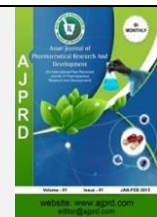


Available online on 15.04.2026 at <http://ajprd.com>

# Asian Journal of Pharmaceutical Research and Development

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Case Study

## Chitosan-Based Nanocarrier Systems for Enhanced Antidiabetic Activity of Linagliptin: A Review

**Barewar Gauri\*, Padole Nitin, Dhapke Pankaj, Dhoble Nilakshi, Baheti Jagdish**

Kamla Nehru College of Pharmacy, Butibori Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur (Maharashtra) India

### ABSTRACT

Diabetes mellitus, particularly Type 2 diabetes mellitus (T2DM), remains a major global health challenge due to persistent hyperglycemia, progressive  $\beta$ -cell dysfunction, and limitations of conventional oral therapies. Linagliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, offers effective glycemic control with minimal risk of hypoglycemia and weight gain; However, its therapeutic potential is restricted by low oral bioavailability caused by poor intestinal permeability, P-glycoprotein efflux, and first-pass metabolism. Chitosan-based nanocarrier systems have emerged as promising strategies to overcome these barriers. Chitosan, a biodegradable, biocompatible, and Mucoadhesive polymer, enhances drug absorption, protects against enzymatic degradation, and provides sustained drug release. Various preparation methods, including ionic gelation, polyelectrolytic complexation, and emulsification-solvent evaporation, have been utilized to develop efficient linagliptin-loaded nanocarriers with improved encapsulation efficiency and controlled release profiles. These advanced delivery systems significantly improve linagliptin's bioavailability, therapeutic efficacy, and patient compliance while reducing dosing frequency and systemic side effects. Additionally, targeted delivery approaches further optimize antidiabetic outcomes. This review highlights the formulation strategies, mechanisms, and therapeutic advantages of chitosan-based linagliptin nanocarriers, emphasizing their potential as innovative platforms for enhanced diabetes management and future clinical application.

**Keywords:** Chitosan Nanocarriers, Linagliptin, Type 2 Diabetes Mellitus, Drug Delivery System, Enhanced Bioavailability**ARTICLE INFO:** Received 17 Dec.2025; Review Complete 21 Jan, 2026; Accepted 22 Feb. 2026; Available online 15 April. 2026**Cite this article as:**

Barewar G, Padole N, Dhapke P, Dhoble N, Baheti J, Chitosan-Based Nanocarrier Systems for Enhanced Antidiabetic Activity of Linagliptin: A Review, Asian Journal of Pharmaceutical Research and Development. 2026; 14(2):203-207, DOI: <http://dx.doi.org/10.22270/ajprd.v14i2.1601>

\*Address for Correspondence:

Nitin Padole, Kamla Nehru College of Pharmacy, Butibori Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur (Maharashtra) India

### INTRODUCTION

Diabetes Mellitus (DM) is an ongoing metabolic disorder characterized by insulin resistance, inadequate secretion of insulin, and prolonged high levels of blood glucose in people who suffer from diabetes around the world. Many people living with T2DM fail to achieve glycemic control due to the progressive decline in  $\beta$ -cell function and due to the limitations of existing oral medications, including episodes of low blood sugar, weight gain, unwanted gastrointestinal side effects, and the need to take multiple oral medication or insulin therapy (1).

Type 2 diabetes mellitus accounts for the majority of diabetes cases worldwide. Type II diabetes makes up more than 90% of total diabetes prevalence. Diabetes mellitus is a long-term

condition characterized by persistent elevated blood sugar levels as a result of insufficient insulin production by the pancreas (insulin deficiency) combined with an inability to properly use insulin (insulin resistance) (2,3).

Diabetes mellitus is one of the five leading causes of death internationally and in 2021 there were approximately 537 million individuals affected by diabetes (according to WHO GHO 2021). It is widely anticipated that diabetes prevalence will continue to grow over the next several years due to the lifestyles of most individuals (4, 42).

#### Challenges in current oral antidiabetic therapy

Type 2 diabetes mellitus is very common and associated with obesity and lifestyle, and has serious complications (micro-

vascular and macro-vascular) such as cardiovascular disease, renal failure, blindness (5, 35).

Patients on standard oral antidiabetic agents (metformin, sulfonylureas, thiazolidinediones, etc.) can develop hypoglycemia, gain weight, have gastrointestinal side effects and lose response to treatment as the function of beta cells diminishes over time. Dipeptidyl peptidase IV (DPP-4) Inhibitors (gliptins, e.g. Linagliptin) are associated with effective, weight-neutral glycemic control and a very low incidence of hypoglycemia; nonetheless, their cost and long-term durability are still a concern (6).

### Introduction to Linagliptin

Linagliptin is an effective and specific inhibitor of DPP-4; as a result, linagliptin promotes the action of incretin hormones GLP-1 and GIP, resulting in decreased blood glucose levels during fasting and after meals. Hypoglycemia occurs infrequently during linagliptin treatment, and it does not cause any change in body weight (7).

Linagliptin exhibits non-linear pharmacokinetics with approximately 30% oral bioavailability; distributes widely to different body tissues; undergoes elimination mainly by non-renal routes; and may be administered at a fixed dose of 5 mg once daily regardless of renal or liver impairment (8).

Linagliptin, classified as a BCS class III drug, exhibits high solubility but low ability to cross cell membranes. It is also a substrate for P-glycoprotein (P-gp), which leads to intestinal efflux of linagliptin and reduced bioavailability of ~29 - 30%. The effects of first pass, the efflux of linagliptin via P-gp, and the intestinal degradation of linagliptin all lead to reduced exposure, which can affect efficacy or lead to increased frequency or higher doses of linagliptin (9).

### Chitosan-Based Nanocarriers for Linagliptin

Chitosan is a natural biopolymer with anti-allergy properties, biocompatibility, is biodegradable, has low toxicity and has mucoadhesive characteristics. It is also straight forward to modify chemically (10, 36).

### In diabetes treatment:

- Chitosan nanoparticles or nanocapsules can protect peptides (e.g., liraglutide) from digestion and provide sustained release over time due to their resistance to degradation in the GI tract (11).
- The Mucoadhesive properties of these nanoparticles or nanocapsules allow them to adhere well to the intestinal lining and thereby improving absorption from the intestine and oral cavity (12).
- Chitosan may be used as a flexible matrix to develop co-delivery systems of hypoglycemic drug combinations along with an antioxidant agent (e.g., pioglitazone + curcumin) that can address hyperglycemia, oxidative stress, and their complications at the same time (13, 39).
- Chitosan may either directly contribute to or assist in the production of environmentally friendly, natural nanostructures with the potential to prevent damage to  $\beta$ -cells of the pancreas, reduce blood glucose levels, and enhance the delivery of insulin, GLP-1, exendin-4, DPP-4 inhibitors, and genetic therapies (10,12).

### Techniques for Preparation

**Ionic gelation (cross-linking with Tripolyphosphate):** Dissolve cationic chitosan in an aqueous solution containing anionic Tripolyphosphate and allow nanoparticle formation through spontaneous assembly and preparation using microfluidics, generally used to fabricate peptide or protein-containing nanoparticles (14).

**Polyelectrolytic complexation:** Chitosan with anionic or cationic polymers (such as alginate or carrageenan) or form colloidal polyelectrolyte complexes for encapsulation of drugs at low temperatures (15).

### Emulsification-solvent evaporation / nanoemulsions:

Create nanocapsules or PLGA/Chitosan hybrids using water-in-oil or multiple emulsions containing chitosan in the aqueous phase; this method allows for high loading and controlled release (15).

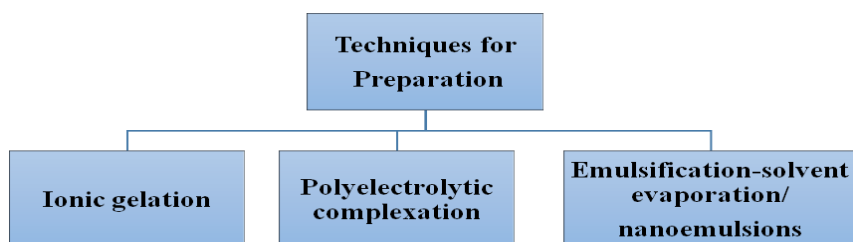


Figure: 1 Techniques for preparation of chitosan formulations.

### Methods of Drug Entrapment

Achieving optimum Encapsulation Efficiency

Chitosan Nanoparticles (NP's) have less than 10-20% drug entrapment efficiency particularly for hydrophobic drugs (16, 41).

### Methods of improving loading include:

Emulsion-based nanocapsules with high drug loading efficiencies (17).

Hybrid systems, such as chitosan coated alginate NPs, inside PLGA microcapsules increasing hydrophilic drug loading and reducing burst release (18, 43).

Optimising ratios of polymer: drug ratios, pH and degree of crosslinking; use of Design of Experiments for linagliptin nanosuspension (36% drug loading; 96% Encapsulation Efficiency) and PLGA-chitosan NPs (89% Encapsulation Efficiency) (19).

### Mechanism of Enhanced Antidiabetic Activity

#### Improved Solubility and Dissolution

- Drugs that are poorly soluble (like curcumin and some orally administered drugs) can exhibit more pronounced antidiabetic properties in the form of nanosuspensions, micelles, or other nanoforms because these enhancements increase surface area, solubility, and the amount of drug uptake into cells. In addition to resulting in better blood glucose control, these enhancements may also produce improved metabolic markers (20).
- Another means of enhancing the solubility and stability of bioactive compounds (such as hesperidin or polyphenols) is through their encapsulation within nanocarriers, which provides enhanced antidiabetic activity (21).

#### Enhanced Intestinal Absorption via Mucoadhesion

- Chitosan and its derivatives (trimethyl, thiolated, PEG-conjugated, alginate-coated) bind to negatively charged mucosa, thus increasing the duration of contact with the epithelium and extending drug residence time (21).
- These systems induce openings (tight junctions), allowing paracellular transport of insulin and peptide products, resulting in an increase in plasma insulin levels and the duration of effect in vivo (22).
- Mucoadhesive buccal or intestinal films and nanoparticles (metformin buccal CS-NPs, for example) provide mucoadhesion and permeability enhancement to provide a route to bypass first-pass metabolism and increase drug bioavailability (23).

#### Sustained / Controlled Drug Release

- A number of nanomaterials (including PLGA, chitosan, alginate, porous silicon/polymer matrixes, and niosomes) have been found to be produced which can be used to achieve the pH-responsive and timed-release of drugs. These materials may release insulin or peptides through a biphasic pattern (i.e., both an initial and a sustained phase) or can be used for an extended release of oral medication for 12 to 14 hours, etc. (24, 38).
- Sustained intestinal delivery of antidiabetic peptides (i.e., RPP's from rapeseed, GLP-1, exenatide, etc.) improves glucose tolerance, raises levels of GLP-1, and enhances the duration of the hypoglycemic response in appropriate animal models (25).

#### Protection from Enzymatic Degradation

- Insulin and peptide encasement in chitosan, alginate, PLGA, or pH-sensitive matrices protects against acid and proteolytic enzymes. This provides significantly increased stability and bioavailability by mouth (26).
- Combination peptide + dipeptidyl-peptidase IV (DPP-IV) inhibitor dual systems in a multiphase nanocarrier protect GLP-1 from enzymatic degradation while improving permeability and providing additive antidiabetic activity in vitro (27).

#### Targeted Delivery Potential

- Surface ligands (folic acid, hyaluronic acid, vitamin B12) and polymers (fucoidan) facilitate receptor-mediated uptake or tissue targeting (intestinal receptors, CD44, folate receptors) resulting in higher concentrations of drug delivered locally and thus increased efficacy (28,37).

Some carriers deliver insulin/peptides with intrinsic antidiabetic activity (fucoidan has hypoglycaemic effect, hesperidin, polyphenols) and therefore provide multifunctional platforms that will address glucose, oxidative stress and their complications simultaneously (12, 21).

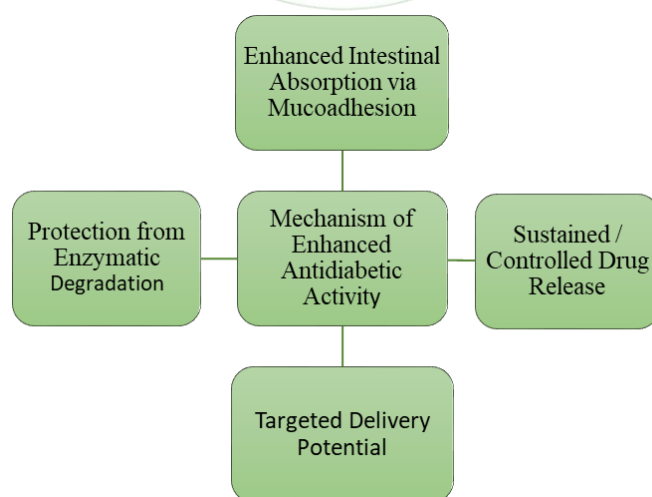


Figure: 2 Mechanism of enhanced antidiabetic activity

### Advantages of Chitosan-Based Linagliptin Delivery

#### Improved Bioavailability

- Linagliptin nanocarrier delivery via buccal chitosan platforms (cubosomes or multi-layered nanosponge

forms) provided an approximate increase of 2-fold in linagliptin AUC after administration to humans; thereby significantly improving systemic exposure relative to standard formulations (29, 40).

- The intranasal cationic chitosan-coated linagliptin nanosuspension achieved nearly complete entrapment (~96%), high drug loading (~36%) and significant increases in solubility, dissolution, and *ex vivo* permeation compared to uncoated linagliptin; therefore, making them suitable for reduced dosing frequency (30).
- Chitosan nanoparticles can also improve oral bioavailability of various compounds (typically by 2–3.5 fold), as they enhance absorption and protect against degradation during transit through the GI tract (31).

### Reduced Dosing Frequency

- Platforms utilizing chitosan often achieve prolonged or controlled release, while CNPs have shown longer retention in both the stomach and intestines after sustained drug release; therefore, they greatly benefit bioavailability by decreasing the number of times that a patient has to take medication (32).
- Chitosan-modified PLGA linagliptin nanoparticles exhibited a clear first burst followed by 3 days of prolonged release - strong evidence of the ability to decrease the frequency of dosing (using a topical type model) (19).

### Enhanced Therapeutic Efficacy

- The combination of chitosan-PVP buccal cubosomes containing the drugs linagliptin and empagliflozin resulted in increased area under the curves (AUCs) for both drugs (linagliptin: 2x; and empagliflozin: 3x) and was suggested to enhance their clinical efficacy in controlling diabetes (33).
- Multilayer nanosponge used to develop chitosan buccal films had similar effects with linagliptin exposure being double, and up to 10x higher for empagliflozin, as these products were designed to maximize dose efficiencies through improved clinical efficacies (29).
- Chitosan nanoparticles (NPs) generally result in enhanced stability, targeting, and cellular interaction, thereby providing higher therapeutic efficiencies with lower doses (17).

### Reduced Side Effects

- The purpose of this research was to enhance the therapeutic effect of the intranasal chitosan-linagliptin nanosuspension while simultaneously aiming to decrease the dose and therefore side effects associated with the use of linagliptin; however, the cognitive effects were also sought to be improved upon as well (30).
- Chitosan nanocarriers have been reported in reviews to allow a decreased therapeutic dose and more localised delivery, which has been associated with reduced systemic adverse effects and improved safety profiles (34).

### CONCLUSION

Chitosan-based nanocarrier systems represent a highly promising advancement in the delivery of linagliptin for the management of Type 2 diabetes mellitus. By addressing the major limitations of conventional linagliptin therapy,

including low bioavailability, poor permeability, and rapid drug degradation, these nanocarriers significantly enhance therapeutic performance. The unique properties of chitosan, such as biocompatibility, biodegradability, mucoadhesion, and controlled-release capability, make it an ideal polymer for developing efficient drug delivery platforms. Through improved intestinal absorption, sustained release, protection from enzymatic degradation, and potential targeted delivery, chitosan formulations can increase drug efficacy, reduce dosing frequency, and minimize adverse effects. Current research highlights their ability to optimize glycemic control while improving patient compliance. Although further large-scale clinical studies are required to confirm long-term safety, efficacy, and commercialization potential, chitosan-based linagliptin nanocarriers offer a novel and effective strategy for future antidiabetic therapy, with strong potential to transform diabetes management through enhanced oral and alternative drug delivery approaches.

**Acknowledgments:** Authors are thankful to Principal Kamla Nehru College of Pharmacy Butibori for providing research facilities.

**Conflicts of interest:** Authors don't have conflicts of interest.

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