



Enhancing Nateglinide Delivery Through Mucoadhesive Buccal Tablets: Formulation and Assessment

Chrishmitha Sequeira¹, Sujatha P Muchalambe¹, Hindustan Abdul Ahad^{1*}, Abhishek Jayanna¹, Pynskhemlin Syiemlieh¹ and Shreya J Poojari¹

^{1*}Department of Pharmaceutics, R.R College of Pharmacy, Bangalore-560090, Karnataka, India

Abstract: Diabetes is a chronic illness that affects how the body converts food into energy. Numerous organs may be harmed as a result of poor diabetes control. The primary goal of the research project is to prepare and assess mucoadhesive buccal tablets of nateglinide for type 2 diabetes treatment, employing HPMC K100, Chitosan, and sodium alginate as mucoadhesive polymers alone and in a mixture through direct compression. The assessment parameters include thickness, hardness, weight variation, friability, drug content, swelling index, surface pH, *in-vitro* drug release, and *ex-vivo* mucoadhesive strength. FTIR analysis indicated no drug-excipient interaction. Physical parameters (thickness, hardness, weight variation, friability) adhered to pharmacopoeia standards, while drug content ranged from 83.65 to 99.76%. The swelling index varied from 100 ± 7.64 to $147.5 \pm 2.89\%$. Formulation F5 (Sodium alginate) exhibited the highest drug discharge ($92.1 \pm 2.37\%$), while F8 (HPMC K100 and Sodium alginate) demonstrated sustained discharge ($79.1 \pm 2.13\%$ at 8 h) and the highest mucoadhesive strength (33.0 ± 2.00 g). Discharge kinetics followed zero-order (F1, F3, F4, F7, and F9) and Korsmeyer Peppas models (F2, F5, and F6). The study concludes that the potential of these formulations for controlled drug discharge and oral mucosal adhesion in diabetes management.

Keywords: Buccal, Chitosan, Diabetes, Nateglinide, Sodium alginate, Tablets

*Corresponding Author

Hindustan Abdul Ahad, Department of Pharmaceutics,
R.R College of Pharmacy, Bangalore-560090, Karnataka,
India

Received On 11 August 2023

Revised On 02 October 2023

Accepted On 18 October 2023

Published On 01 November 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Chrishmitha Sequeira, Sujatha P Muchalambe, Hindustan Abdul Ahad, Abhishek Jayanna, Pynskhemlin Syiemlieh and Shreya J Poojari, Enhancing Nateglinide Delivery Through Mucoadhesive Buccal Tablets: Formulation and Assessment.(2023).Int. J. Life Sci. Pharma Res.13(6), P332-P343 <http://dx.doi.org/10.22376/ijlpr.2023.13.6.P332-P343>

This article is under the CC BY- NC-ND Licence (<https://creativecommons.org/licenses/by-nc-nd/4.0>)

Copyright © International Journal of Life Science and Pharma Research, available at www.ijlpr.com

Int J Life Sci Pharma Res., Volume13., No 6 (November) 2023, pp P332-P343



1. INTRODUCTION

Diabetes mellitus (DM) is a multifaceted metabolic complaint categorized by the body's inability to either produce adequate insulin or successfully use the insulin it makes¹. Insulin is a crucial hormone that plays a pivotal role in converting the sugar, carbohydrates, and other nutrients from our food into energy that the body can use². When this process is disrupted, it leads to a build-up of excess sugar in the bloodstream. This condition can have dire consequences, as it can result in impairment to multiple organs and tissues within the body. In recent times, DM has taken on the proportions of a global epidemic, ranking as one of the primary causes of mortality in both developed and developing nations³. There are two primary types of DM viz., type 1 (T1DM) and type 2 (T2DM). T1DM is primarily characterized by a severe shortage of insulin, often requiring lifelong insulin replacement therapy⁴. On the other hand, T2DM is caused by a combination of factors including insulin resistance (where the body's cells do not reply effectively to insulin), compromised insulin secretion, and increased production of glucose by the liver⁵. Effectively managing DM is of utmost importance to prevent its complications. This management includes various approaches such as maintaining a healthy lifestyle with regular exercise and a balanced diet. Additionally, medications play a vital role in controlling blood sugar levels⁶. These medications can include biguanides, thiazolidinediones, α -glucosidase inhibitors, meglitinides, sulfonylureas, and dipeptidyl peptidase inhibitors⁷. One such medication that holds promise is nateglinide, an amino acid derivative of D-phenylalanine⁸. Nateglinide acts as a potent insulin secretagogue, meaning it stimulates the discharge of insulin from the pancreatic beta cells. This is achieved by nateglinide binding to and blocking the ATP potassium channels within these cells, leading to an increase in calcium influx. As a result, this initiates the release of insulin, aiding in the regulation of blood sugar levels⁹. To effectively administer such medications, the buccal region of the mouth has emerged as an appealing pathway. Buccal drug administration involves delivering medications through the mucosal lining of the oral cavity¹⁰. This strategy offers various benefits, including swift absorption due to the abundant blood supply in the oral mucosa, convenience, and the ability to bypass the initial metabolic process that takes place in the liver. Moreover, bioadhesive drug delivery systems have been formulated, which, upon contact with saliva, become sticky and adhere to the oral mucosa for an extended duration. This facilitates the controlled release of medicinal components into the oral cavity, aiding in their absorption into the systemic circulation¹¹. The primary objective of the current research project is to develop and assess mucoadhesive buccal tablets (MBT) containing nateglinide for the treatment of T2DM. This involves incorporating mucoadhesive polymers like HPMC K100, Chitosan, and Sodium alginate into the tablet formulation. The main goal of these efforts is to extend the duration of drug discharge, leading to less frequent administration. By achieving sustained and controlled drug discharge, the project goal is to enhance patient compliance and contribute to more effective DM management.

2. MATERIALS AND METHODOLOGY

2.1. Materials

The nateglinide drug in its pure form was procured from Dhamtec Pharma and Consultants, Mumbai. The research

employed analytical-grade chemicals from SD Fine Chemicals, Mumbai.

2.2. Pre- formulation studies

The obtained nateglinide sample was identified by the following tests

2.2.1. Solubility analysis

Determination of the solubility was made by adding solvent in small incremental amounts to a test tube containing a fixed quantity of solute. After each addition, the system is vigorously shaken and examined visually for any undissolved solute particles. Following the established protocol, the solubility of Nateglinide was assessed in various solvents, including water, ethanol, methanol, chloroform, ether, phosphate buffer at pH 6.8, and phosphate buffer at pH 7.4¹².

2.2.2. Melting point

The melting point of nateglinide was resolute utilizing Thiel's tube method. In this procedure, finely powdered nateglinide was introduced into one end of a capillary tube, which was subsequently sealed at the other end. This capillary tube was affixed to a thermometer and submerged in a Thiel's tube containing liquid paraffin. The temperature at which the Nateglinide substance transitioned from solid to liquid state was then recorded after subjecting the tube to heat¹³.

2.3. Determination of Standard Curve and Maximum wavelength of nateglinide

A standard solution of nateglinide with a concentration of 10 $\mu\text{g/ml}$ was subjected to absorbance scanning using a UV double-beam spectrophotometer. The scanning covered the wavelength range of 200 to 400 nm¹⁴. A precisely measured amount of 100 mg of nateglinide was introduced into a 100 ml volumetric flask and dissolved in 100 ml phosphate buffer solution with a pH of 6.8. This resulting solution was then subjected to further dilution to produce multiple variations using the same phosphate buffer with a pH of 6.8. The optical absorbance of these prepared solutions was gauged using a UV-visible spectrophotometer, specifically at a wavelength of 247 nm, where the phosphate buffer with a pH of 6.8 was employed as the reference or "blank" solution. Following this, the data points generated from the absorbance-concentration ($\mu\text{g/ml}$) chart were subjected to analysis via linear regression¹⁵.

2.4. Drug-Excipient compatibility by FTIR studies

FTIR (Fourier-transform infrared) investigations were conducted on both pure nateglinide and the excipients to ascertain the compatibility of the drug with the excipients employed in the formulation. This analysis is expected to examine any potential interactions between the drug and the selected polymers. The peaks observed in the spectra were compared with those of pure nateglinide and the peaks generated from the polymer mixtures¹⁶.

2.5. Flow properties assessment

The flow properties and compressibility of the powder mixture were assessed by measuring the angle of repose, bulk

density, tapped density, Hausner's ratio, and compressibility index using the fixed funnel technique¹⁷.

2.6. Mucoadhesive buccal tablet preparation

MBT of nateglinide was fabricated using the direct compression technique, incorporating the mucoadhesive polymers HPMC K100, Chitosan, and Sodium alginate¹⁸. The precise weights of the drug, polymers, and excipients were

measured according to the specified batch formula¹⁹. Thorough mixing of all components was achieved by using a mortar and pestle for a consistent duration of 15 min. Subsequently, the lubricant and glidant were added to the powder blend, and further blending ensued for an additional 2 min²⁰. The equivalent quantity of the resulting powder for a single tablet was meticulously weighed and subsequently molded using a multi-station rotary punching machine (Table I).

Table I: Various formulations of Nateglinide buccal tablets									
Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nateglinide	60	60	60	60	60	60	60	60	60
HPMC K100	20	10	-	-	-	-	15	15	-
Chitosan	-	-	20	10	-	-	15	-	15
Sodium Alginate	-	-	-	-	20	10	-	15	15
Mannitol	90	100	90	100	90	100	80	80	80
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Ethylcellulose	20	20	20	20	20	20	20	20	20
Total	200	200	200	200	200	200	200	200	200

2.7. Evaluation of MBT

2.7.1. Tablet thickness

Ensuring uniform tablet size, the thickness of the tablets holds importance. To measure this, vernier calipers were employed, allowing precise measurement of the tablet thickness²¹.

2.7.2. Hardness

The purpose of the hardness test was to evaluate the tablet's ability to withstand chipping or breakage during storage, transportation, and handling. Five tablets were randomly

chosen, and their hardness was measured using a Pfizer hardness tester. Hardness is usually expressed in kg/cm². This test provides insights into the tablet's structural integrity²².

2.7.3. Friability test

To assess tablet durability, a Roche friability tester was employed, quantified as a percentage (%). Initially, ten tablets were weighed (W_{initial}) and placed into the friabilator. The friabilator was set to operate at 25 rpm for a duration of 4 min or until it reached 100 revolutions²³. Following this, the tablets were reweighed (W_{final}). The percentage friability was subsequently computed using the designated by e.q.1.

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100 \text{--- (1)}$$

2.7.4. Weight Variation test

Twenty tablets were chosen randomly and weighed individually. The mean weight was determined, and the standard deviation was calculated. A tablet is considered to pass the assessment if a maximum of two tablets exceed the percentage limit specified in the pharmacopoeia, and furthermore, none of the tablets deviate by more than double that percentage²⁴.

2.7.5. Swelling studies

Single buccal tablets from every batch were weighed separately as W_1 and put into individual Petri dishes with 15 ml of pH 6.8 phosphate buffer. At designated time intervals (1, 2, 3, 4, 5, 6, 7, and 8 h), the tablets were cautiously extracted from their respective Petri dishes. Any surplus surface moisture was delicately eliminated using filter paper²⁵. Subsequently, each expanded tablet's weight was re-measured as W_2 , and the swelling index (SI) was determined using the e.q.2²⁶.

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100 \text{--- (2)}$$

Where W_1 = Initial weight of the tablet; W_2 = Weight of the tablet after a specific time interval.

2.7.6. Surface pH

The buccal tablets were introduced into 1 ml of water and left to swell for a duration of 2 h at room temperature.

Subsequently, the surface pH of the swollen buccal tablets was ascertained using pH paper at intervals of 1, 2, 3, 4, 5, 6, 7, and 8 h²⁷.

2.7.7. Drug content uniformity

For assessing the drug content of the buccal tablets, a random selection of 5 tablets was made and pulverized using a mortar and pestle. A predetermined quantity of powder, equivalent to a single dose, was carefully measured out. Subsequently, the powder was dissolved in pH 6.8 phosphate buffer using sonication for a duration of 30 min. The resultant solution was then filtered using Whatman filter paper. The concentration of the drug within the solution was examined spectrophotometrically at 247 nm using a UV-spectrophotometer²⁸.

2.7.8. Mucoadhesion strength

To assess the mucoadhesion strength of the tablets, a modified physical balance approach was adopted. Fresh sheep buccal mucosa obtained from a nearby slaughterhouse, within 2 h of slaughter, was used. The mucosal membrane was cleansed with distilled water and treated with pH 6.8 phosphate buffer²⁹. A dual-arm physical balance was arranged, and a strong thread of appropriate length was suspended from the left arm³⁰. A glass stopper with a uniform surface was attached to the end of the thread. The buccal mucosa was securely

placed with the mucosal side upwards, and fastened with thread over the base of an inverted 50 ml glass beaker. This assembly was immersed in a 500 ml beaker filled with pH 6.8 phosphate buffer, maintained at 37°C to ensure the buffer kept the mucosal membrane moist³¹. Using adhesive (Cyanoacrylate glue), a buccal tablet was fixed to the glass stopper and positioned on one side of the mucosal membrane. Before starting the experiment, equilibrium between both sides of the balance was achieved by adding weights to the right pan. Subsequently, a 5 g weight was removed from the right pan, causing the glass stopper along with the tablet to descend across the mucosal membrane³². This arrangement was maintained for 3 min. Following that, weights were added to the right pan until the tablet detached from the mucosal membrane. The surplus weight on the right pan (total weight minus 5 g) was used to compute the mucoadhesive strength³³. For each formulation batch, the average of three trials was taken into consideration. To ensure consistent results for each formulation, the tissue was thoroughly rinsed with phosphate buffer after each measurement and allowed to rest for 5 min before introducing a new tablet (Figure 1). Following the determination of mucoadhesion strength, the adhesive force was calculated using the provided e.q.³⁴.

$$\text{Force of Adhesion (N)} = \frac{\text{Mucoadhesive strength} \times 9.8}{1000} \text{--- (3)}$$

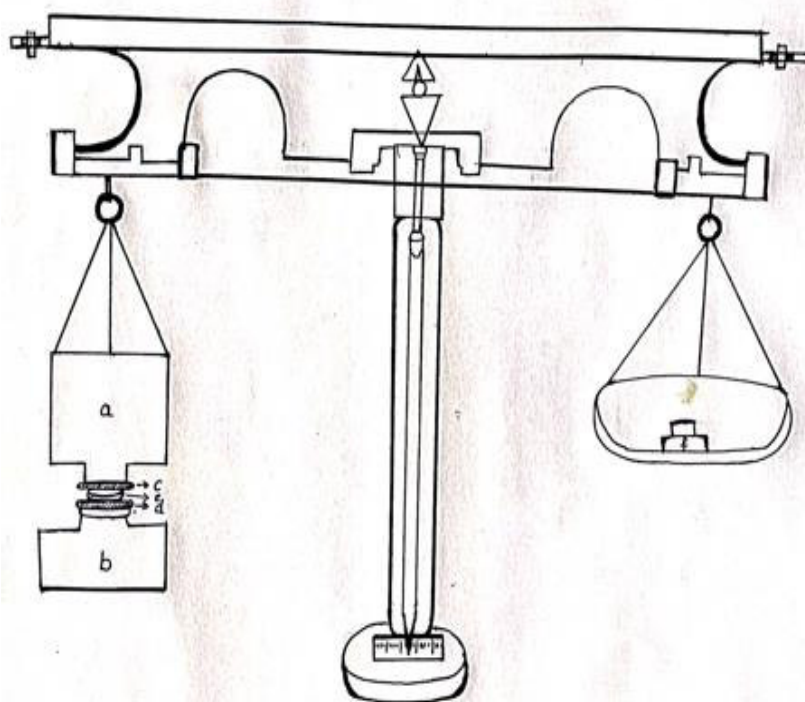


Fig. 1: Modified balance method for the determination of mucoadhesive strength

2.8. In vitro drug discharge study

The USP II apparatus employing the rotating paddle method was utilized to evaluate the drug discharge from buccal tablets. The dissolution medium consisted of 900 ml of phosphate buffer at pH 6.8, maintained at a constant temperature of 37±0.2 °C. The paddle was set to rotate at a speed of 50 rpm. The tablet's backing layer was affixed to a glass slide using adhesive. This slide was positioned at the bottom of the vessel, facilitating unidirectional drug discharge from the buccal

tablet³⁵. At specified and predetermined time intervals, a 5 ml sample was withdrawn from the dissolution medium, while an equivalent volume of fresh buffer was introduced to maintain the volume. The collected sample was then filtered using Whatman filter paper before being subjected to analysis with a UV spectrophotometer, following appropriate dilution. This process allowed for the measurement of drug concentration over time and facilitated the evaluation of the discharge profile from the buccal tablets.

3. RESULTS

3.1. Drug Identification

The drug displays high solubility in methanol, ethanol, and chloroform, while also showing solubility in ether and

phosphate buffer at pH 6.8 (Figure 2). The melting point of pure nateglinide was resolute to be approximately $139.5^{\circ}\text{C} \pm 2.12^{\circ}\text{C}$.

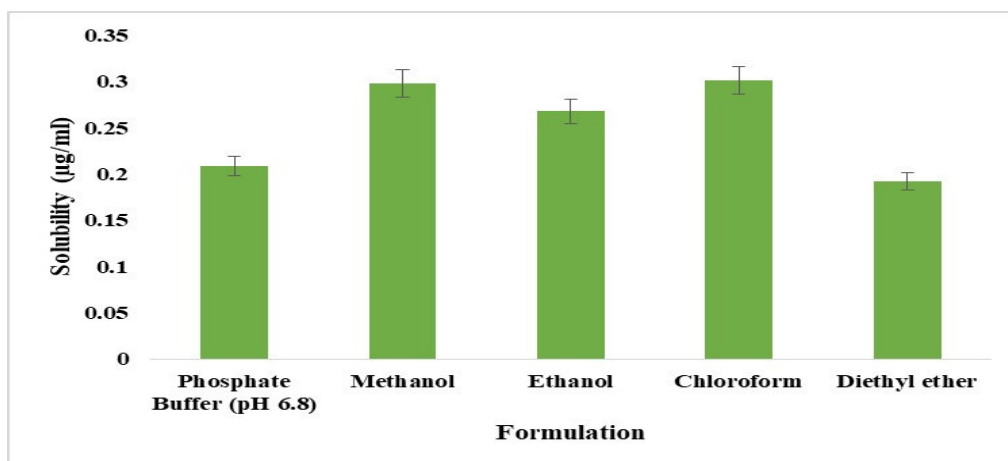


Fig. 2: Solubility of Nateglinide in various solvents

3.2. Compatibility outcome

The FTIR spectra obtained by analyzing the drug along with the excipients used in the formulation exhibited distinct peaks corresponding to the drug at their respective wavelengths. Notably, there were no significant shifts observed, indicating the compatibility of the drug with the excipients employed in the formulation (Figure 3).

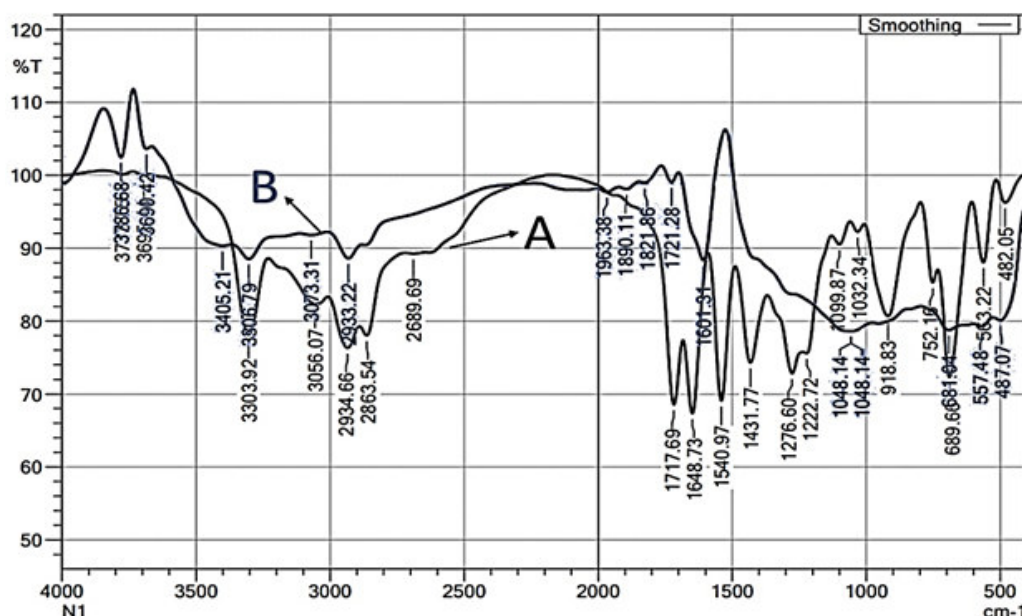


Fig.3: A) FTIR spectra of pure drug (nateglinide); B) Nateglinide with excipients

3.3. Calibration curve

When the standard solution of nateglinide ($10 \mu\text{g/ml}$) was subjected to scanning in the wavelength range of 200 – 400 nm, the highest absorbance was observed at 247 nm (Figure 4 A). Using Microsoft Excel, the standard calibration curve of nateglinide in Phosphate buffer at pH 6.8 was plotted, including its slope and regression coefficient. The results demonstrated linearity, evident by an R^2 value of 0.991, confirming compliance with the Beers-Lambert rule (Figure 4B).

3.4. Pre- compression assessment

The pre-compressional parameters applied to the powder blend for formulations F1 to F9 were analyzed. The angle of repose ranged from $33.67^{\circ} \pm 0.92$ to $38.34^{\circ} \pm 0.09$, indicative of favorable flow characteristics. The compressibility index varied from 6.92 ± 0.25 to 14.81 ± 1.12 , while Hausner's ratio ranged from 1.07 ± 0.02 to 1.17 ± 0.01 (Table 2).

Table 2: Pre-compression evaluation parameters of the powder blend

Formulation code	Angle of repose (°)	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr's index (%)	Hausner's ratio
F1	35.92±0.25	0.290±0.02	0.325±0.03	10.65±0.37	1.12±0.07
F2	36.57±0.52	0.278±0.02	0.308±0.02	9.90±0.77	1.11±0.01
F3	33.77±0.82	0.286±0.01	0.319±0.02	10.35±1.01	1.14±0.06
F4	38.34±0.09	0.278±0.01	0.313±0.01	11.27±0.38	1.12±0.06
F5	35.24±0.54	0.281±0.01	0.302±0.02	6.92±0.25	1.07±0.02
F6	33.67±0.92	0.295±0.02	0.339±0.01	13.07±0.73	1.15±0.01
F7	35.16±0.66	0.279±0.01	0.314±0.01	10.93±0.44	1.12±0.06
F8	35.19±0.84	0.276±0.01	0.310±0.03	10.74±0.87	1.12±0.05
F9	37.50±0.53	0.291±0.02	0.342±0.01	14.81±1.12	1.17±0.01
Values in mean±SD					

3.5. Post-compression assessments

The tablet thickness remained consistent across all formulations, ranging from 3.93±0.06 to 4.01±0.03 (within the specified pharmacopeia limit of ±7.5%). Formulations exhibited friability between 0.33±0.02 and 0.73±0.01 (accepted range of 1%). Formulations demonstrated hardness spanning from 4.80±0.20 to 5.93±0.15, adhering to the official standards of more than 4 kg/cm². The surface pH values of all batches ranged from 6.70±0.02 to 7.13±0.02, closely approximating neutrality and affirming the formulation's oral cavity friendliness. The drug content across all formulations spanned from 83.65±0.19 to 99.76±0.39, maintaining compliance with the pharmacopoeia standards (Table 3).

Table 3: Post-formulation parameters of nateglinide tablets

Post-formulation	Thickness (mm)	Hardness (kg/cm ²)	Weight variation (mg)	Friability (%)	Surface pH	Drug content (%)
F1	4.00±0.02	5.60±0.15	197.6±3.43	0.72±0.05	7.04±0.01	99.58±0.33
F2	4.01±0.03	5.60±0.20	197.2±3.61	0.39±0.03	6.87±0.04	94.41±0.30
F3	3.93±0.06	4.90±0.26	196.5±4.09	0.45±0.03	6.92±0.05	90.58±0.25
F4	3.94±0.09	4.80±0.20	196.5±3.64	0.33±0.02	6.83±0.03	83.65±0.19
F5	4.00±0.02	5.93±0.15	198.0±2.90	0.56±0.01	6.98±0.02	99.76±0.39
F6	4.00±0.08	5.83±0.05	196.5±3.97	0.63±0.02	7.03±0.01	95.49±2.36
F7	3.96±0.08	5.23±0.31	194.9±3.81	0.42±0.02	6.70±0.02	85.08±0.16
F8	3.96±0.06	5.16±0.25	197.1±3.02	0.73±0.01	7.13±0.02	98.98±0.28
F9	4.00±0.05	5.70±0.20	196.5±3.67	0.69±0.01	6.89±0.03	91.73±2.35
Values in mean±SD						

3.6. Swelling index properties

Notably, among all the formulations, F5 containing Sodium alginate as the polymer exhibited the highest swelling index of 147.5% ±2.89, whereas F4 containing Chitosan displayed the lowest swelling index of 100.0% ±7.64 (Figure 4C).

3.7. In-vitro drug discharge and kinetic data

Drug release studies were conducted over an 8 h period using the USP paddle method, with phosphate buffer at pH 6.8 as the dissolution medium. Among the formulations, F5, which included Sodium alginate as a mucoadhesive polymer, exhibited the highest drug release rate of 92.10%. Meanwhile, Formulation F8, which combined HPMC K 100 and Sodium alginate, achieved a drug release rate of 79.11% at the end of the 8 h period. This indicates a sustained and controlled drug

release compared to the other formulations (Figure 4C). To analyze the drug release pattern, the in-vitro release data were fitted to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations. Among the formulations, F1, F3, F4, F7, F8, and F9 followed zero-order kinetics, with corresponding R² values of 0.9849, 0.9877, 0.9771, 0.9903, and 0.9788 (as detailed in Table 4). This implies that the drug release rate in these formulations is not dependent on concentration. On the other hand, formulations F2, F5, and F6 displayed R² values of 0.9841, 0.9814, and 0.9942, respectively, indicating that their drug release is influenced by both diffusion and erosion mechanisms. Additionally, the diffusion exponent (n) for the solute exceeded 0.89, indicating a super case II transport mechanism for drug release in these specific formulations (Figure 4D to Figure 4H).

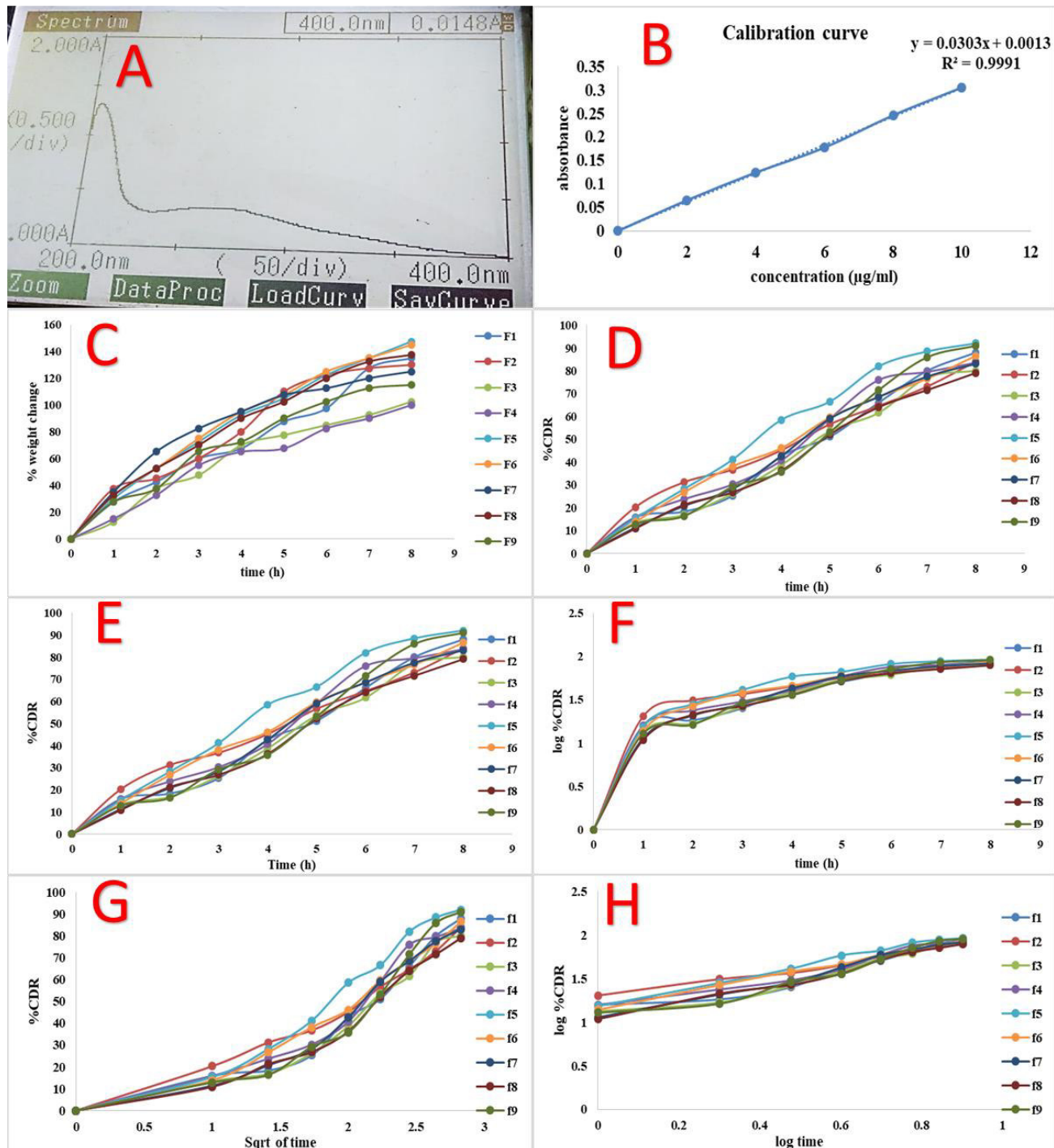


Fig.3: A) Absorbance maxima of nateglinide; B) Standard calibration curve of nateglinide; C) Swelling index of nateglinide buccal tablets (F1 - F9); D) *In-vitro* dissolution profile of nateglinide tablet formulations; E) Zero order plot of nateglinide tablet formulations; F) First order plot of nateglinide tablet formulations; G) Higuchi model plot of nateglinide tablet formulations; H) Korsmeyer- Peppas model of nateglinide tablet formulations

Table 4: Kinetic modeling plot of nateglinide tablet formulations (F1-F9)					
Formulation	Zero-order	First order	Higuchi model	Korsmeyer- Peppas	
				R ²	n
F1	0.9849	0.9683	0.9322	0.9303	1.0846
F2	0.9841	0.9647	0.9597	0.9847	1.2833
F3	0.9877	0.9566	0.8874	0.9584	1.0344
F4	0.9771	0.9495	0.9035	0.9650	1.1423
F5	0.9814	0.8872	0.9451	0.9934	1.1924
F6	0.9942	0.9064	0.9462	0.9983	1.1532
F7	0.9903	0.9256	0.9060	0.9898	1.0302
F8	0.9920	0.9383	0.9007	0.9885	1.0177
F9	0.9788	0.9651	0.8536	0.9541	1.0076

3.8. Ex-vivo mucoadhesive strength results

The mucoadhesive strength of prepared MBT were studied and the results were shown in Figure 5 and 6). The maximum of 33 ± 2 g of mucoadhesive strength was shown by the

formulation F8 containing a combination of HPMC K100 and Sodium alginate as mucoadhesive polymers. The lowest of 20.6 ± 1.55 g of mucoadhesive strength was shown by formulation F4 because of a lower tendency to swell.

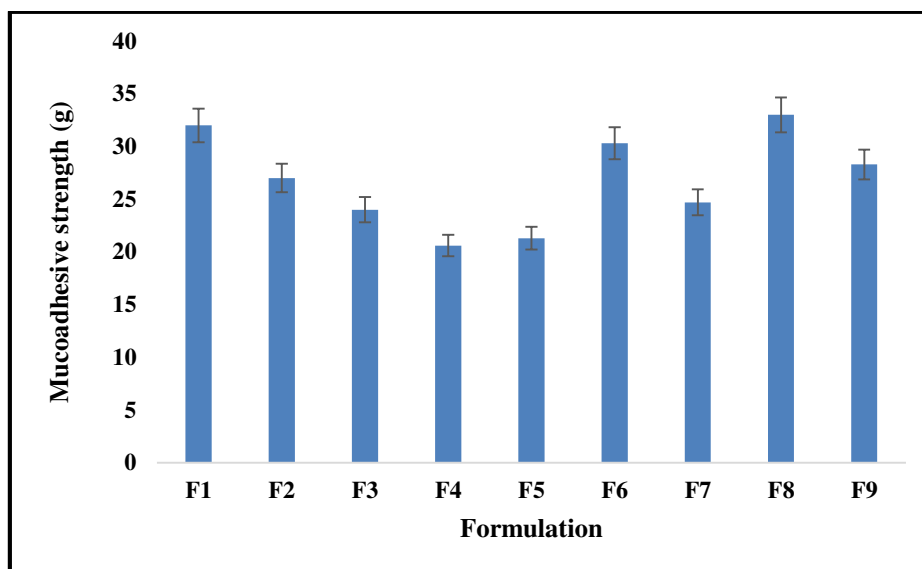


Fig.5: Mucoadhesive strength of nateglinide tablets (F1- F9)

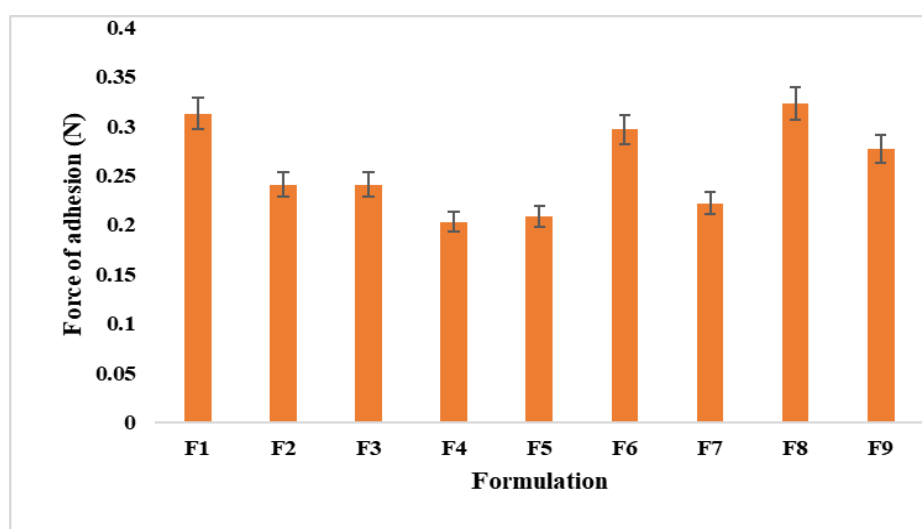


Fig.6: Mucoadhesive force for the prepared tablets

4. DISCUSSION

The drug displays high solubility in methanol, ethanol, and chloroform, while also showing solubility in ether and phosphate buffer at pH 6.8. However, its solubility is somewhat reduced in phosphate buffer at pH 7.4, and it remains insoluble in water. These solubility profiles across different solvents are crucial factors to consider when formulating the drug for its intended applications. Pandey et al., 2016 also observed the free solubility of nateglinide in ethanol.³⁶ The melting point of a compound is a unique physical property that is often used to identify and assess the purity of a substance. A pure compound will generally have a sharp melting point range, whereas impurities or mixtures can lead to a broadening or depression of the melting point. The nateglinide was shown melting point as per its monograph specifications. Such identification was also practiced by Bruni et al., 2009³⁷. UV-visible spectrophotometric analysis of

nateglinide reveals its highest absorbance at 247 nm. A standard calibration curve constructed using Microsoft Excel demonstrates linearity with an R^2 value of 0.991, validating adherence to the Beers-Lambert law. This technique allows for accurate quantification of nateglinide levels in pharmaceutical applications. Kanapura et al., 2016³⁸ found absorption maxima for Nateglinide at the same wavelength. In the FTIR analysis, distinct peaks corresponding to the drug and excipients were observed at their specific wavelengths. Importantly, no significant shifts were noted, indicating that the drug is compatible with the excipients used in the formulation. The consistency in these pre-compressional parameters across formulations F1 to F9 is encouraging. The favorable flow properties, as evidenced by the angle of repose and Hausner's ratio, suggest that the powder blends are suitable for efficient and reproducible tablet manufacturing. The range of compressibility index values indicates that the powders possess a range of compressibility, allowing for flexibility in

adjusting tablet hardness and disintegration characteristics. The observed favorable flow characteristics, compressibility, and Hausner's ratio within the powder blends for formulations F1 to F9 highlight their potential as suitable candidates for tablet formulation. These parameters collectively contribute to the efficient and reliable production of tablets with consistent quality, which is pivotal for successful pharmaceutical manufacturing and delivery of effective medications. The collective data on tablet characteristics demonstrates the formulations' quality, consistency, and suitability for their intended use. The results indicate that the manufacturing processes have been well-controlled, leading to tablets with uniform properties, adequate mechanical strength, and desirable oral compatibility. This information is crucial for regulatory compliance, patient safety, and successful pharmaceutical product development. The swelling behavior of a material refers to its capacity to absorb fluids and increase in volume. It's a crucial parameter for various applications, especially in pharmaceuticals where controlled discharge, dissolution, and stability are of concern. The observed progressive increase in swelling over time suggests that the formulations are absorbing the surrounding fluid, which could have implications for drug discharge, dissolution, and stability. The differences in swelling behavior among the formulations, with F5 (containing Sodium alginate) showing the highest and F4 (containing Chitosan) the lowest swelling index, indicate the varying influence of different polymers on the water-absorbing capacity of the formulations. This can be attributed to the specific chemical and physical properties of the polymers, such as their molecular weight, crosslinking, and interactions with water. Patel et al., 2015³⁹ observed 54.6% of swelling using Compritol ATO 888 and Precirolwre. Venaktesh et al., 2020⁴⁰ observed good swelling using xathan gum. The exceptionally high drug discharge of 92.10% observed in Formulation F5 (Sodium alginate) suggests that the mucoadhesive nature of Sodium alginate could contribute to rapid and efficient drug discharge. Mucoadhesive polymers can interact with mucous membranes, prolonging drug contact and potentially enhancing absorption. Formulation F8, containing a blend of HPMC K 100 and Sodium alginate, demonstrated a sustained drug discharge of 79.11% over 8 h. This sustained discharge could be attributed to the combination of polymers, which might have influenced the discharge kinetics. HPMC K 100 is known for its ability to form gel matrices, slowing down drug diffusion and promoting sustained discharge. Sharma et al., 2013 observed sustained drug release using HPMC and eudragit⁴¹. The comparison of drug discharge profiles among formulations helps identify the influence of different polymers and their combinations on drug discharge behavior. Formulation F5's rapid discharge and Formulation F8's sustained discharge highlight the versatility of polymers in tailoring drug discharge kinetics for specific therapeutic requirements. Ryakala et al., 2015 found sustained release from the tablets using natural gums (guar gum & xanthan gum)⁴². Formulations F1, F3, F4, F7, F8, and F9 displayed a good fit to zero-order kinetics, as evidenced by high R^2 values ranging from 0.9771 to 0.9903. This implies that the drug discharge rate in these formulations remains constant over time, regardless of the drug level. Such kinetics might be advantageous for achieving consistent drug levels for therapeutic efficacy. Formulations F1, F3, F4, F7, F8, and F9 displayed a good fit to zero-order kinetics, as evidenced by high R^2 values ranging from 0.9771 to 0.9903. This implies that the drug discharge rate in these formulations remains constant over time, regardless of the drug level. Such kinetics might be

advantageous for achieving consistent drug levels for therapeutic efficacy. Waidya et al., 2019 observed such release in repaglinide buccal tablets⁴³. The diffusion exponent (n) greater than 0.89 observed for formulations F2, F5, and F6 is indicative of a super case II transport mechanism. This suggests that the drug discharge process in these formulations is influenced by factors beyond traditional Fickian diffusion, possibly involving swelling, relaxation, or other complex mechanisms. Understanding these transport mechanisms is important for predicting and controlling drug discharge accurately. Koirala et al., 2021 saw a similar release in mucoadhesive buccal tablets of aceclofenac⁴⁴. The diffusion exponent (n) greater than 0.89 observed for formulations F2, F5, and F6 is indicative of a super case II transport mechanism. This suggests that the drug discharge process in these formulations is influenced by factors beyond traditional Fickian diffusion, possibly involving swelling, relaxation, or other complex mechanisms. Understanding these transport mechanisms is important for predicting and controlling drug discharge accurately. Palem et al., 2011 found fickian diffusion from their prepared bioadhesive buccal tablets⁴⁵. Understanding the drug discharge kinetics is critical for optimizing therapeutic outcomes. Zero-order kinetics can be beneficial for maintaining consistent drug levels, which might be crucial for drugs with a narrow therapeutic window. Formulations exhibiting diffusion and erosion mechanisms might provide tailored discharge profiles for specific therapeutic needs. Boyapally et al., 2010 observed concentration-independent release from theophylline buccal tablets⁴⁶. Mucoadhesive strength is a critical parameter in buccal drug delivery systems as it determines the tablets' ability to adhere to mucosal surfaces in the oral cavity. This adhesive property is essential for achieving prolonged drug discharge, enhancing therapeutic efficacy, and improving patient compliance. Nafee et al., 2004⁴⁷ found good mucoadhesive strength. Formulation F8, which incorporates a combination of HPMC K100 and Sodium alginate as mucoadhesive polymers, exhibited the highest mucoadhesive strength of 33 ± 2 g. This high strength implies strong interaction with mucous membranes, potentially resulting from a synergistic effect between the polymers. This formulation could offer improved retention and prolonged drug discharge within the buccal cavity. Such observation was found by Alur et al., 1999⁴⁸. In contrast, Formulation F4 showed the lowest mucoadhesive strength of 20.6 ± 1.55 g. This lower strength can be attributed to the formulation's lower tendency to swell upon contact with mucous membranes. Mucoadhesion often relies on the ability of the formulation to swell and create an effective contact area with the mucosa. The reduced swelling tendency could have led to weaker adhesion in this case. Gowthamarajan et al., 2012 found good mucoadhesion with the cashew nut tree gum⁴⁹. The observed variation in mucoadhesive strength among formulations underscores the influence of polymer choice and formulation design on the adhesive properties. Mucoadhesive strength directly impacts the tablets' residence time in the oral cavity, which in turn affects drug discharge kinetics. Patel et al., 2007 found appreciable mucoadhesion with sodium alginate and carbopol⁵⁰.

5. CONCLUSION

The study concludes that the promising potential of mucoadhesive buccal tablets containing a combination of HPMC K 100, Chitosan, and Sodium alginate as a novel

approach for managing Diabetes mellitus. The significant mucoadhesive strength and sustained drug release over 8 hours, as well as the unique release kinetics observed, set these formulations apart from others. These findings suggest that such formulations could lead to more effective and convenient therapeutic options for diabetes patients. The extended drug release may help reduce dosing frequency and improve patient adherence to treatment protocols, ultimately enhancing the overall management of this chronic condition. Further research and clinical trials are warranted to validate these promising results and bring these innovative formulations closer to clinical application.

6. AUTHORS CONTRIBUTION STATEMENT

Chrishmitha S contributed to the conception, study design, and data analysis. Sujatha PM contributed to the study process and data acquisition. Pynskhemlin S contributed to the literature search, Abhishek Jayanna checked the grammar and

the punctuation and Hindustan Abdul Ahad drafted the manuscript. All the authors read and approved the final manuscript.

7. ABBREVIATIONS

HPMC-Hydroxy Propyl Methyl Cellulose; pH-Negative logarithm of hydrogen ion concentration; FTIR-Fortier Transform Infra-red spectroscopy; DM-Diabetes Mellitus; T1DM- Type 1 Diabetes Mellitus; T2DM Type 2 Diabetes Mellitus; ATP-Adenosine triphosphate; µg-microgram; ml-milliliter; UV-Ultra violet; mg- milligram; nm- nanometer; min-minutes; %- percent; rpm- rotations per minute; g- grams; °C-degree conscious; MBT- mucoadhesive buccal tablets.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

9. REFERENCES

- Darenskaya MA, Kolesnikova LI, Kolesnikov SI. Oxidative stress: pathogenetic role in diabetes mellitus and its complications and therapeutic approaches to correction. *Bull Exp Biol Med.* 2021;171(2):179-89. doi: 10.1007/s10517-021-05191-7, PMID 34173093.
- Shravani Y, Ahad HA, Haranath C, gari Poojitha B, Rahamathulla S, Rupasree A. Past decade work done on cubosomes using factorial design: A fast track information for researchers. *Int J Life Sci Pharm Res.* 2021;11(1):124-35.
- Jwalapuram R, Ahad HA, Haranath C, Thadipatri R, Varshitha C, Kumar YB. A desktop reference to the solubility enhancement of drugs with the aid of surfactants. *Int J Life Sci Pharm Res.* 2020;11(5):11-6.
- SantaCruz-Calvo S, Bharath L, Pugh G, SantaCruz-Calvo L, Lenin RR, Lutshumba J, et al. Adaptive immune cells shape obesity-associated type 2 diabetes mellitus and less prominent comorbidities. *Nat Rev Endocrinol.* 2022;18(1):23-42. doi: 10.1038/s41574-021-00575-1, PMID 34703027.
- Ahad HA, Haranath C, Kondaveeti S, Konjeti S, Gangireddy S, Ibrahim O. Herbs in dentifrices for dental care and hygiene: a comprehensive Review. *Res J Pharm Technol.* 2020;13(10):5052-4. doi: 10.5958/0974-360X.2020.00885.9.
- Hahr AJ, Molitch ME. Management of diabetes mellitus in patients with CKD: core curriculum 2022. *Am J Kidney Dis.* 2022;79(5):728-36. doi: 10.1053/j.ajkd.2021.05.023, PMID 34600745.
- Bytzer P, Talley NJ, Jones MP, Horowitz M. Oral hypoglycaemic drugs and gastrointestinal symptoms in diabetes mellitus. *Aliment Pharmacol Ther.* 2001;15(1):137-42. doi: 10.1046/j.1365-2036.2001.00896.x, PMID 11136287.
- Weaver ML, Orwig BA, Rodriguez LC, Graham ED, Chin JA, Shapiro MJ, et al. Pharmacokinetics and metabolism of nateglinide in humans. *Drug Metab Dispos.* 2001;29(4 Pt 1):415-21. PMID 11259325.
- Shah P, Rahman SA, Demirbilek H, Güemes M, Hussain K. Hyperinsulinaemic hypoglycaemia in children and adults. *Lancet Diabetes Endocrinol.* 2017;5(9):729-42. doi: 10.1016/S2213-8587(16)30323-0, PMID 27915035.
- Razzaq S, Syed MA, Irfan M, Khan I, Sarfraz RM, Shakir R, et al. Optimization of metronidazole SR buccal tablet for gingivitis using genetic algorithm. *Pak J Pharm Sci.* 2021;34(6):2149-58. PMID 35034875.
- Koirala S, Nepal P, Ghimire G, Basnet R, Rawat I, Dahal A, et al. Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. *Heliyon.* 2021;7(3):e06439. doi: 10.1016/j.heliyon.2021.e06439, PMID 33786387.
- Veseli A, Žakelj S, Kristl A. A Review of methods for solubility determination in biopharmaceutical drug characterization. *Drug Dev Ind Pharm.* 2019;45(11):1717-24. doi: 10.1080/03639045.2019.1665062, PMID 31512934.
- Noya EG, Vega C, de Miguel E. Determination of the melting point of hard spheres from direct coexistence simulation methods. *J Chem Phys.* 2008;128(15):154507. doi: 10.1063/1.2901172, PMID 18433235.
- Jain S, Bhandari A, Purohit S. Spectrophotometric determination of nateglinide in bulk and tablet dosage forms. *Asian J Pharm.* 2009;3(3). doi: 10.4103/0973-8398.56301.
- Venkatesh S, Jyothi S, Chiluka R, Padmavathi Y. Development of uv-spectrophotometric method for the simultaneous estimation of nateglinide and piperine in combined tablet dosage form. *Asian J Pharm Anal.* 2020;10(3):134-40. doi: 10.5958/2231-5675.2020.00024.1.
- Puviarasan N, Arjunan V, Mohan S. FT-IR and FT-Raman studies on 3-aminophthalhydrazide and N-aminophthalimide. *Turk J Chem.* 2002;26(3):323-34.
- Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. *AAPS PharmSciTech.* 2008;9(1):250-8. doi: 10.1208/s12249-008-9046-8, PMID 18446489.
- Sogias IA, Williams AC, Khutoryanskiy VV. Chitosan-based mucoadhesive tablets for oral delivery of ibuprofen. *Int J Pharm.* 2012;436(1-2):602-10. doi: 10.1016/j.ijpharm.2012.07.007, PMID 22842627.
- Ahad HA, Chinthaginjala H, Priyanka MS, Raghav DR, Gowthami M, Jyothi VN. Datura stramonium Leaves mucilage aided buccoadhesive films of aceclofenac using

- 3² factorial design with design-expert software. Indian J Pharm Educ Res. 2021;55.
20. Ahad HA, Dasari RR, Haranath C, Gowthami M, Varam NJ, Sravanthi P. Bygone exertion on mucoadhesive bilayered tablets. Res J Pharm Technol. 2021;14(11):5991-2.
21. Sharma S, Thakur SL, Joshi SK, Kulkarni SS. Measurement of gingival thickness using digital vernier caliper and ultrasonographic method: a comparative study. J Investig Clin Dent. 2014;5(2):138-43. doi: 10.1111/jicd.12026, PMID 23355379. Sharma S, Thakur SL, Joshi SK, Kulkarni SS. Measurement of gingival thickness using digital vernier caliper and ultrasonographic method: a comparative study. J Investig Clin Dent. 2014;5(2):138-43. doi: 10.1111/jicd.12026, PMID 23355379.
22. Mulhall JP, Goldstein I, Bushmakini A, Cappelleri J, Hvidsten K. Validation of the erection hardness score. *The 15th Anniversary of the First Oral Therapy for Erectile Dysfunction*. 2014;11(2):123-4.
23. Osei-Yeboah F, Sun CC. Validation and applications of an expedited tablet friability method. Int J Pharm. 2015;484(1-2):146-55. doi: 10.1016/j.ijpharm.2015.02.061, PMID 25724139.
24. Katori N, Aoyagi N, Kojima S. The study of the applicability of content uniformity and weight variation test—the state of commercial tablets and capsules in Japan. Chem Pharm Bull (Tokyo). 2001;49(11):1412-9. doi: 10.1248/cpb.49.1412, PMID 11724231.
25. Jena K, Das M, Das M, De A, Mitra D, Samanta A. Determination of efficacy of a natural tablet binder: characterization and in-vitro release study. Asian J Pharm Clin Res. 2014;7(3):184-68.
26. Ahad HA, Haranath C, Rahul Raghav D, Gowthami M, Naga Jyothi V, Sravanthi P. Overview on recent optimization techniques in gastro retentive microcapsules by factorial design. Int J Pharm Sci Res. 2019;10(9):247-54.
27. Mundarinti SHB, Ahad HA. Impact of Pistacia lentiscus Plant Gum on Particle Size and Swelling Index in Central Composite Designed amoxicillin trihydrate mucoadhesive Microspheres. Ind J Pharm Educ Res. 2023;57(3):763-72. doi: 10.5530/ijper.57.3.93.
28. Kadam PB, Dias RJ, Mali KK, Havaladar VD, Mahajan NS. Formulation and evaluation of buccoadhesive tablets of atenolol. J Pharm Res. 2008;1(2):193-9.
29. Babu GN, Muthukaruppan M, Ahad HA. Impact of Azadirachta indica Fruit Mucilage on particle size and swelling index in Central Composite Designed acyclovir mucoadhesive microspheres. Baghdad Sci J. 2023;20(2):0425-. doi: 10.21123/bsj.2022.6786.
30. Babu GN, Muthukaruppan M, Ahad HA. Neem fruit mucilage impact on acyclovir release at different intervals: A central composite design screening. Int J Pharm Res Allied Sci. 2021;10(4):131-41. doi: 10.51847/Uh1ekmZM0d.
31. Singh S, Govind M, Bothara SB. A review on in vitro—in vivo mucoadhesive strength assessment. PhaTechMed. 2013;2:221-9.
32. Kavitha K, Kumar MR, Singh SJ. Novel mucoadhesive polymers-a Review. J Appl Pharm Sci. 2011(Issue):37-42.
33. Chinthaginjala H, Telkar MB, Hindustan AA, Bhupalam P. Formulation development and optimization of famotidine mucoadhesive tablets by central composite design. Indian J Pharm Educ Res. 2022;56(4):1044-51. doi: 10.5530/ijper.56.4.185.
34. Ahad HA, Chinthaginjala H, Meharajunnisa B, Vandana N, Gudisipalli R, Nikhila P. Past work done on the matrix tablets: A quick reference for the research beginner in sustained-release dosage forms. Int J Pharm Investigation. 2023;13(3):367-72. doi: 10.5530/ijpi.13.3.047.
35. Hossain MS, Jahan S, Al Rezwan Rahman SAR, Rahman M, Kumar D, Paul S, et al. Design expert software assisted development and evaluation of empagliflozin and sitagliptin combination tablet with improved in-vivo anti-diabetic activities. Heliyon. 2023;9(3):e14259. doi: 10.1016/j.heliyon.2023.e14259, PMID 36938401.
36. Pandey N, Sah NA, Mahara K. Formulation and evaluation of floating microspheres of nateglinide. Int J Pharm Sci Res. 2016;7(11):453-64.
37. Bruni G, Berbenni V, Milanese C, Girella A, Cardini A, Viganò E et al. Thermodynamic relationships between nateglinide polymorphs. J Pharm Biomed Anal. 2009 Dec 5;50(5):764-70. doi: 10.1016/j.jpba.2009.06.017, PMID 19570642.
38. Kanakapura B, Penmatsa VK. A review of analytical methods for the determination of nateglinide in pharmaceuticals and biological samples. Pharm Chem J. 2016 Mar;49(12):854-67. doi: 10.1007/s11094-016-1386-1.
39. Patel KB, Vyas JR, Upadhyay UM. Formulation and evaluation of sustained release matrix tablets of nateglinide. J Drug Deliv Ther. 2015 Sep 21;5(5):19-25. doi: 10.22270/jddt.v5i5.1130.
40. Venkatesh DN, Meyyanathan SN, Shanmugam R, Zielinska A, Campos JR, Ferreira JD et al. Development, in vitro release and in vivo bioavailability of sustained release nateglinide tablets. J Drug Deliv Sci Technol. 2020 Feb 1;55:101355. doi: 10.1016/j.jddst.2019.101355.
41. Sharma PR, Lewis SA. Design and in vitro/in vivo evaluation of extended release matrix tablets of nateglinide. J Young Pharm. 2013 Dec 1;5(4):167-72. doi: 10.1016/j.jyp.2013.11.003, PMID 24563597.
42. Ryakala H, Dineshmohan S, Ramesh A, Gupta VR. Formulation and in vitro evaluation of bilayer tablets of nebivolol hydrochloride and nateglinide for the treatment of diabetes and hypertension. J Drug Deliv. 2015;2015:827859. doi: 10.1155/2015/827859, PMID 25648606.
43. Waidya KP, Sri SR, Janaki T. Formulation development and characterisation of repaglinide buccal tablets. Asian J Pharm Technol. 2019;9(2):79-88. doi: 10.5958/2231-5713.2019.00014.X.
44. Koirala S, Nepal P, Ghimire G, Basnet R, Rawat I, Dahal A et al. Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. Heliyon. 2021 Mar 1;7(3):e06439. doi: 10.1016/j.heliyon.2021.e06439, PMID 33786387.
45. Palem CR, Gannu R, Yamsani SK, Yamsani VV, Yamsani MR. Development of bioadhesive buccal tablets for felodipine and pioglitazone in combined dosage form: in vitro, ex vivo, and in vivo characterization. Drug Deliv. 2011 Jul 1;18(5):344-52. doi: 10.3109/10717544.2011.557786, PMID 21351826.
46. Boyapally H, Nukala RK, Bhujbal P, Douroumis D. Controlled release from directly compressible theophylline buccal tablets. Colloids Surf B

- Biointerfaces. 2010 Jun 1;77(2):227-33. doi: 10.1016/j.colsurfb.2010.01.031, PMID 20188529.
47. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive delivery systems. I. Evaluation of mucoadhesive polymers for buccal tablet formulation. Drug Dev Ind Pharm. 2004 Jan 1;30(9):985-93. doi: 10.1081/DDC-200037245, PMID 15554223.
48. Alur HH, Pather SI, Mitra AK, Johnston TP. Evaluation of the gum from Hakea gibbosa as a sustained-release and mucoadhesive component in buccal tablets. Pharm Dev Technol. 1999 Jan 1;4(3):347-58. doi: 10.1081/PDT-100101370, PMID 10434280.
49. Gowthamarajan K, Jawahar N, Wake P, Jain K, Sood S. Development of buccal tablets for curcumin using Anacardium occidentale gum. Carbohydr Polym. 2012 May 16;88(4):1177-83. doi: 10.1016/j.carbpol.2012.01.072.
50. Patel VM, Prajapati BG, Patel HV, Patel KM. Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS PharmSciTech. 2007 Sep;8(3):E77. doi: 10.1208/pt0803077, PMID 17915827.