and physical barriers of the GI tract. Several types of NP have achieved, by different mechanisms, the efficient transport of insulin into the bloodstream through oral administration[7]. However, the NP used for this purpose differ in size, material, absorption mechanism and several other properties; therefore, proper comparison is needed to establish which offers the most benefits.

Firstly, liposome-based systems are some of the most used because of their biodegradability, biocompatibility, low toxicity and capability to entrap lipophilic and hydrophilic drugs; additionally, this system facilitates site-specific drug delivery[16]. Typically, liposomes are coated with a molecule that facilitates insulin absorption, like chitosan. This is a linear polysaccharide used as a permeation enhancer for the absorption of hydrophilic molecules like insulin[17]. Likewise, chitosan can permeate tight junctions between epithelial cells, increasing paracellular permeability for peptides like insulin[18]. Lin et al.[19] reported that chitosan-insulin NP prolongs the residence of insulin in the small intestine along with increased paracellular permeation of insulin into the bloodstream.

Along these lines, Wu et al.[20] tested the effectiveness of chitosan-coated NP in Kunmin mice, and it was found that these NP had a hypoglycemic effect as effective as parenteral insulin for about 4 hours. In addition, the authors suggested that the best possible effect was achieved at a chitosan concentration of 0.2%. Furthermore, Mukhopadhyay et al.[21] developed a self-assembled model of chitosan-insulin NP for oral delivery. Average particle size ranged from 200 to 550 nm with an almost spherical shape and an average insulin encapsulation of 85%. In addition, in vitro studies showed that these NP efficiently retained insulin in gastric conditions while effectively releasing it in simulated intestinal conditions. Likewise, oral administration of the latter NP resulted in lower blood glucose levels in diabetic mice.

Furthermore, chitosan preparation and conjugation with other molecules greatly varies across studies. For instance, Mukhopadhyay et al.[22] prepared chitosan with 83-86% deacetylation conjugated with alginate. The average particle size was 216 nm, with an 80% insulin entrapment efficiency. Insulin-loaded chitosan-alginate NP showed a reduction in blood glucose to 104 mg/dL at the highest dosage, with a sustained effect of up to 9 hours. On the other hand, He et al.[23] conjugated 85% deacetylated chitosan with sodium tripolyphosphate (TPP), with an average particle size of 46 nm and over 90% insulin entrapment efficiency. The latter model had negligible insulin release between 2.5 and 6.6 pH, whereas optimal release was achieved within a few hours at 7.4 pH. Results showed a 51% reduction in blood glucose

was achieved at 60 IU/kg within 8 hours, with little change when the dosage was doubled.

On the other hand, niosomes are another NP system that consist of microvesicles mainly formed by non-ionic surfactants incorporated with cholesterol as an excipient. These agents, like liposomes, offer excellent biocompatibility and low toxicity due to their non-ionic nature[24]. In 2005, Ning et al.[25] studied niosomes NP with sorbitan monoester as a carrier for vaginal insulin delivery. The average size particle for Span 40 and Span 60 niosomes were 242 and 258 nm, respectively. However, niosomal entrapment efficiency was 26.68 and 28.82% for Span 40 and Span 60 niosomes, respectively. It was found that after administration, the maximum blood glucose reduction was 47% for Span 40 niosomes and 46 for Span 60 niosomes. Additionally, the bioavailability of the two preparations was 9.11% and 8.43%, respectively; both of which were higher than that of subcutaneous administration.

Another study by Pardakhty et al.[26] analyzed niosomes of polyoxyethylene alkyl ethers for oral insulin administration. In the absence of cholesterol, niosomes did not form, probably because of relatively large polar head groups compared to their alkyl chains. After stabilization and niosome formation, sustained-release was achieved during 24 hours in simulated intestinal fluid, indicating that niosomes could be developed as sustained-release oral dosage forms for insulin delivery. Likewise, Moghassemi et al.[27] prepared a niosomal NP containing Span 60, cholesterol and N-trimethyl chitosan. The efficiency of this NP delivery system was assessed in a Caco-2 cell monolayer, an intestinal membrane model. The prepared niosomes were 100-180 nm in size, and were stable for over 60 days; furthermore, insulin permeability through the intestinal membrane was enhanced 4-fold by niosomal NP in contrast to insulin alone. Indeed, niosomes appear to be a more desirable drug delivery system than liposomes due to their greater stability and relative cost.

Lastly, metallic NPs have shown great potential concerning DM treatment. Various trace elements have been linked with glucose homeostasis, such as zinc, selenium, silver and gold. It is well known that these metals are cofactors of biochemical reactions, meaning that this type of NP can have pleiotropic beyond insulin administration[28]. There is considerable evidence showing that zinc oxide NP have antioxidant properties[29]. Additionally, it was demonstrated that zinc oxide NP and silver NP exhibit a substantial hypoglycemic effect; however, it does not appear to be enough to achieve normoglycemia[30].

Regarding their drug transport capabilities, Zhou et al.[31] developed a biodegradable nanocomposite microsphere encapsulated with a metal-organic framework (MOF). Initially, an iron-based MOF-NP was synthesized as a carrier with an insulin entrapping capacity of 35%. Although the latter model enhanced the permeation across Caco-2 models, the NP was further optimized by embedding it into a biodegradable microsphere delivery system. This microsphere system effectively protected the MOF-NP from rapid acidic degradation while effectively releasing the insulin in the simulated intestinal fluid. After oral administration, increased insulin levels were detected compared to free insulin, leading to a remarkable glucose-lowering effect with a relative bioavailability of 7.8%. The authors concluded that MOF-NP incorporated into microspheres might provide a viable strategy for effective oral insulin delivery.

Consequently, Zou et al.[32] used acid-resistant MOF-NP (UiO-68-NH2) to encapsulate insulin and coated the exterior with targeting proteins (transferrin). This model effectively protected insulin against acid and enzymatic degradation. Insulin absorption was mediated by the transferrin receptor, yielding 30% bioavailability with an effective hypoglycemic effect. Despite the evidence shown, studies directly comparing different types of NP remain scarce. At present, metallic NP appear to show the best overall profile, although further research is required.

CONCLUSIONS

Significant advances have been made in the interest of achieving viable alternatives to administer insulin orally. Most of these advances are due to the implementation of nanotechnology to a variable extent. Different types of NP have been designed and produced, effectively achieving satisfying endpoints, like increasing insulin oral bioavailability, obtaining an excellent hypoglycemic effect, and sustaining an acceptable profile of side effects. A large amount of evidence supports the implementation of different drug delivery systems like liposomes, niosomes and metallic NP, and most of this evidence has given encouraging results indistinctly of the nature of the molecule. More quality research is advised to consolidate NP as delivery tools for insulin.

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