



IJRASET

International Journal For Research in
Applied Science and Engineering Technology



INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 14 **Issue:** IV **Month of publication:** April 2026

DOI: <https://doi.org/10.22214/ijraset.2026.80759>

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Formulation and Evaluation of Buccoadhesive Tablets of Nateglinide

Susmitha Pilli¹, Tamma Kusuma², Meer Hussain Shaik³, Doppasani Meenakshi⁴, Birudugadda Lisha⁵, Chamataboina Mounika⁶, Pragallapti Rambabu⁷, V.Bhaskara Raju⁸

^{1, 2, 3, 4, 5, 6}UG Scholars, ⁷Associate Professor, ⁸Principal & Professor, Department of Pharmaceutics, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India

Abstract: The present study focuses on the formulation and evaluation of buccoadhesive tablets of Nateglinide, an oral antidiabetic drug used in the management of type 2 diabetes mellitus. Due to its short half-life and extensive first-pass metabolism, buccal delivery offers an alternative route to improve bioavailability. Buccoadhesive tablets were prepared using different polymers such as HPMC, Carbopol, and sodium CMC by direct compression method. The prepared formulations were evaluated for physicochemical parameters, swelling index, drug content uniformity, and in-vitro drug release. The results indicated that the optimized formulation showed satisfactory adhesion, controlled drug release, and improved drug availability, suggesting buccal delivery as a promising approach for Nateglinide administration.

Keywords: Nateglinide, Buccoadhesive tablet, Mucoadhesion, Controlled release, Diabetes mellitus

I. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia due to defects in insulin secretion or action [1]. Long-term complications include cardiovascular diseases, neuropathy, and nephropathy [2].

Nateglinide, a meglitinide analog, stimulates rapid insulin secretion and is primarily used to control postprandial glucose levels [6]. However, its oral bioavailability is limited due to extensive first-pass metabolism and short biological half-life (~1.5 hours), necessitating frequent dosing [7,8].

Buccal drug delivery systems offer several advantages such as avoidance of hepatic first-pass metabolism, improved bioavailability, rapid onset of action, and enhanced patient compliance [3,9]. Mucoadhesive systems prolong drug residence time at the absorption site, thereby improving therapeutic efficiency [4,10].

Polymers such as Carbopol and HPMC are widely used in buccoadhesive formulations due to their excellent swelling and adhesion properties [11–13].

The present study aims to formulate and evaluate mucoadhesive buccal tablets of Nateglinide using different polymer combinations to achieve controlled drug release and improved bioavailability.

A. CHALLENGES WITH CONVENTIONAL ORAL HYPOGLYCEMIC AGENTS

Conventional dosage forms (tablets and capsules) of oral hypoglycemic agents used in Diabetes Mellitus present several limitations that affect therapeutic efficacy. Many drugs such as Metformin and Glibenclamide exhibit poor and variable bioavailability due to limited solubility and extensive first-pass metabolism. These formulations often produce rapid drug release, leading to fluctuating plasma drug concentrations with peaks and troughs, which may result in inadequate glycemic control or an increased risk of hypoglycemia. Additionally, the lack of site-specific delivery reduces drug efficiency and contributes to systemic side effects.

Furthermore, conventional oral formulations require frequent dosing because of their short half-life, which can reduce patient compliance in long-term diabetes management. Gastrointestinal side effects, particularly with Metformin, such as nausea and diarrhea, further limit patient adherence. Variability in drug absorption due to food interactions and instability in the gastrointestinal environment also affects therapeutic outcomes. These challenges highlight the need for advanced drug delivery systems to improve efficacy, safety, and patient compliance.

B. OBJECTIVES FOR SELECTING NATEGLINIDE FOR BUCCAL DRUG DELIVERY

The selection of Nateglinide for buccal drug delivery is primarily aimed at overcoming the limitations associated with its conventional oral administration. Nateglinide undergoes significant first-pass metabolism in the liver, resulting in reduced bioavailability and variable therapeutic response.

Buccal delivery helps bypass hepatic first-pass metabolism, thereby enhancing systemic drug availability. Additionally, its relatively short half-life necessitates frequent dosing in conventional forms; a buccal system can provide controlled and sustained drug release, improving glycemic control in patients with Type 2 Diabetes Mellitus.

Another important objective is to improve patient compliance and reduce gastrointestinal side effects. Buccal drug delivery avoids direct exposure of the drug to the gastrointestinal tract, minimizing irritation and degradation in the acidic environment. Furthermore, the rich vascularization of the buccal mucosa allows rapid drug absorption and quick onset of action, which is beneficial for managing postprandial blood glucose levels. Thus, selecting Nateglinide for buccal delivery aims to enhance bioavailability, ensure controlled release, improve patient convenience, and achieve better therapeutic outcomes.

II. NEED OF WORK

The development of buccoadhesive tablets of Nateglinide is necessitated by the limitations associated with its conventional oral dosage forms. Nateglinide undergoes extensive first-pass metabolism in the liver, leading to reduced and variable bioavailability. In addition, its short biological half-life requires frequent dosing, which can compromise patient adherence. Buccoadhesive drug delivery offers a promising alternative by enabling drug absorption directly through the buccal mucosa, thereby bypassing hepatic metabolism and improving systemic availability. This approach is particularly beneficial in the management of Type 2 Diabetes Mellitus, where consistent plasma drug levels are essential for effective glycemic control.

Furthermore, buccoadhesive tablets can provide controlled and sustained drug release, reducing dosing frequency and minimizing fluctuations in plasma drug concentration. This system also avoids gastrointestinal degradation and irritation, enhancing drug stability and patient comfort. The mucoadhesive nature of the formulation ensures prolonged residence time at the site of absorption, leading to improved therapeutic efficacy. Therefore, the development of buccoadhesive tablets of Nateglinide is essential to enhance bioavailability, improve patient compliance, and achieve better overall treatment outcomes.

III. AIMS AND OBJECTIVES

A. AIM

The primary aim of the present study is to develop and evaluate buccoadhesive tablets of Nateglinide in order to enhance its bioavailability, provide controlled drug release, and improve therapeutic efficacy in the management of Type 2 Diabetes Mellitus.

B. OBJECTIVES

- 1) To formulate buccoadhesive tablets of Nateglinide using suitable mucoadhesive polymers.
- 2) To overcome first-pass metabolism and improve the bioavailability of the drug.
- 3) To achieve controlled and sustained release of Nateglinide through buccal delivery.
- 4) To evaluate the prepared formulations for physicochemical parameters such as hardness, friability, weight variation, and drug content.
- 5) To study the mucoadhesive strength and residence time of the buccal tablets.
- 6) To perform in vitro drug release studies and analyze the release kinetics.
- 7) To assess the stability of the optimized formulation under suitable storage conditions.

IV. MECHANISM OF ACTION

Nateglinide acts as a rapid-acting insulin secretagogue used in the management of Type 2 Diabetes Mellitus. It primarily stimulates insulin release from pancreatic β -cells by binding to specific receptors associated with ATP-sensitive potassium (K^+) channels on the cell membrane. This binding leads to the closure of K^+ channels, causing membrane depolarization.

As a result of depolarization, voltage-gated calcium (Ca^{2+}) channels open, allowing an influx of calcium ions into the β -cells. The increased intracellular calcium concentration triggers the exocytosis of insulin-containing granules, leading to a rapid release of insulin. This mechanism closely mimics the early-phase insulin secretion seen in normal physiology, thereby effectively reducing postprandial glucose levels.

V. DRUG AND EXCIPIENT PROFILE

A. DRUG PROFILE: Nateglinide

Category: Antidiabetic agent (Meglitinide analog)

Chemical Name: N-[[[(trans-4-isopropylcyclohexyl)carbonyl]-D-phenylalanine]

Molecular weight Formula: $C_{19}H_{27}NO_3$

Molecular Weight: 317.43 g/mol

Structure of nateglinide is shown in Fig.1

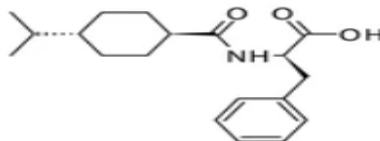


Fig.1 Structure of nateglinide

Pharmacokinetic Properties

- Bioavailability: ~70%
- Half-life: ~1.5 hours
- Protein binding: ~98%
- Metabolism: Hepatic (CYP2C9 and CYP3A4)
- Excretion: Urine and feces

B. EXCIPENT PROFILE:

1) Carbopol 934P

Category: Mucoadhesive polymer

Description:

Carbopol 934P is a high molecular weight cross-linked polyacrylic acid polymer widely used in controlled drug delivery systems.

2) Hydroxypropyl Methylcellulose (HPMC K4M)

Category: Hydrophilic polymer

Description:

HPMC is a semi-synthetic polymer commonly used in sustained-release formulations.

HPMC contributes to controlled and sustained drug release.

3) Sodium Carboxymethyl Cellulose (NaCMC)

Category: Mucoadhesive polymer

Description:

NaCMC is a cellulose derivative with good swelling and bioadhesive properties.

Provides additional adhesion and supports controlled release.

4) Lactose

Category: Diluent

Description:

Lactose is a commonly used filler in tablet formulations.

Ensures uniform tablet weight and proper compression.

5) Magnesium Stearate

Category: Lubricant

Description:

Magnesium stearate is widely used to reduce friction during tablet compression.

Improves manufacturability of tablets.

6) Talc

Category: Glidant

Description:

Talc improves flow properties of powder blend.

Ensures uniform die filling during compression.

VI. MATERIALS AND MERHODS

A. MATERIALS

Nateglinide, Carbopol 934P, HPMC K4M, Sodium CMC, Lactose, Magnesium stearate, and Talc were used [14]

Method of Preparation

Tablets were prepared by direct compression method, which is widely used due to simplicity and cost-effectiveness [15]. All ingredients were sieved (#80), blended uniformly, lubricated, and compressed.

B. PROCEDURE

1) Weighing of Ingredients

All ingredients—Nateglinide, Carbopol, Sodium CMC, HPMC, lactose, and magnesium stearate—are accurately weighed using a calibrated analytical balance according to the formulation design.

The drug is weighed as per the required dose (e.g., 60 mg or 120 mg per tablet). Polymers are selected based on desired mucoadhesive strength and release profile. Lactose is used as a diluent, and magnesium stearate (1–2%) as a lubricant. Accurate weighing ensures dose uniformity and reproducibility.

2) Sieving of Ingredients

All weighed ingredients except magnesium stearate are passed through a #80 sieve to remove lumps and ensure uniform particle size, improving flow and mixing. Magnesium stearate is sieved separately through a finer sieve (#60).

3) Mixing of Drug and Mucoadhesive Polymers

Nateglinide is mixed thoroughly with Carbopol, Sodium CMC, and HPMC using a mortar–pestle or blender for 10–15 minutes. This ensures uniform drug dispersion within the polymer matrix, which is essential for controlled drug release and effective mucoadhesion.

4) Addition of Diluent and Other Excipients

Lactose is added to the drug–polymer mixture and blended for about 10 minutes. It improves compressibility, flowability, and uniformity of tablet weight. No binder is required as the method used is direct compression.

5) Lubrication

Magnesium stearate is added and mixed gently for 2–3 minutes. It prevents sticking during compression. Overmixing is avoided as it may reduce tablet hardness and drug release.

6) Final Blending

The final blend is mixed uniformly and evaluated for flow properties such as angle of repose and bulk density. The blend should be free-flowing and homogeneous to ensure uniform tablet compression.

7) Storage Conditions (Final Blend)

The final blend should be stored in a tightly closed, airtight container at controlled room temperature (20–25°C). It must be kept in a dry place with low humidity, protected from moisture, and used as soon as possible to prevent segregation and stability issues.

Evaluation of Powder Blend

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner ratio

These parameters indicate flow properties essential for tablet uniformity [16,17].

C. EVALUATION OF TABLETS

- Hardness
- Friability
- Thickness
- Weight variation
- Drug content

These parameters ensure mechanical strength and uniformity of dosage forms [18].

D. IN-VITRO DRUG RELEASE STUDY

Drug release studies were performed using dissolution apparatus II in phosphate buffer (pH 6.8) and analyzed using UV spectrophotometry at 214 nm [19].

VII. RESULTS AND DISCUSSION

TABLE 1: FORMULATION AND EVALUATION TABLE

INGREDIENTS	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)
Nateglinide	60	60	60	60	60	60	60	60
Carbopol 934P	30	40	50	60	55	45	40	35
HPMC K4M	45	35	25	15	30	35	40	45
Sodium CMC	15	15	15	15	15	15	15	15
Lactose	40	40	40	40	35	35	35	35
Magnesium streate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
TOTAL	200	200	200	200	200	200	200	200
WEIGHT VARIATION	200±0.91	200±0.95	200.3±1.1	199.6±0.86	200.1±0.98	199.9±0.99	200.1±0.98	200.7±0.91
HARDNESS (kg/cm ²)	5.9±2.5	6.16±1.78	6.46±1.7	5.54±1.98	6.36±1.73	6.14±1.79	6.64±1.66	5.94±1.85
THICKNESS	3.48±2.29	3.58±2.23	3.78±2.11	3.32±2.41	3.68±2.17	3.54±1.41	3.92±2.04	3.42±2.34
FRIABILITY (%)	0.77	0.76	0.92	0.62	0.92	0.77	0.76	0.77
Drug Content (%)	99.24±0.61	100.26±0.59	101.14±0.62	98.44±0.56	100.8±0.62	100±0.55	102.1±0.77	99.56±0.55

The statistical analysis of weight variation data revealed that all formulations exhibited low standard deviation and %RSD values (<2%), indicating excellent uniformity in tablet weight. All batches complied with IP specifications, confirming good flow properties and uniform die fill during compression.

The hardness of all formulations ranged between 5.5 to 6.7 kg/cm², indicating adequate mechanical strength. Low %RSD values (<3%) confirm uniformity in tablet hardness. The results suggest proper compression and suitability of the formulations for sustained drug release.

The thickness of all formulations was found to be within the acceptable range, with low standard deviation and %RSD values (<3%), indicating uniform die fill and consistent compression. The results confirm the reproducibility of the tablet manufacturing process.

The friability values for all formulations were found to be less than 1%, indicating good mechanical strength and resistance to abrasion. The results confirm that all formulations comply with pharmacopoeial limits and are suitable for handling, packaging, and transportation.

The drug content uniformity study showed that all formulations contained the drug within the acceptable pharmacopoeial limits of 95–105%. The low standard deviation and %RSD values indicate uniform distribution of the drug in the formulation, confirming the efficiency of the mixing and compression processes.

In vitro drug release studies of Nateglinide buccoadhesive tablets prepared by Carbopol as mucoadhesive polymer and HPMC as release controlling polymer:

The in vitro dissolution study showed that all formulations exhibited sustained drug release over 16 hours. Among them, formulation F7 demonstrated optimal release (~100%) with controlled kinetics, whereas F3 showed faster release indicating lower matrix retardation. The results confirm that polymer concentration significantly influences the release profile of nateglinide.

Release rates: F7 > F3 > F5 > F2 > F6 > F1 > F8 > F4

F7 consists of equal amounts of HPMC and Carbopol which control release rates, shows ~100% release whereas in F4 the concentration of Carbopol is same as that of drug and that of HPMC is very less comparatively (F4 has least concentration of HPMC thus showing least release profiles).

F3 releases fast due to bursting so less ideal for sustained release.

The in vitro dissolution data were fitted to various kinetic models. The highest correlation coefficient ($R^2 \approx 0.995-0.997$) was observed for the Higuchi model, indicating that drug release follows a diffusion-controlled mechanism. The Korsmeyer–Peppas model showed n values between 0.5 and 0.7, suggesting non-Fickian (anomalous) transport involving both diffusion and polymer relaxation. The graphical representation of in vitro drug release rates is shown in Fig.2

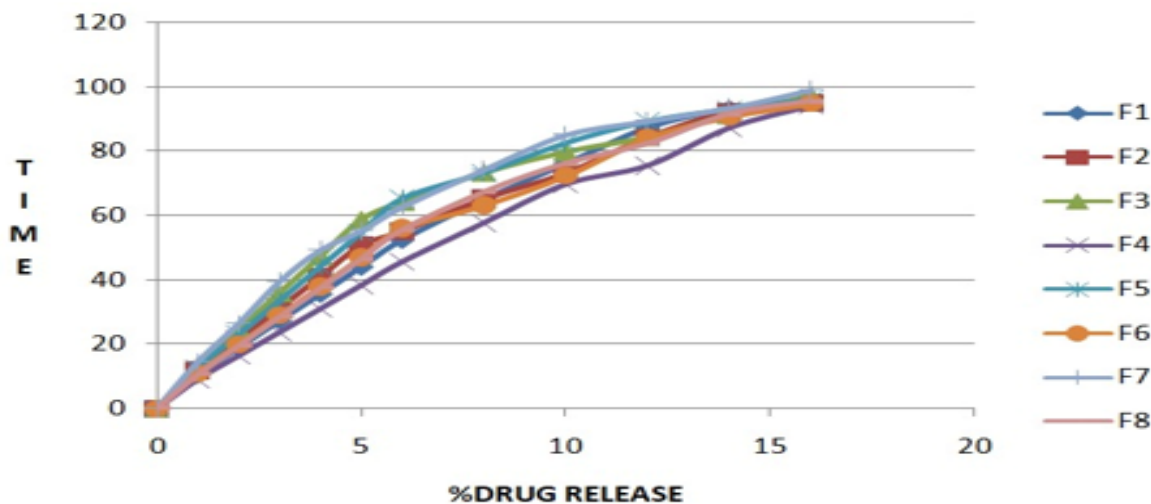


Fig 2. In vitro drug dissolution rates

A.SURFACE PH

The surface pH of all formulations was found to be in the range of 6.6 to 7.2, which is close to the physiological pH. This indicates that the formulations are non-irritant and suitable for administration without causing discomfort or irritation.

F7 shows highest PH due to highest polymer composition.

B.SWELLING INDEX

The swelling index study revealed that all formulations exhibited time-dependent swelling behavior. Formulation F7 showed the highest swelling index, indicating strong gel formation due to higher polymer concentration. The results suggest that swelling plays a crucial role in controlling drug release from the matrix system.

VIII. CONCLUSION AND SUMMARY

A. SUMMARY

The present study was carried out with the objective of developing and evaluating mucoadhesive buccal tablets of Nateglinide to overcome the limitations associated with its conventional oral administration. Nateglinide is a short-acting antidiabetic drug used in the management of Type 2 Diabetes Mellitus, but its therapeutic efficacy is limited due to short half-life, extensive first-pass metabolism, and frequent dosing requirements.

To address these issues, a sustained release buccal drug delivery system was designed. Buccal delivery offers several advantages such as bypassing hepatic first-pass metabolism, improving bioavailability, and providing controlled drug release, thereby enhancing patient compliance and therapeutic efficacy.

Preformulation studies were carried out to evaluate the physicochemical properties of the drug and its compatibility with excipients. The results confirmed that the drug was compatible with selected polymers such as Carbopol and HPMC, which were used as mucoadhesive and release-retarding agents.

A total of eight formulations (F1–F8) were prepared using the direct compression method by varying polymer concentrations. The prepared tablets were evaluated for various parameters including weight variation, hardness, thickness, friability, drug content, surface pH, swelling index, and in vitro drug release.

The evaluation results showed that all formulations complied with pharmacopoeial standards. The tablets exhibited acceptable hardness (5.5–6.7 kg/cm²), low friability (<1%), uniform thickness, and consistent weight variation, indicating good mechanical strength and uniformity. Drug content uniformity was found within the acceptable range of 95–105%, confirming uniform distribution of the drug.

Surface pH of all formulations was found to be within 6.6–7.2, which is close to physiological pH, indicating that the formulations are non-irritant and suitable for buccal administration. Swelling studies revealed that all formulations exhibited time-dependent swelling behavior, which plays a crucial role in controlling drug release.

In vitro dissolution studies demonstrated that all formulations exhibited sustained drug release up to 16 hours. Among them, formulation F7 showed optimal drug release (~100%), whereas formulation F3 showed faster release due to burst effect. The order of drug release was found to be:

F7 > F3 > F5 > F2 > F6 > F1 > F8 > F4

The release kinetics data revealed that the drug release followed the Higuchi model, indicating a diffusion-controlled mechanism. The Korsmeyer–Peppas model showed 'n' values between 0.5 and 0.7, suggesting non-Fickian (anomalous) transport, where both diffusion and polymer relaxation contribute to drug release.

Overall, the study successfully demonstrated that the use of appropriate polymer combinations can effectively control the release of Nateglinide and improve its therapeutic performance.

B. CONCLUSION

From the results of the present study, it can be concluded that mucoadhesive buccal tablets of Nateglinide were successfully formulated and evaluated. The developed formulations exhibited satisfactory physicochemical properties and complied with pharmacopoeial specifications.

The study confirmed that polymer concentration plays a crucial role in controlling drug release behavior. Among all formulations, F7 was identified as the optimized formulation, as it showed controlled and sustained drug release (~100% in 16 hours) with desirable mechanical properties and stability. The balanced combination of Carbopol and HPMC in F7 contributed to effective gel formation, swelling, and controlled drug diffusion.

The in vitro release studies indicated that the formulations followed a diffusion-controlled release mechanism, best described by the Higuchi model. The non-Fickian release behavior suggests that both polymer swelling and drug diffusion are responsible for the sustained release profile.

The buccal drug delivery system proved to be a promising alternative to conventional oral dosage forms by:

- Enhancing bioavailability
- Reducing first-pass metabolism
- Providing sustained drug release
- Improving patient compliance

Thus, the developed formulation offers significant advantages in the management of Type 2 Diabetes Mellitus by maintaining consistent plasma drug levels and reducing dosing frequency.

In conclusion, the study successfully achieved its objectives of developing a stable, effective, and patient-friendly sustained release formulation of Nateglinide. The optimized formulation (F7) can be considered a promising candidate for further in vivo studies and potential clinical application.

IX. FUTURE SCOPE

The present study successfully developed and evaluated mucoadhesive buccal tablets of Nateglinide with sustained drug release characteristics. However, there remains significant scope for further research and development to enhance the formulation and its clinical applicability.

Future studies can focus on in vivo evaluation of the optimized formulation (F7) to establish a correlation between in vitro and in vivo drug release profiles (IVIVC). This would provide a better understanding of the pharmacokinetic behavior and therapeutic efficacy of the formulation in human subjects.

Further research can be directed toward bioavailability studies to confirm the enhancement in drug absorption and reduction in first-pass metabolism through buccal delivery. Clinical studies may also be conducted to evaluate the safety, efficacy, and patient compliance of the developed formulation.

The formulation can be optimized further by exploring novel polymers and polymer combinations, including natural and biodegradable polymers, to improve mucoadhesion, swelling behavior, and drug release control. Additionally, the use of permeation enhancers may be investigated to enhance drug permeation across the buccal mucosa.

Advanced formulation techniques such as nanotechnology-based drug delivery systems (e.g., nanoparticles, nanoemulsions) can be incorporated into buccal tablets to further improve drug solubility and bioavailability.

Stability studies under various environmental conditions (as per ICH guidelines) can be extended to determine the long-term stability and shelf life of the formulation.

Moreover, scale-up and industrial feasibility studies can be carried out to evaluate the commercial viability of the formulation. This includes optimization of manufacturing processes and quality control parameters.

Finally, similar approaches can be extended to other drugs with poor bioavailability and extensive first-pass metabolism, thereby broadening the application of buccal drug delivery systems in pharmaceutical development.

The study demonstrated that polymer concentration significantly influenced drug release behavior. Carbopol increased mucoadhesion and controlled release, while HPMC contributed to sustained drug release [11,12].

The combination of polymers in F7 resulted in optimal swelling, adhesion, and drug diffusion, leading to improved release profile [20–22].

Similar findings have been reported in previous studies on buccoadhesive systems [23–25].

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