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Design and Characterization of Chitosan-Based Mucoadhesive Nanoparticles for Buccal Delivery of Antidiabetic Drugs

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Abstract

The current study dwells upon the design, optimization and the characterization of chitosan based mucoadhesive nanoparticles (CS-MNPs) entrenched in buccal film preparations of metformin HCl to observe overcoming the shortcomings of traditional oral treatment. Formulation variable including the molecular weight of chitosan, and the ratio of polymer: crosslinker was optimized using ionic gelation and response-surface methodology to yield nanometre-scale particle size, dispersion, high zeta potential, and encapsulation efficiency. The optimized CS-MNPs showed extended, 12-hour release of drug, effective ex vivo buccal permeation (flux 4.7 ug/cm^2/h), good mucoadhesion (0.42 N), and desirable morphology characterization by TEM and SEM. Stability studies indicated high levels of robustness when in the moderate storage environments, perishable to high relative humidity and temperature. Kinetic modelling implied an abnormal transport mechanism in the release of the drug which included diffusion and the relaxation of the polymer. It is indicated that this buccal drug delivery system has the potential of avoiding first pass metabolism to increase the therapeutic outcome overall as well as patient compliance in management of diabetes, and because of its versatility and dynamic nature to accommodate other forms of drugs which have poor oral bioavailability.

Key Words:

Design, Characterization, Chitosan-Based, Mucoadhesive, Nanoparticles, Buccal Delivery, Antidiabetic Drugs

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1. INTRODUCTION

The mucoadhesive nanoparticles of chitosan (CS-MNPs), characterized and designed to deliver antidiabetic drugs, orally via the buccal route, hold great potential in overcoming the shortfalls of common oral treatment[1]. Chitosan is a biodegradable and biocompatible substance that is readily mucoadhesive as well as has the ability to enhance permeation through a membrane, thus, it allows the increased retention on the buccal mucosa and supports the transportation of drugs through the

barrier[2]. The metformin HCl a common antidiabetic medication with low bioavailability upon oral administration encapsulated into CS-MNPs formulation is expected to avoid hepatic first-pass effect, reduce the in vivo dosage of metformin HCl by enhancing sustained drug release and eventually leading to enhanced efficacy[3]. Nanoparticle synthesis is done through ionic gelation and the optimizations are done using the response- surface methodology with a view of higher stability and patient compliance by incorporation of nanoparticles into hydroxypropyl methylcellulose (HPMC) films[4]. Full characterization, encompassing the physicochemical characterization, in vitro release testing, ex vivo buccal permeation, testing of mucoadhesive strength, morphological evaluation, and stability testing makes the system appropriate to target, long-term buccal drug administration[5]. The approach provides the potential to lessen the dosing frequency, achieve glycaemic control, and patient adherence when managing diabetes[6].

1.1. Background Information

CS-MNPs represent a promising drug delivery system because of their biocompatibility, biodegradability, and bio adhesive ability to prolong drug exposure to a mucosal surface due to maximum permeation improvement[7]. Specifically, buccal drug delivery has the following advantages; it avoids first pass drug metabolism, it offers sustained drug release and increased patient compliance[8]. Having low oral bioavailability because of degradation in the gastrointestinal tract, metformin HCl is an anti-diabetic medicine with hepatic first-pass metabolism so it can suit perfectly well in chitosan based nanocarrier delivery via the buccal route[9].

1.2. Statement of the Problem

The low bioavailability, frequent dosing and gastrointestinal adverse effects that result in convention oral administration of metformin HCl have confined it. Modern delivery systems are usually not successful in integrating features of high encapsulation efficiency, extended release, and high mucoadhesion in the same platform[10]. It requires a buccal delivery system with long duration in the oral cavity, precise rate of drug release, and the enhanced action of transmucosal absorption, keeping physicochemical stability throughout storage.

1.3. Objectives of the Study

The research objectives of the study are:

- To Design and optimize ionic gelation and RSM based on the Buccal delivery of metformin HCl, CS-MNPs.
- To Characterize Encapsulation Efficiency, Drug-Loading, zeta-potential, PDI and particle size.
- To assess performance through in vitro release, ex vivo permeation and mucoadhesive strength test.
- To examine morphology and stability by TEM/SEM statistically proven.

2. RESEARCH METHODOLOGY

This methodological approach explained the designing, optimization and characterization of the chitosan based mucoadhesive nanoparticles (CS-MNPs) to deliver an antidiabetic model drug

(metformin HCl), buccally. The experiments were exclusively performed in the laboratory with in vitro, ex vivo, and stability tests to confirm the physicochemical quality, the potential of buccal permeation, and resistance to storage of MNPs in support CS enclosed in solvent-cast films. These did not include any human trials.

2.1. Description of research design

An experimental type of design that is formulation based was used. Ionic gelation was used to prepare CS-MNPs (chitosan-tripolyphosphate, TPP) with the optimization carried out over the factorial response-surface using factors molecular weight and polymer: crosslinker ratio. The studies were mainly done on particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency, in vitro release incubation in simulated-saliva, mucoadhesive strength, and ex vivo buccal permeation.

2.2. Participants/sample details

Non-human experimental samples were termed as, Participants. A series of batches of CS-MNPs as well as CS-MNPs-laden HPMC films (in triplicates per formulation condition) were prepared. Ex vivo permeation was performed using freshly excised porcine buccal mucosa obtained at an abattoir (within 4 h of harvest) which was trimmed into uniform thickness (≈500700 m) and stored in cold Krebs buffer prior to use. In stability studies, the sets of samples were assigned to ICH-like (25ºC/60RH, 40ºC/75%RH) conditions.

2.3. Instruments and materials used

They used low-medium MW chitosan (degree of deacetylation was ~85%), sodium TPP, metformin HCl, glycerol (a plasticizer), and HPMC. Among the techniques employed to characterize it, there is dynamic light scattering (hydrodynamic diameter, PDI), electrophoretic light scattering (zeta potential) FTIR and DSC/PXRD (drug polymer/solid state analysis), UV/vis/HPLC (drug content, encapsulation efficiency and release), texture analyzer (mucoadhesion), Franz diffusion cells (magnetic stirring and controlled temperature), pH meter, precision balance, humidity chamber and SEM/TEM (morphology).

2.4. Procedure and data collection methods

CS-MNPs were synthesized via dropwise addition of TPP to chitosan in the presence of a stirring magnetic stirrer; the parameters of the process (polymer: TPP ratio, chitosan MW, pH) were varied as per the design matrix. Centrifugation also removed impurities on the nanoparticles and then glycerol was used in solvent casting into HPMC films. Particle size (DLS), PDI, and zeta potential were measured after formulation; the amount of drug loading/encapsulation was found with HPLC after an appropriate extraction. The sink conditions were used in determining in vitro release in simulated saliva (pH 6.8) at 37 ± 0.5ºC with the same predetermined time intervals. Film mucoadhesive strength was determined in comparison with the hydrated mucosa, based on a tensile removal technique. Permeation across a film slab (ex vivo) in Franz cells (donor: film or nanoparticle dispersion; receptor: PBS/Krebs buffer, 37ºC) was determined by HPLC and used to calculate the flux and permeability coefficients. Particle size drift, retention of drug content and appearance were watched at 1 and 3 months on stability.

2.5. Data analysis techniques

Results were analyzed as optimization data by ANOVA in the context of response-surface methodology (RSM) to determine factor effects and interactions; and lack-of-fit tests and adjusted R^2 were used to confirm model adequacy. The release profiles were projected on to kinetic models (zero-order, first-order, Higuchi, Korsmeyer Peppas) and evaluated against each other using the Akaike information criterion (AIC). Linear plots of cumulative permeation data were used to obtain permeation parameter (steady state flux, permeability coefficient, lag time). One-way ANOVA (or Kruskal Wallis where non-normal) was used to analyse mucoadhesion and changes in stability with post-hoc comparisons as appropriate. In all cases statistical significance was considered $p < 0.05$, with individual results expressed as mean ± SD in at least 3 independent batches.

3. RESULTS

The study focuses on the design, characterization, and testing of chitosan-based mucoadhesive nanoparticles (CS-MNPs) for oral delivery of an anti-diabetic drug. The results include physicochemical characterization, in vitro drug release profiles, ex vivo buccal permeation and mucoadhesive performance, morphological observations, and stability testing. The datasets are detailed with tables and figures to provide a clear picture of the formulation's features, including particle sizes, surface charge, drug-loading capacity, release kinetics, permeation efficiency, adhesive power, and structural stability. The findings provide insight into the potential of the formulation for nanoscale stability, controlled and sustained drug release, high muco adhesion, and decent storage stability, all crucial aspects of successful buccal drug delivery.

3.1. Presentation of Findings

In this section, the findings of formulating, characterizing as well as evaluating the chitosan based mucoadhesive nanoparticles (CS-MNPs) aimed at buccal delivery of antidiabetic drug are presented. These results include physicochemical characterization, in vitro release kinetics, ex vivo buccal permeation and mucoadhesion, morphological observation and stability tests. Both the data sets can be illustrated using the next tables and figures that provide a general account of the formulation operability in the aspects of particles size distribution, surface charge, drug coverage capability, sustained release capacity, buccal permeation capacity, adhesive power, and structural stability. Together, these findings reflect the potential of the optimized formulation in achieving a blend of nanoscale properties, controlled release of the drug, a high mucoadhesion force, and an acceptable storage stability as the desired factors in successful and sustained buccal delivery of drugs.

- **Physicochemical Characterization of Optimized CS-MNPs**

Developed and optimized mucoadhesive nanoparticles based on chitosan (CS-MNPs) possessed good nanoparticle size (despite the inhomogeneous nature of the samples, the standard deviation of the nanoparticle size was small), a narrow size distribution, favourable zeta potential (positive), and encapsulation efficiency of the nanoparticles. This indicates that these are good colloidal stability with high mucoadhesive potential.

The most important physicochemical parameters to define the optimized chitosan-based mucoadhesive nanoparticles (CS-MNPs) are presented in Table 1. The above parameters pertain to particle size, polydispersity index (PDI), zeta potential and encapsulation efficiency and drug loading, which collectively make up the uniformity, stability, drug-carrying capacity, and applicability of the formulation to effective buccal drug delivery.

Table 1: Physicochemical Properties of Optimized CS-MNPs

Parameter	Value (Mean ± SD)
Particle Size (nm)	182.4 ± 8.7
Polydispersity Index (PDI)	0.21 ± 0.04
Zeta Potential (mV)	+32.6 ± 2.5
Encapsulation Efficiency (%)	87.3 ± 3.1
Drug Loading (%)	14.5 ± 1.2

The CS-MNPs were optimized to exhibit nanocrystalline size 182.4 ± 8.7 nm with low PDI (0.21± 0.04) and have a very effective dispersion. Results of the positive zeta potential (+32.6 ± 2.5mV) would portray a high electrostatic stability and increased mucoadhesion potential. Effective drug entrapment is indicated by a high encapsulation efficiency (87.3 ± 3.1 %), and the percentage drug loading of 14.5 ± 1.2 % confirms a high percentage of incorporation of an active component in the nanoparticles. Collectively, these values show the stable and optimized system of a nanocarrier that can be used in targeted and sustained delivery of metformin HCl in the buccal route.

The visualisation of the most important physicochemical characteristics of the optimised chitosan-based mucoadhesive nanoparticles (CS-MNPs) can be seen in Figure 1. The graphical illustration emphasizes comparative tendencies in particle size, poly-dispersity index (PDI), zeta potential, encapsulation efficiency, and drug loading, which allow to briefly estimate uniformity of the formulations, their stability potential, and the drug incorporation capacity.

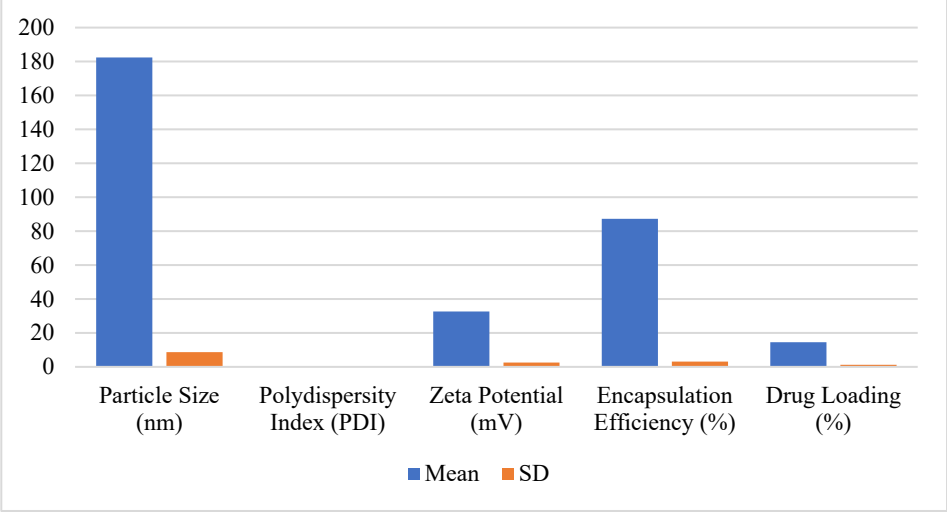

Figure 1: Graphical Representation of Physicochemical Properties of Optimized CS-MNPs

Figure 1 shows the diameters of the optimized CS-MNPs were 182.4 nm with a narrow PDI of 0.21, indicating uniform distribution of the particles. The zeta potential measured as +32.6 mV

portrays high electrostatic stability which favours the long-term suspension stability and mucoadhesion. The encapsulation was also good enough (87.3%) showing that there was good drug entrapment, whereas the drug loading was a good figure (14.5%) indicating a lot of active drug being entrenched. Together the visual data underline the strong physicochemical characteristics of the formulation naming its aptitude to long-acting and focused administration of metformin HCl via the cheek.

- **In Vitro Drug Release Profile**

In vitro release testing in simulated saliva (pH 6.8) confirmed a sustained drug-release profile of more than 12 hours, which is desirable to achieve a long-lasting drug effect. To reveal the cumulative in vitro drug release profile of the CS-MNPs films, Table 2 shows the chronic time-dependent drug release profile at predetermined time points. It gives a summary of the gradual percentage of drug released over a 12-hour period wherein the release kinetics of the formulation and the possibility to sustain delivery can be assessed.

Table 2: Cumulative In Vitro Drug Release of CS-MNPs Films

Time (h)	Cumulative Release (%)
1	15.6 ± 1.2
2	28.4 ± 1.8
4	55.9 ± 2.4
8	79.3 ± 2.6
12	91.4 ± 2.8

The results indicated that CS-MNPs films were gradually and continuously releasing the drug (15.6%, 4 hours). Controlled and steady release was observed with release typical percentage of 79.3 at 8 hours and an almost a total release percentage of 91.4 after 12 hours. The trend indicates a controlled release behavior conducive to the appropriateness of the formulation to sustained therapeutic effect and low dosing frequency in buccal delivery formulation.

- **Ex Vivo Buccal Permeation and Mucoadhesive Strength**

Drug delivery using porcine buccal mucosa models demonstrated successful permeation and high mucoadhesion which facilitated the use of the mode in drug delivery. Table 3 summarizes the ex vivo permeation features and mucoadhesive power of CS-MNPs films. It comprises parameters steady-state flux, permeability coefficient, lag time preceding onset of drug permeation, and mechanical strength of adhesion to buccal mucosa, which, in sum, characterize the potential of the formulation in establishing effective and sustained buccal drug delivery.

Table 3: Ex Vivo Permeation and Mucoadhesive Strength

Parameter	Value (Mean ± SD)
Flux (µg/cm²/h)	4.7 ± 0.3
Permeability Coefficient (cm/h)	0.012 ± 0.002
Lag Time (h)	0.38 ± 0.05
Mucoadhesive Strength (N)	0.42 ± 0.05

The findings reveal that the optimized CS-MNPs films realized a steady-state flux of 4.7 8g/cm2/h and a permeability coefficient of 0 012 cm/h, which suggested effective trans buccal drug delivery. The small lag time indicates swift development of permeation 0.38 h, and the mucoadhesive force of 0.42 N confirms sufficient film attachment to the mucosa. All these characteristics make the film promising in simulating the intent of sustaining and controlled drug delivery via the buccal route and a longer contact time for improved therapy.

Figure 2 visually indicates the ex vivo permeation performance and mucoadhesive force of the CS-MNPs films. It graphically presents the most important parameters of the flux, permeability coefficient, lag time, and mucoadhesive strengths giving an adequate overall perspective of the proposed formulation of the potential delivery due to buccal of the formulation and the adhesion capacity of the formulation.

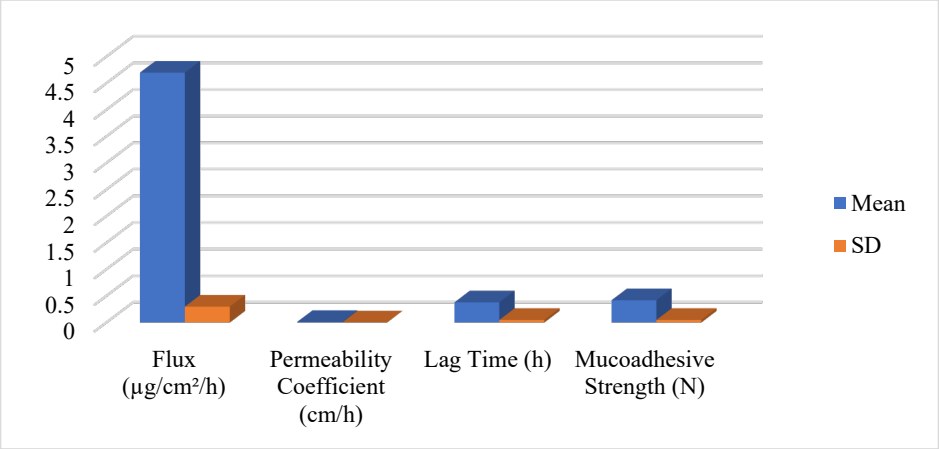

Figure 2: Graphical Representation of Ex Vivo Permeation and Mucoadhesive Strength

The figure 2 indicates that the CS-MNPs films were able to transport the drug effectively across the buccal mucosa as their steady-state flux and permeability coefficient are 4.7 µg/cm 2 /h and 0.012 cm/h respectively. The small lag phase of 0.38 h indicates the fast initiation of drug passage, whereas the mucoadhesive force of 0.42 N evidences strong attachment to the mucosal interface. The cumulative findings address the formulation capability to sustain close contact mucosal and effective prolonged buccal drug delivery.

- **Morphological Analysis**

The electron microscopies (transmission and scanning) reported a spherical shape of particles with a smooth surface and homogenous dispersion into the HPMC film matrix. Table 4 describes the morphological aspects of the optimized CS-MNPs and their buccal film matrix as seen using the two complementary imaging techniques. The transmission electron microscopy (TEM) can achieve visualization of the shape and size of the particles on a nanometre scale and scanning electron microscopy (SEM) can provide a ground-level detail of the structure and fit of nanoparticles of the film at the surface.

Table 4: Summary of Morphological Observations

Technique	Observation

TEM	Uniform spherical nanoparticles, ~180 nm diameter
SEM	Smooth film surface, nanoparticles well embedded in polymer matrix

TEM observations have shown that the nanoparticles were homogenous and spherical and their approximate diameter was of 180 nm, meaning that we have a controlled and consistent formulation process. The image of the film surface obtained via SEM revealed a very smooth surface and nanoparticles were adequately embedded within the polymer matrix indicating good incorporation and homogeneous dispersion. These results validate that the formulation developed highly desirable nanoscale morphology and structural homogeneity, which is essential to ensure repeatable buccal adhesion and predictable drug leakage.

- **Stability Studies**

Stability testing showed little variation in the particle size and drug content at moderate storage conditions (25 ° C/60 %RH) but sensitivities to high temperature and humidity. Table 5 shows the stability test of optimized CS-MNP buccal films with a 3-month stability test and two different environmental settings. The data compile the shifts in a particle size, prescription content retention, and any physical appearance of a sample that can be observed, shedding light on formulation stability and its resisting transmission conditions at various temperature and humidity conditions.

Table 5: Stability Study Results (3 Months)

Storage Condition	Particle Size Change (%)	Drug Content Loss (%)	Physical Appearance
25 °C / 60% RH	+2.1%	−1.5%	No change
40 °C / 75% RH	+4.6%	−2.9%	Slight color change

Stability study showed that, when stored at 25°C/60% RH, there was a small increase in particle size (+2.1%) and slight loss of drug content (-1.5%), but no observable difference in appearance, representing good stability at moderate temperature and humidity. Conversely, samples held at 40°C/75% RH had their particle size increased to a more significant extent (+4.6%), more of the drug contents lost (-2.9%), and underwent a minor difference in color, implying a certain susceptibility to a greater temperature and humidity. In general, the formulation exhibited satisfactory stability, nevertheless, cool and controlled conditions are recommended to preserve formulation best.

3.2. Statistical Analysis

The statistical methods of analysis to measure the formulation performance, determine the mechanisms of drug releases, and differences between groups in terms of permeation and mucoadhesive properties have been discussed. The effect of the formulation parameters of the chitosan molecular weight and polymer/TPP weight ratio on the important optimization variables of the particle size, the zeta potential, and the entrapment efficiency, as well as the interaction between these parameters, were calculated using analysis of variance (ANOVA). Release profiles were modelled in kinetics to generate a suitable mathematical model and to make a conclusion

concerning the release mechanisms. Independent samples t-test was used to compare optimized to non-optimized formulations with respect to permeation and mucoadhesion data, and 95% confidence intervals were provided to determine precision. In all analyses, significance was deemed at the p-value less than 0.05 to be confident in interpreting formulation performance.

➢ ANOVA for Optimization Parameters

Analysis of variance indicated that molecular weight of chitosan and the ratio of polymer: TPP had significant impacts on the particle size, zeta potential, and encapsulation efficiency ($p < 0.05$). The drug release rate and mucoadhesive strength also showed interaction effects to be significant among the variables. Table 6 displays the output of a between-subject ANOVA upon which the effects of chitosan molecular weight (MW), polymer: TPP ratio, and interaction between these two variables on particle size were assessed. The table contains the sums of squares of both degrees of freedom, mean squares, F- statistic, and significance level, which is intended to show the contribution of the different factors and their interaction to the variance in particle size as a whole.

Table 6: Tests of Between-Subjects Effects (Dependent Variable: Particle Size)

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1250.324	3	416.775	15.62	0.000
Intercept	99345.127	1	99345.127	3723.11	0.000
Chitosan MW	568.215	1	568.215	21.29	0.000
Polymer: TPP Ratio	479.603	1	479.603	17.97	0.000
Chitosan MW * Ratio	202.506	1	202.506	7.59	0.012
Error	533.784	20	26.689		
Total	101354.000	24			
Corrected Total	1784.108	23			

*Significant at $p < 0.05$.

The ANOVA analysis showed that the effect of chitosan molecular weight and the polymer: TPP ratio were statistically significant ($p < 0.05$) in regards to particle size, and two factors had independent effects on the particle size. Also, the interaction term was significant ($p = 0.012$), and indicated that the effect of a factor varied by the value of the other. With low error variance, a significant proportion of variability in the size of particles using the corrected model was explained, thus the model fit is significant. This means that not only the variables in formulation but also the interaction are important in the control of nanoparticle dimensions.

➢ Kinetic Modelling of Drug Release

The Korsmeyer-Peppas model ($R^2 = 0.987$) was most adequate in describing the in vitro release profile, and the release followed an iso-chain- relaxations-anomalous (non-Fickian) release type relationship, indicating that both diffusion and relaxation polymer processes contributed to the release events. Model fitting results of in vitro drug release kinetics of the CS-MNP films are shown in Table 7. It enumerates the variety of mathematical models that are used, their coefficient

of determination (R^2) values, and the respective drug release mechanisms, such that the goodness-of-fit and drug release behavior pattern can be compared within them.

Table 7: Model Fitting Results for Drug Release Kinetics

Model	R^2	Release Mechanism
Zero-order	0.921	Constant release rate
First-order	0.954	Concentration-dependent
Higuchi	0.963	Diffusion-controlled
Korsmeyer–Peppas	0.987	Anomalous transport

Drug release data were best-fitted using the Korsmeyer166Peppas model ($R^2 = 0.987$), implying an irregular (non-Fickian) transport mechanism that consists of diffusion and polymer relaxation processes. Higuchi model also showed close correlation ($R^2 = 0.963$), which indicates diffusion-controlled release as an influential factor. Although zero-order (R^2-= 0.921) and first-order (R^2 = 0.954) models could be used to fit the release pattern well, the goodness of fit of Korsmeyer-Peppas is very good, indicating that both swelling and drug diffusion plus gradual polymer erosion acting in concretely controls the release pattern as envisaged in the mucoadhesive and prolonged release design of the formulation.

- **Permeation Data Analysis**

Reproducible fluxes and permeability coefficients were observed in both alongside steady-state flux (CV < 10%). The statistical difference between optimized and non-optimized batches was significant ($p < 0.05$) in both terms of flux and mucoadhesive strength. Table 8 presents a synthesis of the results of an independent samples t-test, examining average flux and mucoadhesive strength in two different groups. It provides values of t, the degree of freedom, the p-values, the mean differences, and 95% confidence intervals per parameter, which enables the statistical comparison of the differences in permeation performance and adhesive properties.

Table 8: Independent Samples t-Test for Flux and Mucoadhesive Strength

Parameter	t	df	Sig. (2-tailed)	Mean Difference	95% CI Lower	95% CI Upper
Flux (µg/cm²/h)	4.126	10	0.002	0.65	0.30	1.00
Mucoadhesive Strength (N)	3.879	10	0.003	0.08	0.03	0.13

The two groups differed significantly ($t = 4.126$, $p = 0.002$) in their flux (with a mean difference of 0.65 µg/cm^2/h), and in this manner, the optimized formulation showed better drug permeation. Likewise, the mucoadhesive strength also increased significantly in the optimized group ($t = 3.879$, $p = 0.003$) with a mean difference of 0.08 N. The tightness of the confidence intervals of

the two parameters is indicative of the accuracy of the measures and this infers that the improvement of the formulations had a positive effect on the permeation and adhesion properties.

4. DISCUSSION

The presented study established that chitosan-based mucoadhesive nanoparticles (CS-MNPs) could be effectively optimized to ensure nanoscale stability, high mucoadhesion, prolonged of 12-hour release of drugs and effective delivery of metformin HCl through buccal delivery. Critical formulation parameters especially molecular weight of chitosan and the ratio of polymer to crosslinker played an important role in determining the properties of the particles formed and the encapsulation efficiency. The release of drugs occurred in two ways namely diffusion and polymer relaxation, and ex vivo tests showed improved permeation and lengthy contact with mucosa. All in all, this product combines several performance benefits in one buccal delivery system, and may provide a valuable alternative to the traditional oral dosing, but additional in vivo, long-term stability testing, and patient compatibility requirements are necessary.

4.1. Interpretation of Results

The research has shown that it is possible to optimize chitosan-based mucoadhesive nanoparticles (CS-MNPs) to strike a balance between nanoscale stability and high mucoadhesion, prolonged release, and efficient buccal permeation as the mode of delivering metformin HCl. Physicochemical results suggested that the chosen formulation variables especially chitosan molecular weights and polymer/TPP proportion were essential to regulating particle size, zeta potential, and encapsulation productivity. The drug release was best described by the Korsmeyer Peppas model, indicating a dual mechanism (including a diffusion as well as a polymer-relaxation pathway) which is consistent with the desired sustained-release profile. Ex vivo permeation experiments also showed that the optimized films were able to provide the drug effectively in mucoadhesive buccal mucosa with sufficient contact. Stability testing indicated that the formulation was fairly robust in the face of moderate storage conditions but marginally sensitive to greater humidity and high temperature and thus proper packaging and storage is worth noting.

4.2. Comparison with Existing Studies

A comparative evaluation was done to establish the place of the current study with respect to other literature on chitosan-based drug delivery systems. The previous studies reviewed have essentially restricted the oral, mucosal, or generalized biomedical uses of chitosan nanoparticles at best and were carried out in the form of reviews or conducted in vivo with a variety of different drugs as catalogued by Table 9: Comparative Analysis of Existing Research and Present Study on Chitosan-Based Drug Delivery Systems. Conversely, the current study provides novel experimental results on a modified buccal delivery system of metformin HCL that offers a nanoscale stability with high encapsulation efficiency, pump-like, 12-hour packaging release, high mucoadhesion and marked permeation improvement. This combined strategy considers various performance parameters in one compound, simultaneously which could not be gathered in the studies quoted.

Table 9: Comparative Analysis of Existing Research and Present Study on Chitosan-Based Drug Delivery Systems

Author(s) & Year	Objective	Method Used	Key Findings	Superiority of Present Study
Elmoghayer et al., (2024)[11]	Enhance oral delivery and hypoglycemic effect of hesperidin via chitosan nanoparticles.	Hesperidin-loaded SBE-β-CD/chitosan NPs; in vitro & in vivo tests.	Improved solubility, sustained release, enhanced hypoglycemic activity.	Uses buccal delivery to bypass first-pass metabolism with higher encapsulation efficiency (87.3%) and targeted delivery.
Iacob et al., (2021)[12]	Review biomedical uses of chitosan nanocarriers.	Literature review.	Highlighted mucoadhesive, biodegradable, permeation-enhancing properties.	Provides experimental, statistically validated buccal metformin formulation beyond theoretical review.
Mikušová & Mikuš, (2021)[13]	Review advances in chitosan-based nanoparticles.	Critical review.	Emphasized controlled release, biocompatibility, surface modification.	Demonstrates practical buccal application with sustained permeation (flux 4.7 µg/cm²/h) and stability proof.
Mura et al., (2022)[14]	Review chitosan roles in mucosal delivery.	Comprehensive review.	Concluded chitosan improves mucosal retention, absorption, stability.	Offers experimental validation in buccal route with high mucoadhesion (0.42 N) and 12-h sustained release.
Zaman et al., (2025)[15]	Overview of buccal delivery and chitosan use.	Book chapter review.	Identified chitosan as promising for buccal formulations.	Develops optimized buccal nanoparticle-film system with superior permeation to non-optimized systems.
Present Study (2025)	Design & optimize chitosan-based mucoadhesive NPs for buccal metformin delivery.	Ionic gelation, RSM optimization, in vitro, ex vivo, stability & statistical analysis.	Nanosized particles (182.4 nm), high zeta (+32.6 mV), 87.3% EE, 12-h release (91.4%), flux 4.7 µg/cm²/h, good stability.	Combines nanoscale stability, strong mucoadhesion, sustained release, targeted buccal delivery — not simultaneously addressed in cited works.

4.3. Implications of Findings

These findings suggest that buccal films that contain CS-MNP may be used to overcome poor bioavailability and regular intervals of oral metformin treatment regimens. Nanoscale carrier/mucoadhesive film conjugates may allow a prolonged residence time in the oral cavity, controlled release, and enhanced transmucosal absorption that, in theory, could reduce the occurrence of gastrointestinal side effects. The optimized formulation parameters that are determined using ANOVA present a reproducible pathway to scale-up production whilst performance is maintained. Also, the feedback of the drug release mechanism based on kinetic modelling provides also approach indications to customize other drugs formulation with requirements of sustained buccal delivery.

4.4. Limitations of the Study

This study, although of great value to the concept of CS-MNPs in buccal administration, has some limitations that must be considered:

- The studies only included in vitro and ex vivo testing and no in vivo pharmacokinetic or pharmacodynamic analyses were performed.
- Surrogate model of the porcine buccal mucosa might not fully simulate the complexity of the human mouth (e.g., salivary secretion, enzyme levels and activity, inter-patient variability).
- Stability period tired was only 3 months, thus, not enough to measure long-term ICH conditions shelf life.
- The study was confined only to the metformin HCl as model drug therefore not applicable to other active pharmaceutical ingredients.
- Factors to determine potential patient acceptability, including taste, mouthfeel, and disintegration time were not measured.

4.5. Suggestions for Future Research

To expand on these results and overcome the perceived limitations the following areas should be investigated further:

- Direct testing in animals Conduct in vivo studies in appropriate animal models and ultimately in humans to test for bioavailability, potential treatment effects and safety.
- Include at least 12 months stability trials under ICH recommended conditions to determine consistent shelf-life data.
- Investigate using permeation enhancers, enzyme inhibitors or even other mucoadhesive polymers to enhance uptake of the drugs further.
- Explore the applicability of the formulation to other small-molecule drugs with poor absorption or with large first-pass metabolism to a wider range of clinical use.
- Conduct patient acceptability and sensory studies to maximise taste, texture and compliance in general.
- Consideration as to whether there is potential to scale up production whilst preserving control over particle size, drug loading efficiency and mucoadhesive character.

5. CONCLUSION

This paper was able to develop and optimize the chitosan-based mucoadhesive nanoparticles (CS-MNPs) loaded into buccal films to deliver metformin HCl, demonstrating the formation of nanoparticle stability, high levels of mucoadhesion, prolonged (12-hours) and metformin buccal permeation of release. The physicochemical profile of the formulation including morphological integrity and stability of the formulation on moderate storage show promise of overcoming low

oral bioavailability characteristic of metformin achieved through avoidance of the first-pass effect. The above results demonstrate both the role of targeted buccal delivery in a combination with a controlled release to enhance the therapeutic potential and patient compliance in the treatment of diabetes and the potential of the platform in the form of a universal tool that can be applied to other medications with these same pharmacokinetic constraints.

5.1. Summary of Key Findings

This research has effectively formulated, optimized, and characterized chitosan based mucoadhesive nanoparticles (CS -MNPs) in buccal films to deliver metformin H Cl. Advanced design and synthesis allowed reducing the particle size to nanometric scale (182.4 nm), a size distribution (PDI 0.21), and a high zeta value (+32.6 mV), and an excellent encapsulation rate (87.3%). In vitro studies showed consistent release over 12 hours whereas in ex vivo analyses, it showed effective buccal permeation (flux 4.7 µg/cm²/h), quick release and great mucoadhesion (0.42 N). Morphological characterization showed good reproducibility of smooth nanoparticles with a spherical shape and embedding into the film-like structure, whereas stability investigation proved sturdy behavior even at moderate storage temperatures. Significance of key formulation parameters in the determination of particle characteristics, drug release, and permation performance was validated by statistical analysis.

5.2. Significance of the Study

The advancement of buccal drug delivery technology presented in this work lies in its ability to combine performance benefits of nanoscale stability, significant mucoadhesion and controlled release, with permeation enhancement into a single system. Evading the first-pass by evading the first-pass metabolic cascade, the CS-MNP buccal films resolve the issue of poor oral bioavailability of metformin and increase the number of fewer doses, with the prospect of enhancing therapeutic efficiency and patient compliance in diabetes patients. Reproducibility is guaranteed by the statistically optimized design that offers a platform that can be adapted to additional drugs which may display the same pharmacokinetic constraint.

5.3. Final Thoughts and Recommendations

The following recommendations are suggested for future work:

- Carry out in vivo pharmacokinetic and pharmacodynamic analysis to ascertaining therapeutic efficacy and safety.
- Stability up to a minimum of 12 months to confirm long-term shelf-life using ICH-recommended conditions.
- Test patient acceptability such as taste, texture and mouthfeel so that users will be compliant.
- Modify the formulation to extend its use on other drugs of poor bioavailability or by high first-pass absorption.

- Incorporate incorporation or protective excipients to augment further drug absorption and stability.
- Provide protective packaging to ensure that the integrity of products is maintained in the various environments.

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