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STRATEGIC INTEGRATION OF QUALITY BY DESIGN PRINCIPLES IN THE DESIGN, FORMULATION, AND OPTIMIZATION OF BUCCAL MUCOADHESIVE TABLETS: A COMPREHENSIVE REVIEW OF RECENT ADVANCEMENTS AND LITERATURE FINDING

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ABSTRACT

This review presents a comprehensive analysis of buccal mucoadhesive tablets prepared using Quality by Design (QbD) principles, integrating both recent advancements and past literature findings. Buccal mucoadhesive tablets offer a promising drug delivery platform characterized by enhanced bioavailability, prolonged drug release, and improved patient compliance. Through a systematic review of the literature, this study examines the application of QbD methodologies in the design, formulation, and optimization of buccal mucoadhesive tablets. Critical quality attributes (CQAs) and critical process parameters (CPPs) relevant to buccal tablet formulation are identified and discussed in the context of QbD. Furthermore, the review explores the utilization of various analytical techniques and mathematical modeling approaches to establish correlations between formulation variables, manufacturing processes, and product performance. Challenges such as mucoadhesion strength, drug release kinetics, and formulation stability are addressed within the QbD framework, emphasizing the importance of understanding and controlling these parameters to guarantee the standard of the product and performance consistency. By synthesizing insights from past literature and recent developments, this review provides valuable guidance for researchers and pharmaceutical scientists in the rational design and optimization of buccal mucoadhesive tablets using QbD approaches.

Keywords: Buccal drug delivery, Formulation, mucoadhesion, Optimization, Release

1. INTRODUCTION

Bio-adhesive buccal distribution stands as a pivotal strategy in pharmaceutical science, particularly for drugs susceptible to first-pass metabolism, where their efficacy may be significantly compromised by the enzymatic activity of the liver or the harsh conditions within the gastrointestinal tract. By circumventing these challenges, buccal drug delivery offers a promising alternative route that ensures the efficient and effective delivery of medications to the systemic circulation or localized mucosal sites within the oral cavity.

The buccal cavity, encompassing the inner cheek and gum area, serves as an advantageous site for drug administration due to its accessibility and permeability. Through the buccal mucosal membrane, medications can be absorbed directly into the bloodstream, bypassing the hepatic portal system and thus avoiding first-pass metabolism in the liver. This route enables drugs to exert their therapeutic effects more rapidly and with increased bioavailability compared to traditional oral administration.

Within the realm of buccal drug delivery, two distinct pathways exist: mucosal and transmucosal. Mucosal delivery entails the localized release of medication onto the mucosa, facilitating targeted effects at the site of administration. In contrast, transmucosal delivery involves the passage of drugs through the mucosal barrier, leading to systemic absorption and distribution throughout the body. This versatility allows for tailored therapeutic approaches, depending on the desired outcome of drug therapy.

One of the notable advantages of buccal drug absorption is its inherent safety mechanism. In cases of drug toxicity or adverse reactions, the absorption process can be promptly halted by removing the dosage form from the buccal cavity. This feature provides healthcare practitioners with a rapid means of intervention, minimizing the risk of systemic toxicity and ensuring patient safety **[1]**.

Furthermore, buccal drug delivery offers a viable option for patients who may have difficulty swallowing or who are unable to tolerate oral medications. By avoiding the gastrointestinal tract, buccal administration mitigates the risk of gastrointestinal irritation or discomfort, enhancing patient compliance and treatment adherence. Additionally, for pediatric or geriatric populations, buccal dosage forms may offer a more convenient and acceptable means of medication administration.

Mucoadhesive dosage forms, including adhesive tablets, gels, and patches, have been specifically developed to optimize buccal drug delivery. These formulations adhere to the mucosal surface, prolonging contact time and facilitating enhanced drug

absorption. By harnessing the adhesive properties of these dosage forms, researchers aim to optimize drug delivery efficiency and therapeutic outcomes **[2]**.

This review analyzes buccal mucoadhesive tablets using QbD principles, integrating recent advancements with past literature. It explores how QbD methods optimize formulation for enhanced bioavailability and patient compliance, identifying critical parameters and addressing challenges like mucoadhesion strength. The objective is to guide researchers in optimizing buccal drug delivery using QbD approaches.

1.1. Advantages of Buccal Drug Delivery System

Drug administration via buccal mucosa offers several distinct advantages viz **[3, 4]**.

- Compared to other mucosal tissues, the buccal mucosa is durable and has a substantial blood supply, making it more permeable.
- Ignore the first-pass effect and prevent the medications from coming into contact with the digestive juices.
- Due to the easily accessible membrane locations, facilitates medication application, localization, and simple removal.
- Augment drug performance by ensuring prolonged mucosal contact.
- High patient acceptance as compared to other non-oral medication methods of administration.
- Increased residence time combined with controlled API release may lead to lower administration frequency.
- Additionally, because of API localization to the illness site, it is significant cost savings and a decrease in dose-related adverse effects may be realized.

1.2. Limitation of buccal drug administration

Certain restrictions apply to medications given by the buccal route are as follows **[5]**:

- Drugs with ample doses are often difficult to administer.
- Possibility of the patients to swallow the tablets being forgotten.
- Eating and drinking are restricted till the end of drug release.
- Drugs that show instability at the pH of the buccal environment shouldn't be taken by this route.
- For medications that are unstable at the pH of the buccal environment, this route is undesirable.

1.3. Drug permeability through buccal mucosa:

There are two routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

- Transcellular (intracellular, passing through the cell)
- Paracellular (intercellular, passing around the cell).

1.4. Structure and Design of Buccal Dosage Form

- Matrix type: Drug adhesive and a combination of additives are present in the buccal tablet, which is depicted in a framework configuration.
- Reservoir type: The buccal patch outlined in a supply framework encompasses a cavity for the sedate and added substances isolated from the adhesive. An impermeable backing is connected to control the heading of medicate conveyance to minimize depreciation and deterioration while within the mouth, and to anticipate medicate loss.

1.5. Buccal mucoadhesive dosage form

Mucoadhesive drug delivery systems function through the use of the bioadhesion of certain polymers, which become stuck when hydrated. This allows the medicine to be delivered to particular regions of the body and stay there for an extended duration of time. The ability to maintain a medication delivery system at a specific site for a prolonged duration is extremely important for both local as well as systemic medication bioavailability. The pharmaceutical elements of mucoadhesion have garnered a lot of attention nowadays because they provide the potential to prevent drug activation utilizing the liver's first-pass metabolism or degradation by the gastrointestinal tract **[6]**.

1.6. Types of buccal mucoadhesive dosage form

- Type I: It is a single-layer device that releases drugs in several directions. This kind of dosage form has substantial medication loss as a result of ingestion.
- Type II: In this kind, an impermeable backing layer covers the drug-loaded bioadhesive layer, forming a double-layered device that stops medication loss resulting from the dosage form's top surface into the oral cavity.
- Type III: The medication is exclusively delivered from the portion that is contiguous to the buccal mucosa, making this a unidirectional release mechanism with minimal drug loss. The goal will be achieved by coating the entire dosage form, except the portion that corresponds with the buccal mucosa **[7]**.

2. METHODS OF MAKING BUCCAL MUCOADHESIVE TABLETS

2.1. Direct compression method

Direct compression is the process of directly compressing materials in powder form into tablets without changing the materials' inherent physical properties. Since this

approach is frequently the least expensive, especially when producing generics that the active ingredient allows, the technology used in this process acquires major relevance in tablet formulations. Many of the issues with both wet and dry granulations are circumvented by direct compression **[8]**.

2.2. Wet granulation method

The wet granulation process is used for the preparation of the Mucoadhesive Buccal tablet. Except for lubricants, all of the materials were combined in ascending weight order and blended for ten minutes inside an inflated polyethylene bag. Then drug was added to this mixture and mixed for min. Granulation was done with a binder solution and the damp mass passed through the sieve after that granules were dried in air and passed through the sieve, magnesium stearate & talc were added and mixed followed by tablet compression **[9]**.

2.3. Drug transport mechanism

The mechanism involved in drug transport through the buccal mucosa employed two major pathways such as transcellular and paracellular pathways. The transcellular route involves the crossing of the cellular membranes with a polar and a lipid domain whereas the paracellular route essentially implicates the passive diffusion through the extracellular lipid domain. It is widely acknowledged that the lipid structure within the extracellular space significantly contributes to the barrier function of the paracellular pathway, particularly for hydrophilic compounds with large molecular weight, such as peptides. To enter systemic circulation, drugs must traverse an enzymatic barrier posed by enzymes present on the mucosal surface and within the mucosa. However, this enzymatic barrier is generally less potent compared to that found in the gastrointestinal tract. Aminopeptidase, carboxypeptidase, and esterase enzymes have been identified in human buccal epithelial cell culture homogenates, as well as in human and porcine buccal mucosae. Nonetheless, the utilization of tissue homogenates does not enable differentiation between membrane-bound and cytoplasmic enzymes. Depending on the transport mechanism (transcellular or paracellular), a drug is probable to meet only some of the aforementioned enzymes, particularly peptide medications that enter the buccal epithelium over a paracellular channel do so only when they come into touch with extracellular enzymes. Recently, researchers discovered that aminopeptidases are the sole peptidases present in the buccal mucosa. They proposed that the proteolytic activity observed on the mucosal surface reflects the presence of surface membrane-bound proteases within the underlying buccal epithelial cells. Penetration enhancers refer to substances capable of enhancing the

transportation of drugs across epithelial barriers. The TR146 cell line, derived from squamous carcinoma of the neck and nodes, is utilized as an immortalized buccal cell line in vitro culture to mimic the buccal epithelium. Sections of the buccal epithelium are – (a) Superficial layer; (b) basal layer; (c) basal membrane and (d) lamina propria **[10]**.

3. EVALUATION OF MUCOADHESIVE BUCCAL TABLETS

The produced formulations were evaluated to determine their physicochemical qualities and release characteristics.

3.1. Pre-compression parameters

3.1.1. Angle of repose

The top of the funnel was set in a stand so that it was 6 cm above the surface. The powder formed a mound after being passed out of the funnel. The equation was used to ascertain the angle of repose once the heap's height and radius were determined (E.q.1)**:**

$$\textbf{Angle of repose } (\Theta) = \tan^{-1}\frac{h}{r} \text{---(1)}$$

Where Θ =Angle of repose, h=height of heap, r=radius

3.1.2. Bulk and tapped densities

The ratio of the powder's total mass to its bulk volume is known as its bulk density. It was calculated by adding the precisely weighed grams of powder blend to a graduated measuring cylinder and noting the total volume. It is communicated in g/ml and is given by (E.q.2)**:**

$$Bd = \frac{m}{Vo} \text{---(2)}$$

Where, m = mass of the powder Vo = bulk volume of powder

Accurately measured amounts of powders were placed into measuring cylinders. These cylinders were subsequently tapped using a bulk-density apparatus for 100 iterations. The resulting heights of the tapped powders were recorded, and the tapped density was then determined using the provided equation (E.q.3)**:**

$$\textbf{Tapped density (TD)} = \frac{\textbf{Weight of the powder sample}}{\textbf{Volume of the tapped powder sample}} \text{---(3)}$$

3.1.3. Compressibility index- The compressibility index (CI) or Carr's index value of prepared formulation was computed according to the following equation where Td-tapped density Bd- bulk density (E.q.4)**:**

The formula used for Carr's Index was:

$$\textbf{CI} = \frac{Td-Bd}{Td} X\textbf{100} \text{--- (4)}$$

3.1.4. Hausner's Ratio

Hausner ratio of the formulation was determined by comparing the tapped density to the bulk density using the equation (E.q.5)**:**

$$\textbf{Hausner's Ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}} \text{---(5)}$$

3.2. Post-compression studies

3.2.1. Tablet weight uniformity

Tablets from each batch are selected at random and weighed individually. The individual weights are compared with the

average weight for the determination of weight variation (E.q.6)**:**

$$\textbf{Weight variation} = \frac{IW-AW}{AW} X100 \text{---(6)}$$

IW= Initial weight

Aw= Average weight

3.2.2. Disintegration test

Six tablets were taken and placed in each compartment of the disintegration apparatus, with a water thermos stated at 37±2^{o}C as the medium and the reading **[11]**.

3.2.3. Tablet thickness

Approximately ten tablets from different formulations were taken and measured with the help of a digital micrometer, and the mean thickness was calculated.

3.2.4. Hardness

The hardness of all the formulations of buccal mucoadhesive tablets was measured by using a Monsanto hardness tester. The compressive force endured by 10 tablets of known weights from each formulation was measured in kg/cm^2, and the mean was computed and displayed with standard deviation. According to the specifications of USP hardness values of 4-5 Kg for tablets are considered an acceptable limit **[12]**.

3.2.5. Friability

The hardness of tablets is not a perfect measure of strength since certain formulations lose their crown locations when compressed into extremely hard tablets. For this reason, the friability of the tablet is assessed, which is another indicator of its strength. The Roche friabilator is used to test tablet strength. Test subjects are given several tablets to experience the combined effects of shock and abrasion through the use of a plastic chamber that rotates for four minutes at a pace of twenty-five revolutions per minute, dropping the tablets six inches each time. After being filled with a sample of pre-weighed tablets, the Roche friabilator was turned on for 100 revolutions **[13]**. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as (E.q.7)**:**

$$F(\%) = \frac{Wo-W}{Wo} X100 \text{---(7)}$$

Where W_0 is the initial weight of the tablets before the test and W is the final weight of the tablets after the test.

3.2.6. Drug content uniformity

Five tablets were powdered separately from each formulation, and an amount corresponding to 100mg of the drug was precisely measured and extracted using an appropriate volume of 0.1 N HCl. Each extract was appropriately diluted and analyzed spectrophotometrically **[6]**.

3.2.7. Surface pH

The buccal tablet's surface pH was measured to look into any potential in vivo adverse effects. It is best to maintain the surface pH as near to neutral as possible since an acidic or alkaline pH may irritate the buccal mucosa. For this, a composite glass electrode was employed. By exposing the

tablet to 1 ml of pH of the desired buffer for two hours at room temperature, the swelling process was facilitated. Following the placement of the electrode in contact with the tablet's surface and allowing it to stabilize for one minute, the pH was measured **[14]**.

3.2.8. Swelling studies

The swelling studies were performed and the swelling of all the tablets was increased as the time proceeds because the polymer gradually absorbs water due to the hydrophilicity of the polymer. Initially, the outer hydrophilic polymer layer of the tablet undergoes swelling, followed by gradual dissolution of the hydrated layer. This hydration swelling process continues towards the newly exposed surfaces, ensuring the integrity of the dosage form. Buccal tablets are weighed individually (W_1) and positioned separately in Petri dishes containing buffer for 8 h at regular intervals of time (1, 2, 4, 6, and 8 h) after that tablets were taken out of the petri dish, and surplus surface water is removed using filter paper **[2]**. The tablets are weighed (W_2) and the swelling index (SI) is calculated as follows (E.q.8)**:**

$$SI = \frac{w2-w1}{w1} X100 \text{---(8)}$$

3.2.9. *In-vitro* drug release studies

The *in-vitro* dissolution test followed the method outlined in the Indian Pharmacopoeia. The rotating paddle method was employed to assess the release of the drug from the tablets. Tablets designated for dissolution testing were utilized. The dissolution medium comprised 900 ml of buffer with the desired pH. The test was conducted at a temperature of 37±0.5°C at a specified rpm. At each described interval, 5 ml samples were withdrawn and replaced with an equal volume of fresh medium. The withdrawn samples were diluted with buffer, filtered, and analyzed using an ultraviolet spectrophotometer. The percentage of drug release was determined using the calibration curve of the standard drug **[15]**.

3.2.10. *In-Vitro Bioadhesive Strength*

The word "bioadhesion" refers to the binding of a medication delivery system to a particular biological site. The modified physical balance was utilized to test the in-vitro bioadhesive strength of the tablets. The porcine buccal mucosa was utilized as a model membrane, and the moistening fluid of the desired buffer solution was taken. The average bioadhesive strength was found by triplicate bioadhesive tests. Based on the mucoadhesive strength and adhesion forces are calculated by (E.q.9) **[16]:**

$$Force\ bioadhesion = \frac{bioadhesive\ strength}{100} X9.81 \text{---(9)}$$

3.2.11. Drug release from the backing layer

Franz diffusion cell was used to measure drug release from the backing layer. A

buccal tablet with two layers was positioned between the receptor and donor compartments. The entire apparatus was kept at 37°C; the receptor compartment held the desired buffer pH with synchronous stirring. The samples were taken out of the donor compartment at prearranged intervals and subjected to UV spectrophotometric examination **[17]**.

4. QUALITY BY DESIGN

It is a systematic approach to pharmaceutical development based on sound science and quality risk management, which begins with predefined objectives and emphasizes product and process understanding and process control, this is what quality-based development, or QbD, is all about. Employing Quality by Design (QbD) principles will enhance scientific comprehension and expertise, facilitating the manufacturing of pharmaceuticals. Pharmaceutical QbD goals may include **[18]**:

- To achieve meaningful product quality specifications;
- To increase process capability and reduce product variability
- To increase pharmaceutical development and manufacturing efficiencies
- To enhance cause-effect analysis and regulatory flexibility.

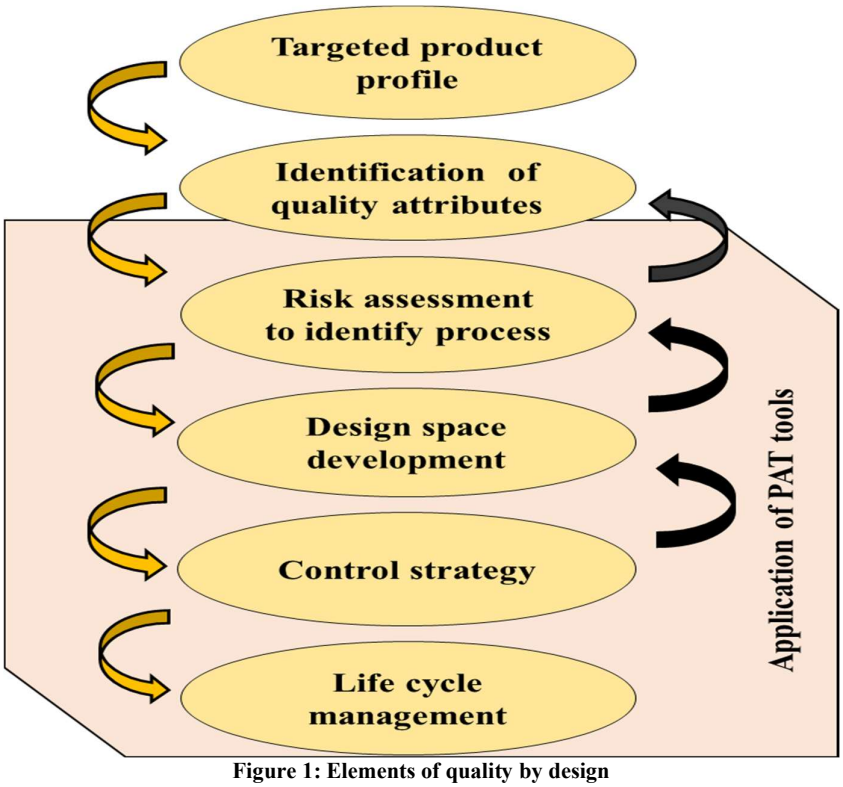

Figure 1: Elements of quality by design

4.1. Steps Involved in Quality by Design Products

Seven steps of quality by design start-up plan as follows **[19]**:

Development of a new molecular entity

- Preclinical study
- Nonclinical study
- Clinical Study
- Scale up
- Submission for market Approval

Manufacturing

- Design Space
- Process Analytical Technology
- Real-time Quality Control

Control Strategy

- Risk-based decision
- Continuous Improvement
- Product performance

4.2. Design-guided method development

Application of DoE principles reduces complexity and unravels the frequency of (any) interactions, making it easier to grasp the many technique parameters and factors that often impact CMAs. Understanding response variables or CMAs and CMVs, their ranges, and the best fitting mathematical model or models, is necessary for the effective completion of the DoE research. Using various experimental designs such as Factorial design, Central Composite design, Box-Behnken design, Optimal design, etc DoE-based Response Surface Methodology (RSM) is useful in the systematic development of analytical techniques including considerable nonlinearity between CMV-CMA relationship. The experimental designs assist in charting the responses according to the investigated objective while exploring Critical Material Attributes (CMAs) at high (+1), medium (0), or low (-1) levels of Critical Material Variables (CMVs). It often reveals the mechanistic knowledge of the interactions and connections between CMVs and CMAs. Several two- and three-dimensional plots, including response surface plots, contour plots, perturbation charts, linear correlation plots, outlier plots, and Box-Cox plots, are important visual aids for experimental designs. After the data have been gathered by the selected design, objective conclusions can be reached by analyzing the data using statistical techniques like Multiple Linear Regression Analysis (MLRA) or mathematical techniques like Artificial Neural Networks (ANN) that depict the flow structure of a standard DoE-based regression model used in data analysis and method development **[20]**.

4.3. Merits of QbD

The advantages of QbD are as follows **[21]**:

- Business benefits are moreover driving constrain to embrace QbD.

- Critical quality qualities are recognized and their impact on the last quality of the item is analyzed.
- It includes item plans and handles development.
- It offers a vigorous strategy or process.
- Quiet security and item viability are focused.
- Science-based hazard appraisal is carried out.
- Scientific understanding of pharmaceutical handling and strategies is done.

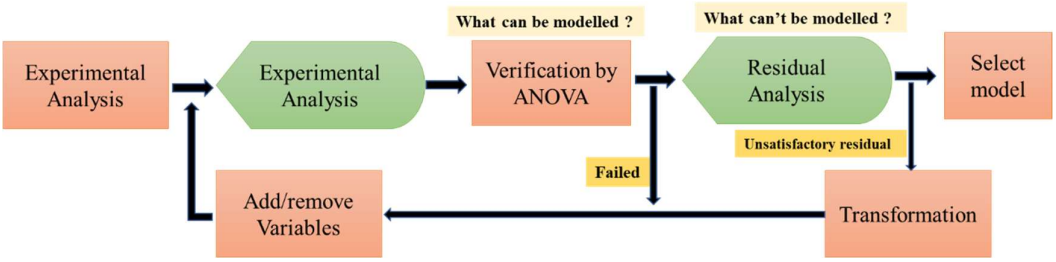

Figure 2: Modelling approach employed during DoE

Drug	Design	Independent variable	Dependent variable	Reference
Carvedilol	**3^2 Full factorial design (FFD)**	**Hydroxypropyl Cellulose (HPC) (X_1) and PEO WSR-1105(X_2)**	**% cumulative release (CDR) (Y_1) and % CDR 4th h (Y_2)**	**[22]**
Repaglinide	**3^2 FFD**	**Hydroxypropyl methylcellulose K100M(HPMC) (X_1), and Xanthan gum(X_2)**	**%CDR (Y_1), Swelling index (SI) (Y_2) and Mucoadhesive strength (MS) (Y_3)**	**[23]**
Atenolol	**Simplex design method**	**HPMC 15CPS (X_1), Carbapol (X_2) and Mannitol (X_3)**	**% CDR (Y_1) and MS (Y_2)**	**[24]**
Risperidone	**Response surface methodology**	**Carbapol (X_1) and Sodium Alginate (X_2)**	**TD (Y_1), *ex vivo* residence time(Y_2) and Peak detachment force (Y_3)**	**[25]**
Simvastatin	**3^2 FFD**	**Hpmc K4M (X_1) and Carbapol 934 P (X_2)**	**MS (Y_1) and % CDR at 8th h (Y_2)**	**[26]**
Nicorandil	**3^2 FFD**	**HPMC K100M (X_1) and Neem gum(X_2)**	**% CDR at 6th h (Y_1) and MS (Y_2)**	**[27]**
Famotidine	**3^2 FFD**	**Sodium CMC (X_1) and Carbapol 934p(X_2)**	**% CDR at 8th h (Y_1), % swelling index (Y_2),**	**[28]**

			bioadhesive strength (Y_3), diffusion coefficient (Y_4) and release rate constant (Y_5)	
Metoprolol tartrate	**3^2 FFD**	**XG (X_1) and locust bean gum (X_2)**	**% CDR (Y_1) and MS (Y_2)**	**[29]**
Nisoldipine;	**3^2 FFD**	**HPMC (X_1) and Carbapol (X_2)**	**MS (Y_1) and force of adhesion (Y_2)**	**[30]**
5-fluorouracil	**3^2 FFD**	**Carbapol (X_1) and Polyvinylpyrrolidone (X_2)**	**% CDR (Y_1) and MS (Y_2)**	**[31]**
Carvedilol	**3^2 FFD**	**Casein (X_1) and HPMC K4M (X_2)**	**Hardness (Y_1), % CDR at 6^{th} h (Y_2) and % CDR at 12^{th} h (Y_3)**	**[32]**
Valsartan	**CCD**	**Gum olibanum (X_1) and Chitosan(X_2)**	**% CDR (Y_1) and *ex vivo* residence Time (Y_2), and MS (Y_3)**	**[33]**
Furosemide	**Box Behnken Design (BBD)**	**Locust bean gum (X_1), Tamarind Seed gum (X_2), and chitosan (X_3)**	***Ex vivo* residence time (Y_1), MS (Y_2) and % CDR at 12^{th} h (Y_3)**	**[34]**
Loratadine	**3^2 FFD**	**SA (X_1) and Lactose monohydrate (X_2)**	**Bioadhesive force (Y_1), % swelling index (Y_2) and disintegration time (Y_3)**	**[35]**
Domperidone	**BBD**	**Gellan Gum (X_1), SA(X_2), Methocel K 100M (X_3), and Starch (X_4)**	**Friability (Y_1), Mucoadhesion Time (Y_2), CDR at 1^{st} h (Y_3) and % CDR at 8^{th} h (Y_4)**	**[36]**
Trimetazidine HCl	**2^3FFD**	**Carbopol 934 (X_1) and Mannitol (X_2)**	**$T_{50\%}$ (Y_1), % CDR at 8^{th} h (Y_3) and Swelling index (Y_3)**	**[37]**
Acyclovir	**3^2 FFD**	**Carbapol (X_1) and HPMC K100F (X_2)**	**MS (Y_1), %CDR (Y_2)**	**[38]**
Timolol maleate	**3^2 FFD**	**Carbopol 974 p (X_1) and SA(X_2)**	**% CDR (Y_1) Bioadhesive force(Y_2)**	**[39]**
Febuxostat	**3^2 FFD**	**XG (X_1) and Vigna mungo (X_2)**	**% CDR (Y_1)**	**[40]**

CONCLUSION

In conclusion, this review highlights the significance of Quality by Design (QbD) principles in the development of buccal mucoadhesive tablets as a promising drug delivery platform. By integrating recent advancements with past literature, the analysis underscores the potential of these tablets in enhancing bioavailability, prolonging drug release, and improving patient compliance. Through a systematic examination of QbD methodologies, critical

quality attributes (CQAs) and process parameters (CPPs) relevant to buccal tablet formulation have been identified and discussed, emphasizing their importance in ensuring product quality and performance consistency. The review also explores the use of analytical techniques and mathematical modeling to establish correlations between formulation variables, manufacturing processes, and product performance, addressing challenges such as mucoadhesion strength, drug release kinetics, and formulation stability within the QbD framework. Overall, by synthesizing insights from past literature and recent developments, this review serves as a valuable guide for researchers and pharmaceutical scientists in the rational design and optimization of buccal mucoadhesive tablets using QbD approaches.

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