Formulation Development of Gliclazide & Glipizide Nanoparticle: A Comparative Systematic Review

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ABSTRACT

The use of nanoparticles (NPs) for the delivery of antidiabetic gliclazide and glipizide is elaborated in the systematic review of the literature. This systematic review presents a proper comparative examination of the development of nanoparticle formulations for gliclazide and glipizide, two sulphonyl urea medications used in the treatment of type 2 diabetes. Because of their potential to increase medication solubility, bioavailability, and grant sustained release, nanoparticle-based drug delivery systems have received a lot of interest. The review gives an overview of the pharmacological characteristics, mechanism of action, and therapeutic applications of gliclazide and glipizide. It then digs into the formulation creation of nanoparticles for these medications, detailing the materials, origin processes, and characterization techniques employed in the investigations.

Keywords: Nanoparticle Gliclazide, Glipizide, Targeted Drug Delivery, Bioavailability, Pharmacokinetic, Pharmacodynamics, Solubility.

INTRODUCTION

Gliclazide and glipizide, a second-generation sulfonylurea has antioxidant effects independent of its hypoglycemic activity [1]. It operates by inhibiting the ATP-dependent potassium channel [2]. This channel is made up of a receptor called the sulfonylurea receptor (SUR) and a subunit. They are detected in large concentrations in cardiac and smooth skeletal muscle [3]. Gliclazide is a Biopharmaceutical Classification System (BCS) class II medication (Campbell et al., 1991) with a low solubility rate [4]. Because of its poor and pH-dependent solubility, gliclazide has an irregular and sluggish absorption rate, which can result in considerable intra- and inter-individual differences in absorption following oral administration [4, 5]. The most prominent side effects of gliclazide include dermatological reactions, epigastric reactions, and biochemical anomalies such as increased serum levels. On the other hand, glipizide only at higher dose, it can inhibit insulin biosynthesis. It has some adverse effects like gastrointestinal reactions, skin reaction, weight gain, vertigo, vomiting, hematologic dysfunction etc. with advantageous pharmacokinetics properties. Nanoparticles are multifaceted drug delivery systems that attempt to achieve longer or controlled drug distribution, increase bioavailability, restrict volatility, and reduce dose frequency, among other things. A comprehensive review of nanoparticles for the transport of gliclazide and glipizide, two anti-diabetic drugs, to the body aims to evaluate and summarize previous research in this field. The review's goal is to provide a thorough analysis of the existing literature on the subject, covering everything from the techniques used to originate and characterize the nanoparticles to their pharmacokinetics and pharmacodynamics, as well as their effectiveness and security in various preclinical and clinical settings. The review may also explore the potential benefits and cons of using nanoparticles to deliver gliclazide and glipizide, as well as any knowledge gaps and opportunities for additional research.

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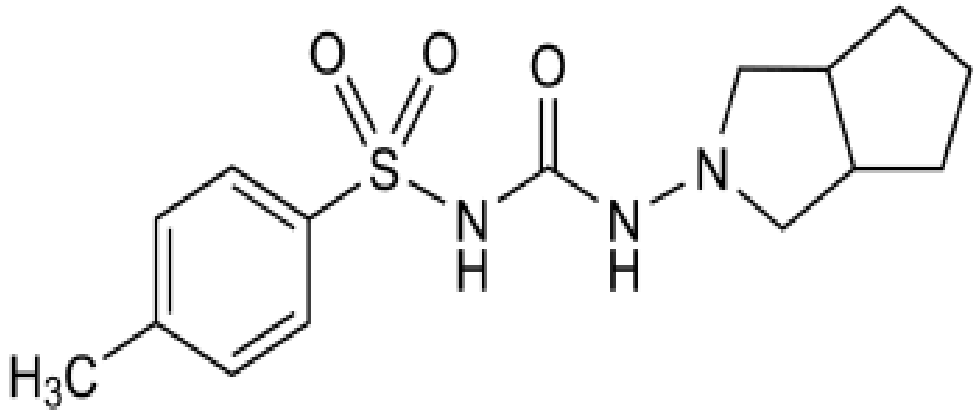

Fig (1): Chemical Structure of Gliclazide

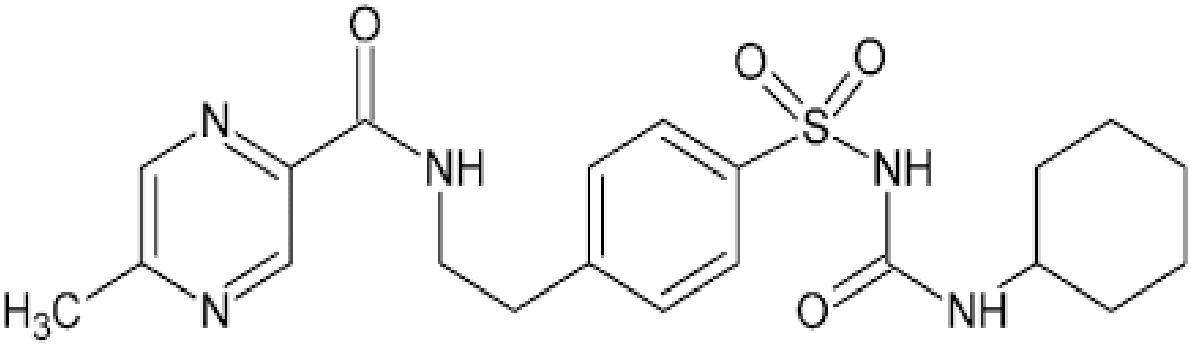

Fig (2): Chemical Structure of Glipizide

METHODOLOGY

We conducted systematic search up to August 2024 using four electronic databases including PubMed, Scopus, Google Scholar, WHO Global Health Library, Virtual Health Library, POPLINE, with the search term: (gliclazide (“pharmacokinetics” OR “Pharmacodynamics” OR “solid dispersion” OR [dispersion] OR “Concept of gliclazide” OR “evaluation of gliclazide”) OR “Toxicity of glipizide” OR “Glipizide” OR “Formulation of glipizide” OR “Antidiabetic activity of glipizide” with limit to human in PubMed, Google Scholar and Scopus. We performed a manual search to find more relevant papers via different means. The references of eligible articles were checked to retrieve supplementary information and records of potentially relevant studies and reports. Authors were contacted in order to get full texts, data clarification, and supplemental data if required.

DISCUSSION

Gliclazide and Glipizide Nanoparticle for Targeted Delivery:

Nanoparticles have a crucial function in medications, such as controlling variation within the therapeutic range, decreasing side effects, decreasing dose frequency, and enhancing patient compliance [6]. A targeted medication delivery system is primarily used to localize and extend treatment with sick tissue. There are several targeted delivery techniques available. The primary purpose for employing SLN is to reduce particle size; this enables for effective absorption in the colon by bypassing metabolism [7]. Electro spraying is another targeted delivery approach that is cost effective on an industrial scale. Preparation of Gliclazide Nanoparticles by Electro spraying Method and Evaluation of Their Physicochemical Properties, 2018. Cubosomes are nanostructured particles with bicontinuous cubic liquid crystalline phase that are employed for medications that are poorly water soluble [8]. The more the chitosan ratio, the more encapsulation. SLN gives better glycemic control over a longer period of time, proved to safe at doses equivalent. In electro spraying method no interaction between drug and polymers were observed. In vitro drug release studies revealed that the drug-release patterns were improved. In a trial to achieve this objective, gliclazide-loaded cubosomal nanoparticles were fabricated. Lypolization is a suitable technique. It shows higher rate and extent of gliclazide absorption.

Table-1: Gliclazide Nanoparticle for Targeted Delivery

First author & ref. no	Preparation methods	Route of administration	Formulation type+ Drug carrier/ Main excipient	Comments on GL NP for targeted delivery improvement
R. Averineni	Encapsulation	Intracellular	Gliclazide loaded chitosan nanoparticles	Having good stability, reduce side effects, avoid immunogenic reactions
A. Nazief	Ultra-sonication technique	Orally	Solid lipid nanoparticle with gliclazide nanoparticle	To improve bioavailability, to prevent toxicity
Solmaz Ghajar	Electro spraying method	Topical	using scanning electron microscopy (SEM). FTIR spectroscopy and X-Ray crystallography.	To evaluate physicochemical properties
M.R	Emulsification	Intraperitoneal	Cubosomal nanoparticles with poly angular particles	To improve oral absorption & antidiabetic activity
H. Mansour	Lypolization	Intraperitoneal	using drug solid dispersion in mannitol, sodium lauryl sulfate (SLS) or polyvinylpyrrolidone (PVP). differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FTIR)	Maintain good stability, ease of reconstitution

Nanoparticulate drug delivery systems (1-1000 nm) are typically designed for oral, parenteral, or topical administration, with the ultimate goal of altering the pharmacokinetic profile of the active chemical [9]. Nanoparticles have an important function in medications by restricting variation within the therapeutic range, reducing adverse effects, and decreasing dose frequency, among other things. Particle size may be controlled using the evaporation tactics and factorial design, and formulation design is used [10]. Alginate-chitosan nanoparticles (ACNP) are one of the most convenient controlled delivery systems for glipizide cause they release both the system's limiting properties and the polymers' bio adhesive nature, with characteristics such as particle size (PS), zeta potential (ZP), entrapment efficiency (EE%), loading percent (LP), and mean release time (MRT), among others.

Comparison between Gliclazide & Glipizide Nanoparticle for Targeted Delivery

Encapsulation, ultrasonication, electro spraying, emulsification, and lypolization are all ways used to originate gliclazide nanoparticles. Glipizide nanoparticles, on the other hand, are generated using processes such as evaporation, gelation, and emulsification solvent evaporation. Gliclazide nanoparticles can be ingested, orally, topically, or intraperitoneally. In contrast, glipizide nanoparticles can be delivered orally, intracellularly, or intraperitoneally. Gliclazide nanoparticles are created with a variety of carriers and excipients, including chitosan, solid lipid nanoparticles, cubosomes, and drug solid dispersions. Glipizide nanoparticles, on the other hand, are made with Eudragit RS100 polymer, alginate, chitosan, and polycaprolactone (PCL) as carriers. Gliclazide nanoparticles have showed advantages such as enhanced stability, fewer adverse effects, avoidance of immunogenic responses, improved oral absorption and antidiabetic efficacy, improved bioavailability, toxicity

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prevention, physicochemical property assessment, and simplicity of administration. Many factors influence the anti-diabetic effectiveness of gliclazide nanoparticle. When using the encapsulation approach, the more viscous the gliclazide solution, the wider the particle size dispersion. Cubosomes, nanostructured particles of bicontinuous cubic liquid crystalline phase, have advantages such as drug encapsulation and loading ability of hydrophilic and hydrophobic (APIs), easy fabrication processes, lipid biodegradability, and so on. Mucoadhesive microspheres filled with Macromolecular polymer formulations are quite clear and spherical, which is why it is utilized as an emulsification solvent by evaporation technique. To test drug-drug interactions, hydrochlorothiazide (HTZ), chlorothiazide (CTZ), benzamide (BZA), and other medicines are utilized [11].

Table-2: Characteristics studies of enhanced antidiabetic efficacy of Gliclazide Nanoparticle

First author & ref. no	**Preparation method**	**Route of administration**	**Formulation type+ Drug carrier/ Main excipient**	**Comments on enhanced antidiabetic efficacy of GL NP**
R. Averineni	Encapsulation	Intracellular	Gelatin of chitosan nanoparticle with sodium citrate	Viscosity prevents leaking droplets, reduce dose frequency, decrease side effects
M.R	Emulsification	Orally	Gliclazide loaded cubosome nanoparticle	Can be a potential carrier fo oral bioavailability and required more study on this
S. Shaikh	Evaporation	Orally	Mucoadhesive microspheres loaded with Macromolecular polymer	Have long systemic half-life; an ideal system in the sustained release manner for Type II Diabetes Mellitus
M. Aljohani	Drug-drug co-crystallization	Orally	Strongly basic conformer leading to salt formation in order to find drug drug interaction	Enhanced dissolution and stable in air

Many factors affect the antidiabetic efficacy of gliclazide nanoparticle. When using encapsulation method, the more viscous gliclazide solution, the wider particle size distribution. By using the single therapy, glipizide succeeded to establish some criteria for instance tolerance level, safety level, efficacy of short term etc. [12]. Recent pharmacoepidemiologic surveys show that the uses of antidiabetic drugs might influence cancer risk in type 2 diabetes mellitus; here glipizide can play a crucial role. It suppresses tumor growth, metastasis etc. [13]. Nanoparticulate drug delivery system (1-1000 nm) is usually intended for oral, parenteral or topical rout with the ultimate objective being the alteration of the pharmacokinetic profile of the active molecule [14]. Another method is evaporation method where drug loading, percentage entrapment efficiency, optimization etc. parameters are determined [15, 16, 17].

Table-3: Characteristics studies of enhanced antidiabetic efficacy of Glipizide Nanoparticle

First author & ref. no	**Preparation method**	**Route of administration**	**Formulation type+ Drug carrier/ Main excipient**	**Comments on enhanced antidiabetic efficacy of Glipizide nanoparticles**
I. De Leeuw	Single agent therapy	Orally	Four treatments-glipizide, glibenclamide, chlorpropamide or phenformin.	Tolerance seems better & side effects are negligible

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Cuiling Qi	High throughput screening	Orally	FDA approved drug library utilizing in vivo chick embryo chorioallantoic membrane (CAM) and yolk sac membrane (YSM) models	Inhibits angiogenesis by up-regulating NPRA expression in the vascular endothelial cells
A. Lokhande	Emulsification solvent evaporation	Intraperitoneal	Glipizide loaded PCL nanoparticle	To improve patient compliance
P. Saharan	Evaporation	Orally	glipizide nanoparticles integrated with Eudragit RS-100	Improving in drug encapsulation efficiency, modifying hysicochemical changes etc.

Gliclazide: Viscosity prevents leaking droplets, reduces dosing frequency, and decreases side effects. Gliclazide-loaded cubosomal nanoparticles show potential as carriers for oral bioavailability. Mucoadhesive microspheres have a long systemic half-life and are ideal for sustained release in Type II Diabetes Mellitus. Drug-drug co-crystallization enhances dissolution and stability. Glipizide: Tolerance seems better, and side effects are negligible. Glipizide suppresses tumor growth and metastasis, inhibiting angiogenesis. Glipizide-loaded nanoparticles improve patient compliance and show physicochemical changes [18, 19, 20].

Table-4: Comparison between Gliclazide & Glipizide Nanoparticle for Antidiabetic Efficacy

Basis of Comparison	**Gliclazide**	**Glipizide**
Preparation Method	Encapsulation, Emulsification, Evaporation, Drug-drug crystallization	Single agent therapy, High throughput screening, Emulsification, Evaporation
Route of Administration	Intracellular, Orally, Topical, Intraperitoneal	Orally, Intraperitoneal
Formulation type+ Drug Carrier/ Main Excipient	Gelatin of chitosan nanoparticle with sodium citrate Gliclazide loaded cuboisomal particles, Mucoadhesive microspheres loaded with Macromolecular polymer, strongly basic conformer leading to salt formation in order to find drug-drug interaction	Four treatments-glipizide, glibenclamide, chlorpropamide or phenformin, FDA approved drug library utilizing in vivo chick embryo chorioallantoic membrane (CAM) and yolk sac membrane (YSM) models, Glipizide loaded nanoparticle, glipizide nanoparticles integrated with Eudragit RS-100
Comments	Viscosity prevents leaking droplets, reduce dose frequency, decrease side effects, can be a potential carrier for oral bioavailability and required more study on this, Have long systemic half-life; an ideal system in the sustained release manner for Type II Diabetes Mellitus, Enhanced dissolution and stable in air	Tolerance seems better & side effects are negligible, to improve patient compliance, physicochemical change, Inhibits angiogenesis by up-regulating NPRA expression in the vascular endothelial cells
First Author & ref.	R. Averineni, M. R, S. Shaikh, H. Mansour, M. Aljohani	I. De Leeuw , Cuiling Qi, P. Saharan, A.Lokhande

Characteristics studies of controlled release of Gliclazide and Glipizide by Nanocarriers by Gliclazide and Glipizide Nanoparticle:

Gliclazide and glipizide are two medications used to treat diabetes. The initial aim to employing SLN is to lessen particle size; this qualifies for effective absorption in the colon by bypassing metabolism [21, 22, 23, 24, 25]. The only way to tell whether using nanoparticles is helpful or bad is to look at their toxicity level. The toxicity level of a medicine can enacts its safety level. The exercise of the solvent evaporation process with glipizide-loaded nanoparticles assures that no toxicity is emanated, hence ensuring the safety profile [26, 27, 28].

CONCLUSION

We searched several elements of Gliclazide and Glipizide nanoparticle formulation development for diabetic treatment. Gliclazide and Glipizide are both thoroughly used diabetic medications, and the preface of nanoparticles provides interesting possibilities for improving their therapeutic efficacy. Encapsulation, emulsification, evaporation, and drug-drug co-crystallization are all procedures used in the formulation creation of Gliclazide and Glipizide nanoparticles. These methods permit for the creation of nanoparticles with controlled release features, increased bioavailability, and targeted drug delivery. As carriers for these antidiabetic medicines, many nanoparticles have been viewed, including solid lipid nanoparticles, cubosomes, mucoadhesive microspheres, and polymeric nanoparticles. The most common methods of administration for Gliclazide and Glipizide nanoparticles are oral and intraperitoneal. These nanocarriers have the potential to increase patient adherence.

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