International Journal of Pharmaceutical Research and Applications
Volume 11, Issue 1 Jan - Feb 2026, pp: 01-09 www.ijprajournal.com ISSN: 2456-4494

Formulation and Evaluation of Mucoadhesive Microspheres of Nateglinide with Resin Complex for Treatment of Diabetes

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Date of Submission: 01-01-2026 Date of Acceptance: 08-01-2026

ABSTRACT
Diabetes mellitus is a long-term metabolic disease that causes high blood sugar levels because the body doesn't make enough insulin, doesn't use it properly, or both. Nateglinide, a short-acting oral antidiabetic drug from the meglitinide class, is commonly employed in the treatment of type 2 diabetes mellitus. But because it has a short biological half-life and is quickly absorbed, it needs to be given often, which makes it hard for patients to follow the instructions. Mucoadhesive microspheres have become a potential way to deliver drugs that can increase the duration they stay in the stomach, make them more bioavailable, and keep them in the body for a longer period of time. Adding ion-exchange resins makes the medicine even more stable, masks the taste, and controls the release. This review looks at the formulation strategies, preparation methods, assessment criteria, and therapeutic potential of mucoadhesive microspheres of nateglinide made with resin complexes. There is also a focus on how mucoadhesive polymers and ion-exchange resins can make diabetes treatment better.

Keywords: Nateglinide, mucoadhesive microspheres, ion-exchange resin, diabetes mellitus, controlled drug delivery.

I. INTRODUCTION

Diabetes mellitus is a long-term, progressive metabolic condition that causes high blood sugar levels because of problems with insulin secretion, insulin action, or both. Due to a lack of exercise, being overweight, eating poorly, and having a family history of diabetes, the disease is becoming more common around the world(1). Type 2 diabetes mellitus (T2DM) represents the predominant form of diabetes and is linked to serious long-term consequences, including cardiovascular illnesses, nephropathy, neuropathy, and retinopathy, which markedly diminish quality of life and escalate healthcare demands(2).Controlling blood sugar levels well is still the most important part of treating T2DM. Oral hypoglycemic medications are generally chosen over injectable therapy because they are more convenient and easier for patients to accept. Insulin secretagogues are very important for regulating high blood sugar after meals. Nateglinide, a second-generation meglitinide derivative, is a fast-acting insulin secretagogue that makes pancreatic β-cells release insulin by inhibiting ATP-dependent potassium channels. Because it works quickly, it is especially good at keeping blood sugar levels stable after meals(3).

Nateglinide has some pharmacokinetic problems, such as a short biological half-life, quick absorption, and a lot of first-pass metabolism, even if it has therapeutic benefits. Because of these reasons, patients need to take the medicine often, which might cause plasma drug levels to change and make it hard for patients to stick to their treatment plan(4). Also, standard immediate-release formulations don't keep plasma concentrations high for lengthy periods of time, which makes it harder to control blood sugar levels over the long run(5).Researchers have looked into new ways to administer pharmaceuticals to improve the bioavailability and effectiveness of antidiabetic drugs in order to get around these problems. People are particularly interested in mucoadhesive drug delivery systems because they can stick to the mucosal surfaces of the gastrointestinal tract(6). This makes the drug stay in the stomach longer and helps it get absorbed better. Mucoadhesive systems can provide continuous and controlled medication release, lower the number of doses needed, and make it easier for patients to follow their treatment by staying close to the mucosa.Microspheres are a more advanced way to administer drugs in small particles that has many benefits over single-unit systems. Mucoadhesive microspheres, made from natural or synthetic polymers, offer the best of both worlds: regulated release and long-lasting adhesion to mucous membranes(7). These methods cut down on dose dumping, make medication effects more consistent amongst people, and improve the therapeutic effects of medicines with short half-lives, like nateglinide.

The use of ion-exchange resins in pharmaceutical formulations has become a useful way to manage how drugs are delivered in the past several years. Ion-exchange resins are polymers that are not soluble and are connected together in such a way that they can form reversible complexes with medicinal molecules that have opposite charges(8). Making drug–resin complexes not only makes drugs more stable and masks their flavor, but it also lets you change how quickly they are released. Adding nateglinide–resin complexes to mucoadhesive microspheres makes drug release last longer and stops it from happening too soon in the gastrointestinal tract(9).Consequently, the development of mucoadhesive microspheres of nateglinide utilizing ion-exchange resin complexes signifies a viable strategy for enhancing oral antidiabetic treatment. This review is to thoroughly examine the formulation strategies, polymer and resin selection, preparation methodologies, and assessment criteria of nateglinide mucoadhesive microspheres. The paper also talks about how this innovative drug delivery system could help treat diabetes mellitus and what the future holds for it(10).

II. NATEGLINIDE: DRUG PROFILE

Nateglinide is an oral antidiabetic medication from the meglitinide class, mainly utilized for the treatment of type 2 diabetes mellitus. It is a short-acting insulin secretagogue that works quickly and efficiently reduces high blood sugar after meals. Nateglinide is widely administered either alone or with additional antidiabetic drugs because it is safe and has a low risk of sustained hypoglycaemia(11).

2.1 Chemical Structure and Physicochemical Properties

The chemical name for Nateglinide is N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine. It is a molecule that is weakly acidic, loves fats, and doesn't dissolve well in water. This affects how well it is absorbed and how available it is in the body. The medicine comes in the form of a white to off-white crystalline powder and stays stable when stored normally.Key physicochemical properties including molecular weight, pKa, and partition coefficient have a big impact on how it behaves in formulations. Nateglinide's lipophilic properties make it easy for the body to absorb it quickly through the stomach, but they also make the amount of medicine in the blood vary. These characteristics require formulation solutions capable of regulating drug release and sustaining therapeutic plasma concentrations for an extended duration(12).

2.2 Mechanism of Action

Nateglinide works as an antidiabetic by making pancreatic β-cells release more insulin. It binds only to the sulfonylurea receptor (SUR1) that is linked to ATP-sensitive potassium (K_ATP) channels on the membranes of β-cells. These binding closes potassium channels, which depolarizes the membrane and opens voltage-gated calcium channels.The entry of calcium ions causes insulin-containing granules to exocytose, which quickly releases insulin. Nateglinide works quickly and for a short time, unlike sulfonylureas, which makes it very similar to how the body naturally releases insulin. This makes it especially good at keeping blood sugar levels stable after meals and lowering the risk of long-term low blood sugar(13).

2.3 Pharmacokinetics

Nateglinide is quickly absorbed when taken by mouth, reaching its highest plasma levels in 1 to 2 hours. The medicine has a moderate amount of bioavailability when taken by mouth since it goes through a lot of first-pass hepatic metabolism(14). It is very tightly attached to plasma proteins, mostly albumin, which affects how it is spread and how it is removed(15).The liver breaks down the medicine a lot, mostly via cytochrome P450 enzymes, especially CYP2C9 and CYP3A4. The metabolites do not have any pharmacological effects and are mostly removed from the body through urine and faeces(16). Nateglinide has a short half-life of about 1.5 to 2 hours;thus, it needs to be taken numerous times a day to keep blood sugar levels under control(17).

2.4 Pharmacodynamics

Nateglinide works pharmacodynamically by lowering blood sugar levels after meals by increasing insulin secretion in the early phase. Its glucose-dependent insulinotropic effect lowers the risk of hypoglycemia, especially when compared to long-acting insulin secretagogues. The medication exhibits negligible impact on fasting blood glucose levels, rendering it especially appropriates for patients with major postprandial hyperglycemia(17).

2.5 Therapeutic Applications

Nateglinide is mostly used to treat type 2 diabetes mellitus, especially in people who can't get their blood sugar levels under control with just diet and exercise. It is often taken alongside metformin or thiazolidinediones to improve overall glycemic control.Because it works quickly and may be taken at any time, the medicine is especially helpful for older people and people who don't eat regularly. Because it doesn't last long, it lowers the risk of late-night or postprandial hypoglycemia(18).

2.6 Adverse Effects and Safety Profile

People usually tolerate nateglinide well, and it has a good safety record. Mild hypoglycemia, dizziness, headache, and stomach problems are the most common side effects that people report(19). Compared to sulfonylureas, the danger of severe hypoglycemia is much lower because it works quickly and only when there is glucose present.Long-term studies have shown that there are very few effects on body weight and risk factors for heart disease. However, people with liver problems should be careful because their liver metabolism is very high(20).

2.7 Limitations of Conventional Nateglinide Therapy

Even though it has certain clinical benefits, traditional oral forms of nateglinide have a number of problems:
1. Short biological half-life necessitating repeated administration.
2. Fast systemic clearance that causes plasma medication levels to change.
3. Poor patient compliance because they have to take many dosages every day.
4. Limited ability to keep blood sugar levels stable over time.

These problems show how important it is to have more advanced medication delivery methods that can make drugs last longer and work better(21).

2.8 Rationale for Developing Novel Drug Delivery Systems for Nateglinide

Researchers have looked for new ways to administer drugs, including mucoadhesive microspheres, to get around the pharmacokinetic and therapeutic problems with traditional formulations. Using ion-exchange resin complexes to add nateglinide to mucoadhesive microspheres can increase stomach retention, offer sustained medication release, and improve bioavailability. This technique looks like a good way to get better control of blood sugar levels with fewer doses(21,22). The mucoadhesive production flowchart was showed in **Fig 1.**

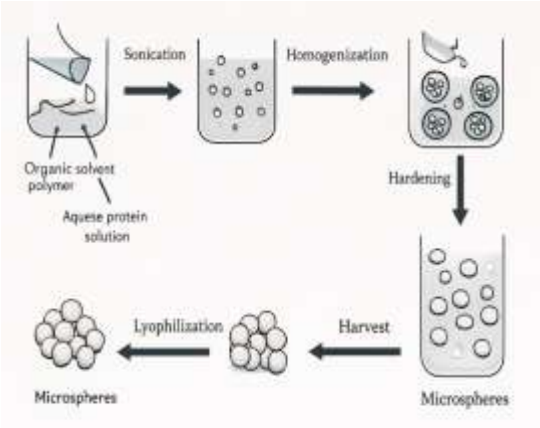

Fig 1: Microsphere Production Process Flowchart

III. MUCOADHESIVE DRUG DELIVERY SYSTEMS

3.1 Concept of Mucoadhesion

MDDS, or mucoadhesive drug delivery systems, are innovative pharmaceutical formulations that are made to stick to the body's mucosal surfaces for a long time. These systems increase the amount of time that drugs stay at the site of absorption, which makes them more bioavailable and effective. In the last few decades, mucoadhesive systems have gotten a lot of attention as a good way to administer medications orally that have short biological half-lives, small absorption windows, or low bioavailability, such nateglinide(22).

3.1 Concept of Mucoadhesion

Mucoadhesion is when a drug delivery device sticks to the mucus layer or epithelial surface of a mucosal tissue. This happens because of different physicochemical interactions between the polymer and the mucin layer, including as hydrogen bonding, electrostatic attraction, van der Waals forces, and physical entanglement(23).The stomach and upper intestines are the best places for mucoadhesive medication administration because they are part of the gastrointestinal system. Adhering to the gastric mucosa increases the duration the drug stays in the stomach, reduces drug loss from peristalsis, and lets the drug be released in a regulated way at the absorption site(24).

3.2 Stages of Mucoadhesion

The mucoadhesion process generally occurs in two main stages**:**

1. **ContactStage:** During this stage, the mucoadhesive system comes into close contact with the mucosal surface due to wetting and swelling of the polymer(25).
2. **Consolidation Stage:** This stage involves the formation of strong adhesive bonds between the polymer and mucin through interpenetration of polymer chains and secondary chemical interactions(26).

3.3 Theories of Mucoadhesion

Several theories have been proposed to explain the mechanism of mucoadhesion:

- **Wetting Theory:** Describes the ability of a polymer to spread and penetrate into the mucus layer.
- **Diffusion Theory:** Explains the interpenetration of polymer chains with mucin chains.
- **Electronic Theory:** Involves electron transfer between mucosal surface and polymer.
- **Adsorption Theory:** Attributes adhesion to secondary bonding forces.
- **Mechanical Theory:** Suggests physical interlocking of polymer into mucus structure(26).

3.4 Advantages of Mucoadhesive Drug Delivery Systems

Mucoadhesive systems offer several advantages over conventional oral dosage forms:

- Prolonged residence time at absorption site
- Sustained and controlled drug release
- Improved oral bioavailability
- Reduced dosing frequency
- Enhanced patient compliance
- Minimized drug degradation in GI tract
- Improved therapeutic efficacy

3.5 Limitations of Mucoadhesive Drug Delivery Systems

Despite their advantages, mucoadhesive systems also have certain limitations:

- Variability in mucus turnover
- Possible irritation to mucosal tissue
- Dependence on hydration and pH
- Limited effectiveness for drugs requiring systemic rapid action

3.6 Mucoadhesive Polymers

Mucoadhesive polymers play a critical role in determining the performance of MDDS. These polymers possess functional groups capable of forming strong interactions with mucin(27).

3.6.1 Natural Polymers

- Chitosan
- Sodium alginate
- Xanthan gum
- Guar gum

3.6.2 Synthetic and Semi-synthetic Polymers

- Carbopol
- Hydroxypropyl methylcellulose (HPMC)
- Polyvinyl alcohol
- Polyacrylic acid

3.7 Factors Affecting Mucoadhesion

Several formulation and physiological factors influence mucoadhesion:

- Polymer molecular weight and concentration
- Degree of cross-linking
- Swelling behavior
- Environmental pH
- Mucus thickness and turnover rate

3.8 Applications of Mucoadhesive Drug Delivery Systems

Mucoadhesive systems have been widely explored for various routes of administration, including:

- Oral
- Buccal
- Nasal
- Vaginal
- Rectal
- Ocular

In oral drug delivery, mucoadhesive microspheres are particularly beneficial for drugs like nateglinide, which require prolonged gastric retention for sustained absorption(28,29).

3.9 Role of Mucoadhesive Systems in Diabetes Management

For antidiabetic drugs, mucoadhesive drug delivery systems provide improved glycemic control by maintaining consistent drug levels in the systemic circulation. By reducing dosing frequency and minimizing plasma fluctuations, these systems enhance patient adherence and therapeutic outcomes(30,31).

3.10 Relevance of Mucoadhesive Microspheres for Nateglinide

The application of mucoadhesive microspheres for nateglinide delivery addresses the major limitations of conventional therapy. The combination of mucoadhesive polymers with ion-exchange resin complexes ensures sustained drug release, enhanced stability, and improved bioavailability, making it a promising strategy for effective diabetes management(32).

IV. MICROSPHERES AS DRUG DELIVERY SYSTEMS

Microspheres are spherical, free-flowing particles typically ranging from 1 to 1000 µm in size. When formulated with mucoadhesive polymers, they can adhere to the gastrointestinal mucosa and release the drug in a controlled manner(33).

Table 1. Ion-Exchange Resins Used in Drug Delivery Systems

S. No.	Resin Name	Functional Group	Nature of Resin	Ionic Charge	Pharmaceutical Application	Reference
1	Indion 234	Carboxylic acid	Weak cation exchanger	Negative	Sustained drug release	(34)
2	Indion 204	Carboxylic acid	Weak cation exchanger	Negative	Taste masking	(34)
3	Indion 244	Carboxylic acid	Weak cation exchanger	Negative	Controlled drug delivery	(35)
4	Amberlite IRP 64	Carboxylate	Weak cation exchanger	Negative	Sustained release formulations	(35)
5	Amberlite IRP 69	Sulfonate	Strong cation exchanger	Negative	Controlled release	(36)
6	Dowex 50WX8	Sulfonic acid	Strong cation exchanger	Negative	Drug–resin complexation	(36)
7	Kyron T-134	Carboxyl group	Weak cation exchanger	Negative	Taste masking and stability	(37)
8	Kyron T-154	Carboxyl group	Weak cation exchanger	Negative	Sustained drug release	(37)
9	Tulsion 335	Sulfonic acid	Strong cation exchanger	Negative	Extended-release formulations	(38)
10	Tulsion 344	Carboxylic acid	Weak cation exchanger	Negative	Controlled release	(38)
11	Cholestyramine	Quaternary ammonium	Strong anion exchanger	Positive	Drug binding and sustained release	(39)
12	Colestipol	Quaternary amine	Strong anion exchanger	Positive	Drug complexation	(39)

4.1 Types of Microspheres

- Bioadhesive microspheres
- Floating microspheres
- Magnetic microspheres
- Polymer-based microspheres

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V. ION-EXCHANGE RESIN COMPLEXES

5.1 Ion-Exchange Resins

Ion-exchange resins are insoluble, cross-linked polymers capable of exchanging ions with surrounding media. They are commonly used to form drug-resin complexes (resinates)(39).

5.2 Advantages of Drug-Resin Complexation

- Controlled drug release
- Improved drug stability
- Taste masking
- Reduction in dose dumping
- Enhanced formulation flexibility

5.3 Nateglinide–Resin Complex

Complexation of nateglinide with suitable ion-exchange resins helps in modulating drug release and protecting the drug from premature degradation in the gastrointestinal tract(40).

VI. FORMULATION OF MUCOADHESIVE MICROSPHERES OF NATEGLINIDE

6.1 Selection of Polymers

Commonly used mucoadhesive polymers include:

- Chitosan
- Sodium alginate
- Carbopol
- Hydroxypropyl methylcellulose (HPMC)

6.2 Preparation Methods

- Emulsion solvent evaporation
- Ionic gelation technique
- Spray drying
- Coacervation phase separation

The drug-resin complex is incorporated into the polymeric matrix to form mucoadhesive microspheres(41).

VII. EVALUATION OF MUCOADHESIVE MICROSPHERES

7.1 Particle Size and Morphology

Particle size analysis is carried out using optical microscopy or laser diffraction, while surface morphology is studied using scanning electron microscopy (SEM)(42).

7.2 Drug Entrapment Efficiency

Entrapment efficiency determines the amount of drug successfully incorporated into the microspheres(43).

7.3 Mucoadhesive Strength

Mucoadhesive properties are evaluated using in vitro wash-off or texture analyzer methods(44,45).

7.4 In Vitro Drug Release Studies

Dissolution studies are performed to assess the release profile of nateglinide from microspheres under simulated gastrointestinal conditions(46,47).

7.5 Stability Studies

Stability studies are conducted as per ICH guidelines to evaluate the physical and chemical stability of the formulation(47,48).

VIII. THERAPEUTIC SIGNIFICANCE IN DIABETES MANAGEMENT

Mucoadhesive microspheres of nateglinide with resin complexes provide sustained drug release, reduce dosing frequency, and improve glycemic control(49). This novel delivery approach can enhance therapeutic efficacy and patient adherence in the long-term management of diabetes mellitus(50,51).

IX. FUTURE PERSPECTIVES

The development of mucoadhesive microspheres combined with ion-exchange resin technology represents a promising strategy for oral antidiabetic therapy. Further in vivo studies and clinical trials are required to establish their safety, efficacy, and commercial feasibility(51,52).

X. CONCLUSION

The creation and testing of mucoadhesive microspheres of nateglinide that include ion-exchange resin complexes is a new and promising way to make oral antidiabetic medication better. Nateglinide is good at regulating high blood sugar after meals, but it has several pharmacokinetic problems. For example, it has a short biological half-life, is absorbed quickly, and needs to be taken often when given in standard dosage forms. These restrictions frequently lead to variable plasma medication concentrations and diminished patient adherence.

Mucoadhesive drug delivery systems provide many benefits, such as increasing the time drugs stay in the stomach and improving drug absorption by coming into close touch with the gastrointestinal mucosa. Using microspheres as a multiparticulate system makes ensuring that the medicine is spread out evenly, lowers the chance of dose dumping, and makes the formulation more stable. Adding mucoadhesive polymers to nateglinide allows it to be released slowly and in a regulated way, keeping therapeutic plasma levels high for a long time.

Adding ion-exchange resin complexes to mucoadhesive microspheres has many benefits, such as making drugs more stable, controlling drug release, and stopping drugs from being released too soon in the gastrointestinal tract. This combined method increases bioavailability while reducing the number of doses and side effects. Tests like particle size analysis, entrapment efficiency, mucoadhesive strength, in vitro drug release, and stability testing show that this delivery system is safe and works well.

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