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APPLICATION OF STATISTICAL TOOLS FOR THE FORMULATION AND OPTIMIZATION OF CARVEDILOL MUCOADHESIVE BUCCAL FILMS BY USING NATURAL POLYMERS

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The aim *and objective of this study was to create mucoadhesive buccal films that contained the multipurpose medical carvedilol, which has a variety of medicinal uses.*
Materials and methods. *The films were equipped using a solvent casting technique and concentrations of natural polymers, including Sweet basil, Lime Basil seeds and Purple basil mucilage. The influence of Carbopol 934 P, a selected natural polymer, was also investigated. The formulation variables were improved by the use of a factorial design of experiments and evaluated for their physico-chemical and in vitro evaluations.*
Result*. These evaluations provided crucial insights into the properties of the buccal films. To evaluate the release profile and release kinetics of carvedilol from the films, in vitro drug release experiments were carried out in a phosphate buffer solution. Ex vivo permeation tests using fresh sheep buccal mucosa were performed to evaluate the drug's permeation through the buccal membrane. Samples were taken at regular intervals, and a UV Spectrophotometer was used for analysis. With a polymer solution concentration at level "3," formulation run R20 showed the best optimized buccal formulation. This formulation shows promise for further in vivo research.*
Conclusions*. The results of this study offer important new evidence about the design and efficacy of mucoadhesive buccal films containing carvedilol. The optimization of formulation parameters and the assessment of physicochemical properties and drug release kinetics contribute to the progress of reproducible buccal films*
Keywords*: natural polymers, mucoadhesive, Carvedilol, buccal film, in vitro studies*

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1. Introduction

Even though oral drug delivery has traditionally been preferred, many patients have trouble swallowing pills and capsules. Different treatment formulations, including oral gels, buccal pills, patches, and fast-acting drug delivery devices, have been developed to address this problem. Since mucoadhesive buccal films may stick to the buccal mucosa and deliver regulated pharmaceutical distribution for both local and transmucosal therapies, they have significant advantages over traditional oral dosing forms. Due to the abundant vascularity of the mucosa, buccal transmucosal administration, a non-invasive systemic route, has benefits such as a quicker beginning of action, avoiding enzymatic degradation in the gastrointestinal tract, and avoiding first-pass metabolism [1, 2]. The accessibility of the buccal mucosa makes buccal administration suitable for patients and reduces the risk of drug discontinuation. However, continuous saliva flow and oral movements, including tongue and jaw motion, can affect the efficacy of drug delivery. Additionally, compared to the small intestine, the buccal mucosa has lesser drug penetrability. However, this can be made up for by a longer residence time [3, 4]. Using mucoadhesive substances can enhance the retention of buccal films on the mucosal surface. Buccal films can be either orodispersible, designed to dissolve quickly, or mucoadhesive, formulated to obey the oral mucosa. The properties of the film will influence the duration of adhesion on the oral mucosa. Key aspects of buccal films include solubilization of poorly soluble drugs, wetting and disintegration characteristics, mucoadhesive influence, and augmentation of the drug delivery [5].

The study's main goal was to create mucoadhesive buccal films for the controlled distribution of carvedilol. The study aimed to select an appropriate natural polymer for formulating the buccal films and optimize the formulation parameters to achieve desired physicochemical properties and drug release profiles. Specifically, the study aimed to determine the optimal levels of these parameters to obtain buccal films with the desired drug content, drug release characteristics, and mechanical properties. By successfully achieving these objectives, the study sought to develop optimized mucoadhesive buccal films as a prospective alternative route of administration for carvedilol, offering improved therapeutic outcomes.

2. Planning (methodology) of research

Buccal drug delivery: the buccal route deals numerous benefits for drug delivery, comprising avoidance of first-pass metabolism, improved bioavailability, and non-invasive administration. Buccal administration of

the beta-blocker carvedilol, which is used to treat hypertension and heart failure, can improve therapeutic results. The scientific justification lies in exploiting the benefits of buccal drug delivery for carvedilol.

Mucoadhesive films: mucoadhesive films adhere to the mucosa in the oral cavity, allowing sustained drug release and prolonged residence time. Natural polymers, such as chitosan, alginate, and gelatin, have been widely studied for their mucoadhesive properties and biocompatibility. Selecting natural polymers as film-forming agents for carvedilol buccal films is justified by their ability to enhance drug residence time and improve drug absorption.

Optimization and formulation: the use of statistical tools, such as Design of Experiments (DoE), is justified for optimizing the formulation of carvedilol buccal films. These tools allow for efficient screening of various preparation variables, such as polymer and plasticizer concentration on drug loading, and also to identify the optimal combination that provides the desired drug release profile and mucoadhesive properties.

The study plan for this research is as follows:

– research objective: clearly define the research objective, such as developing a mucoadhesive buccal film formulation for carvedilol using natural polymers. Specify the specific parameters that will be optimized, such as polymer concentration, plasticizer type and concentration, drug loading, and film thickness;

– selection of natural polymers: evaluate different natural polymers commonly used in mucoadhesive buccal films based on the properties of the polymers, like solubility, swelling capacity, viscosity, and mucoadhesive properties;

– experimental design: select an appropriate experimental design to optimize the formulation parameters systematically. Determine the factors and levels to be investigated, such as polymer concentration, plasticizer type and concentration, drug loading, and film thickness. Decide on the number of experimental runs based on the chosen design and the available resources;

– film preparation and characterization: prepare the mucoadhesive buccal films using the selected natural polymers and the determined formulation parameters. Characterize the films for their properties, such as thickness, tensile strength, surface morphology, and mucoadhesive properties. Perform release studies to evaluate the release kinetics of carvedilol films;

– experimental execution: conduct the experiments according to the experimental design, ensuring randomization and replication of runs. Follow appropriate protocols for film preparation, drying, and characterization techniques. Document all experimental parameters, observations, and results accurately;

– statistical analysis: analyze the experimental data using suitable statistical tools, such as analysis of variance (ANOVA), regression analysis, or mathematical modelling. Assess the effects of different formulation parameters on film properties and drug release. Identify significant factors and interactions using statistical significance tests;

– optimization: Use the statistical analysis results to optimize the formulation and identify the optimal levels of the parameters for desired film characteristics and drug release profiles. Apply response surface optimization techniques or numerical optimization algorithms to determine the optimum formulation conditions. Validate the optimized formulation through additional experimental runs or comparing the predicted values with experimental results;

– evaluation and validation: evaluate the optimized buccal film formulation for its physicochemical properties, mucoadhesive properties, and drug release behaviour. Consider performing in vitro studies to assess the release characteristics of carvedilol from the optimized buccal films.

3. Materials and methods

Carvedilol was procured from Swaroop Pharmaceuticals (Maharashtra, India); HPMC (Hydrophilic polymer), CP (Swelling agent) and PVP (Film forming polymer) were procured from Drugs India (Hyderabad, India); Propylene glycol (Plasticizer), DMSO (Solvent and permeation enhancer) and ethanol (Solvent) were obtained from LobaChemie (Mumbai, India). All other chemicals and reagents employed were of analytical grade.

3. 1. Experimental methodology

The fabrication of Carvedilol mucoadhesive buccal films was carried out using the widely employed solvent casting method. Pre-lubricated Petri plates were used as substrates, and concentrations of natural polymers, including Lime Basil seeds, Sweet basil, and Purple basil mucilage, as listed in Table 1, were utilized. Additionally, the impact of Carbopol 934 P, a selected natural polymer, was compared according to Table 2.

3. 2. Fabrication of Buccal Films

To determine the optimal polymer, a screening design was employed, identifying basil seed mucilage at a quantity of 1.5 % w/v as the most suitable. This polymer was then used in the optimization design. The estimated quantity of polymer was dispersed in 50 % v/v ethanol, trailed by the 30 % w/w propylene glycol (PG). Carvedilol (10 mg) was accurately weighed and added to the polymeric solutions. A homogeneous viscosity was attained by stirring the solution with a magnetic stirrer at 60 RPM. The solution was sonicated in a bath sonicator at a pulse rate of roughly 5 kV/5 min to remove air bubbles, and then DMSO was added. The polymer solution was then poured onto a coated Petri plate with a 4.5 cm diameter, sealed with a funnel to keep the solvent in, and allowed to dry at room temperature for an entire night. The dried films were then removed, covered in aluminium foil, and preserved in desiccators until additional examination. Carvedilol buccal films' screening design, comprising components and evaluations, is shown in Table 1. The optimization results for these films are shown in Tables 2, 3 [6–8].

3. 3. Design of 3^3 factorial designs

The principles of Quality by Design (QbD) and risk analysis can be applied to the design of carvedilol buccal films using natural polymers in the following ways.

Quality by Design (QbD).

Define the desired characteristics and performance requirements of the buccal films (Target Product Profile – TPP). Identify critical quality attributes (CQAs) directly impacting the films' safety, efficacy, and performance. Establish a design space by considering the critical formulation variables influencing the CQAs. To identify potential risks and hazards related to the formulation and optimization process, conduct a risk analysis. Develop a control strategy to ensure consistent quality attributes and implement continuous improvement measures.

Risk analysis.

Identify and assess potential risks related to material selection, formulation variability, manufacturing processes, and patient safety. Develop strategies and mitigation plans to minimize or eliminate identified risks. Monitor and control risks throughout the formulation and optimization process. Document the risk analysis process, including identified risks, mitigation strategies, and outcomes. By incorporating QbD and risk analysis principles, researchers can achieve the desired quality attributes, identify and mitigate risks, and ensure compliance with regulatory requirements, leading to improved safety, efficacy, and performance of the buccal film formulation.

A first-order response surface model was utilized to examine the outcomes obtained from a 3^3-factorial experimental design consisting of 27 runs. Pre-screening procedures were employed to determine the polymer solution concentration. Based on preliminary investigations, three factors were selected and tested within predetermined ranges: polymer solution concentration (%), including 0.5, 1, and 1.5 %; plasticizer concentration (%), including 0.25, 0.5, and 0.75 %; and permeation enhancer concentration (%), including 0.5, 1.0, and 1.5 %. To further optimize the concentration ranges, a 3^3-factorial design was employed using the JMP Design Expert program. The link between the components and their influence on the observed response could be evaluated by factorial design. Three levels – low (1), medium (2), and high (3) – of the examined parameters, $X1$ (Polymer concentration – Basil seed mucilage), $X2$ (Plasticizer Concentration – PG 10 % in % w/v), and $X3$ (Permeation enhancer – DMSO % w/v), were altered. The evaluation was conducted on the comparable measured responses $Y1$ (Drug Content in %), $Y2$ (Percentage of Drug Release), and $Y3$ (Folding Endurance) [9–12].

Factorial experiment analysis: The physicochemical estimation of the buccal films included the assessment of various characteristics:

Thickness: using a digital verniercalliper, the thickness of each film was determined at six separate spots, and the average thickness was computed [13].

Weight of films: using a digital scale, 10 films were weighed separately to ascertain the weight. The average weight of the three films was then calculated [14].

Folding endurance: the folding endurance test involved folding individual films from all compositions repeatedly until they ruptured at the same location. The film's folding durability was determined by counting the amount of folds it could endure before breaking. The average folding endurance was determined using three films [15].

Percentage moisture absorption (PMA): the % moisture absorption test assessed the buccal films' physical resilience in a high-humidity setting. Three 1 cm films were accurately weighed and put into desiccators that were kept at a relative humidity (RH) of 75 % while also containing a saturated aluminium chloride solution. The films were taken off after three days, weighed again, and the percentage of moisture absorption was measured. Three films were used to determine the average value [16, 17].

$$Percentage\ Moisture\ Absorption = \\ = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100.$$

3. 4. Moisture loss percentage

The strength of the films was evaluated using the % moisture loss test under dry conditions. Three 1 cm films were divided into three equal pieces and put into desiccators with fused anhydrous calcium chloride. The films were precisely weighed before being removed after three days, reweighing them, and calculating the percentage moisture loss. The average value was calculated based on three films [18].

$$Percentage\ Moisture\ Loss = \\ = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100.$$

3. 5. Percentage of swelling (%S)

A buccal Carvedilol film was transferred to a petri dish that was clean and contained 50 mL of pH 6.8 phosphate buffer solution. By combining 15-minute periods for a total of 60 minutes, the film's weight was calculated. The correct calculation was used to determine the swelling's degree [19].

$$\%S = \frac{X_t - X_0}{X_0} \times 100,$$

where $\%S$ is the swelling percentage, X_t is the weight of the swollen film at time t, and X_0 is the weight of the film at time zero.

3. 6. Drug content estimation

Each buccal film was divided into three similar pieces and placed in a 100 mL phosphate buffer solution at pH 6.8. The mixture was subjected to agitation for a period of 24 hours and subsequently filtered. The resulting filtrate was appropriately diluted as required, and the absorbance was determined at 240 nm utilizing a UV Spectrophotometer. The drug content was determined by averaging the results obtained from three separate films [20].

3. 7. Measurement of bucco adhesive strength

A modified balance technique was used to quantify the bucco adhesive strength for ex-vivo evaluation. After the sheep was put down for euthanasia, fresh buccal muco-

sa was removed. By eliminating underlying fat and frail tissues, the mucosal membrane was meticulously isolated. After washing with distilled water, the membrane was next moistened with isotonic phosphate buffer (pH 6.8). The sheep buccal mucosa was placed on a glass slide that was taped to the bottom of a smaller beaker to set up the study. The smaller beaker was put inside, and the bigger beaker was inverted. The buccal mucosa was brought to the surface by adding isotonic phosphate buffer (pH 6.8) to the bigger beaker. The buccal film was firmly fastened to the top clamp's lower surface using cyanoacrylate adhesive. For initial hydration and swelling, phosphate buffer was applied to the exposed patch surface and kept on for 30 seconds. The platform was slowly elevated till the film's surface made contact with the mucosa. Before the test, a weight was put on the right-hand pan to guarantee equilibrium. The strain applied to the patch covering the mucosa was lessened after a 5 g weight was removed from the right-hand pan. The balance was maintained in this posture for five minutes in total [21].

$$Force\ of\ adhesion\ (N) = \left[Bioadhesive\ strength\ (g) \times 9.8\right]/1000.$$

3. 8. Mechanical Strength measurement

The mechanical strength of the Carvedilol buccal films was evaluated using a specially designed apparatus comprising a microprocessor force gauge connected to a motor, along with a stand and a cell. Circular cutouts of 20 mm diameter films, exhibiting minimal visible damage, were positioned with a 3 cm gap between two clamps. Careful positioning of the clamps ensured no harm was caused to the film. The lower clamp was securely locked in place, while the upper clamp was gradually moved at a speed of 2 mm/sec until the film fractured. The point of fracture and the corresponding extension measurement were recorded. Subsequently, the tensile strength and elongation at break were calculated using the appropriate formulas [22, 23].

$$Tensile\ strenghy\ \left(\mathrm{kg}\cdot\mathrm{mm}^2\right) = \frac{Force\ at\ break\ \left(\mathrm{kg}\right)}{Initial\ cross-sectional\ area\ of\ the\ sample\ \left(\mathrm{mm}^2\right)};$$

$$Elongation\ at\ break\ \left(\%\ \mathrm{mm}^2\right) = \frac{Increase\ in\ length\ \left(\mathrm{mm}\right)}{Original\ length\ \left(\mathrm{mm}\right)} \times \frac{100}{Cross\ sectional\ area\ \left(\mathrm{mm}^2\right)}.$$

3. 9. *In-vitro* drug release studies

For in-vitro release studies, a modified dissolving apparatus was employed in a 100 ml phosphate buffer solution (pH 6.8) at 37 °C. The experimental arrangement consisted of a 250 ml beaker serving as the receptor compartment and an open-end tube acting as the donor compartment. A magnetic stirrer assembly with a temperature-controlled hot plate was utilized to maintain the dissolving media's temperature. A semi-permeable barrier was positioned between the donor compartment and the medium, with the buccal film placed inside. Subsequently, the donor tube was submerged in the dissolving medium (receptor compartment), which was maintained at 37 °C and stirred at 100 rpm using a magnetic stirrer. At specific time intervals, one millilitre of samples were withdrawn. To ensure a constant volume and sink condition, an equal amount of phosphate buffer was added to the dissolving media after each sample removal. The diluted solutions were analyzed spectrophotometrically at 240 nm, and the withdrawn samples were further diluted tenfold [24].

3. 10. *In-vitro* drug release kinetics studies

By applying the in-vitro release data to various equations and kinetic models, the release kinetics of carvedilol from the buccal films were examined. These models included Higuchi, Peppas, and zero-order. The findings of the buccal film formulations were plotted using various kinetic models, such as Higuchi's model and Peppa's model. To explicitly evaluate how carvedilol was released from buccal films, Higuchi's model was used. The diffusion exponent values (*n*) acquired from the Peppas model reveal the mechanism of drug release. In contrast, the correlation coefficient values (*r*) obtained from Higuchi's model represent the kinetics of drug release [24].

3. 11. An examination of ex-vivo penetration via sheep buccal mucosa

Fresh sheep buccal mucosa was used in ex vivo permeation research with carvedilol in a modified diffusion cell at 37 °C. The fresh sheep buccal mucosa was placed in between the donor and receptor compartments to create a barrier. The donor compartment, which was shaped like an open-ended cylinder, had the sheep buccal mucosa firmly fastened to one end. To achieve good adherence, the buccal film was carefully placed on the mucosal membrane. Isotonic phosphate buffer (PPB), pH 6.8, was introduced to the receptor chamber. The complete set-up was agitated magnetically and kept at a temperature of 37 °C. Samples were taken and examined using a UV Spectrophotometer set at a wavelength of 240 nm at predefined intervals [25, 26].

4. Results

4. 1. Selection of polymer by screening studies

An appropriate polymer for the creation of buccal film was found by screening studies, as shown in Table 1. The types and amounts of natural polymer mucilage extracted from basil seeds, sweet basil, and purple basil were changed using a hydroalcoholic (50:50 % V/V) maceration extraction approach. Nine buccal films were created using the solvent casting technique. The formulation P3 from the trial formulations with 1.5 mg of basil seed mucilage as the film-forming polymer displayed the highest qualities, with a Mucoadhesive Strength (MS) of around 30.5 1.8 and a % Drug Content (%DC) of roughly 84.50 2.8 %. Therefore, 1.5 mg of Basil seed mucilage was selected as an econom-

ically viable natural polymer for further optimization in order to build a cost-effective buccal film. The formulations made with tamarind and purple basil, on the other hand, showed lower %DC and MS values, indicating that they were not suitable as advantageous polymers for the subsequent buccal film formulation.

The effects of key critical material attributes (CMAs), such as polymer solvent concentration (basil seed mucilage) at various percentages weight/volume (w/v), plasticizer concentration (PG 10 %) in percentage weight/volume (w/v), and permeation enhancer [DMSO] in percentage weight/volume (w/v), on critical quality attribute (CQA) factors like percent drug content, percent the quantity of drug release, and folding endurance, are shown in Tables 3–7 and Fig. 1–4. The discussion that follows will go into further detail about these results.

Table 1

Screening investigations into how different natural polymers affect buccal films

Formulation code	Drug	Natural Polymers mucilage (%)			Solvents (ml)			Evaluation parameter	
	Carvedilol	Lime basil seeds	Sweet basil	Purple basil	Ethanol (50 % v/v)	PG (30 %w/w)	DMSO (5 %W/V)	% DC	MS
P1	10	0.5	–	–	10.0	0.5	0.25	68.60±2.4	20.5±1.8
P2	10	1.0	–	–	10.0	0.5	0.25	76.42±2.2	26.4±1.2
P3	10	1.5	–	–	10.0	0.5	0.25	84.50±2.8	30.6±1.8
P4	10	–	0.5	–	10.0	0.5	0.25	46.66±2.4	11.8±1.4
P5	10	–	1.0	–	10.0	0.5	0.25	53.40±3.2	15.4±2.6
P6	10	–	1.5	–	10.0	0.5	0.25	54.42±3.0	18.6±1.8
P7	10	–	–	0.5	10.0	0.5	0.25	63.40±3.4	12.4±1.6
P8	10	–	–	1.0	10.0	0.5	0.25	68.66±3.2	13.8±1.8
P9	10	–	–	1.5	10.0	0.5	0.25	72.48±3.8	14.4±2.2

Table 2

Screening of natural vs. synthetic polymer in carvedilol buccal films

Formulation code	Drug (mg)	Polymers (%)			Solvents (ml)			Evaluation parameter	
	Carvedilol	Lime Basil Seed mucilage	PVP	Carbopol 934	Ethanol (50 % v/v)	Propylene Glycol (30 %w/w)	DMSO	% DC	MS
F1	10	0.5	–	0.5	10.0	0.5	0.25	54.42±2.4	18.8±1.2
F2	10	1.0	–	0.5	10.0	0.5	0.25	68.60±2.2	20.5±1.6
F3	10	1.5	–	0.5	10.0	0.5	0.25	92.48±2.4	32.5±2.2
F4	10	2.0	–	0.5	10.0	0.5	0.25	93.40±2.8	32.8±1.4
F5	10	2.5	–	0.5	10.0	0.5	0.25	94.50±3.2	33.4±2.6
F6	10	–	0.5	0.5	10.0	0.5	0.25	46.66±3.2	10.6±1.4
F7	10	–	1.0	0.5	10.0	0.5	0.25	53.40±2.2	14.3±2.6
F8	10	–	1.5	0.5	10.0	0.5	0.25	72.66±2.4	16.4±1.6
F9	10	–	2.0	0.5	10.0	0.5	0.25	76.42±2.6	22.8±1.4
F10	10	–	2.5	0.5	10.0	0.5	0.25	82.72±2.4	23.4±2.6

Note: all values are expressed as mean±SD, n=3

Table 3

Absolute values of levels of CMA employed in 3^3 factorial design

S. No.	CMA	Levels			
		Coded	1	2	3
1	Polymer solvent Concentration (Lime Basil seed mucilage) in %w/v	*X*1	0.5	1	1.5
2	Plasticizer Concentration (PG 10 %) in % w/v	*X*2	0.25	0.5	0.75
3	Permeation enhancer [DMSO] (% w/v)	*X*3	0.5	1.0	1.5
4	Carvedilol – 10 mg in all formulations	–	–	–	–
5	Ethanol (50 % v/v) – 10 ml in all formulations				
Response		Constraint			
*Y*1	% drug content	Maximum>85 %			
*Y*2	% amount of drug release at 24 h	Maximum>85 %			
*Y*3	folding endurance	Maximum>350			

Table 4

Optimization of Carvedilol buccal film formulation by 3^3 factorial design and effect of CMA on CQA

Run	CMA			Critical quality attribute		
	*X*1	*X*2	*X*3	% drug content	% amount of drug release at 24 h	Folding endurance
R1	3	2	1	98.4±2.2	74.2±2.0	386±14
R2	2	2	1	76.8±2.8	66.8±2.4	354±12
R3	1	1	2	60.2±2.6	58.4±2.6	268±10
R4	1	3	1	54.2±2.4	52.4±2.4	366±12
R5	2	2	2	68.4±2.8	66.8±2.4	302±14
R6	2	3	1	64.2±2.2	62.6±2.8	368±16
R7	2	1	3	72.8±2.8	70.6±2.2	296±12
R8	1	3	3	74.6±2.2	70.8±2.4	384±10
R9	1	2	2	62.8±2.2	60.6±2.6	286±14
R10	2	3	3	70.2±2.6	68.4±2.4	398±12
R11	1	1	3	58.8±2.2	56.8±2.2	284±14
R12	1	2	3	59.4±2.8	57.8±2.4	304±16
R13	2	1	1	72.8±2.6	69.6±2.2	292±12
R14	3	2	2	97.6±2.2	90.8±2.4	442±16
R15	3	1	2	86.4±2.6	82.4±2.4	290±12
R16	3	3	3	92.4±2.2	92.8±2.2	464±18
R17	2	3	2	71.6±2.4	69.8±2.6	430±16
R18	3	1	3	92.2±2.2	74.6±2.2	296±12
R19	3	1	1	74.6±2.6	68.6±2.8	302±16
R20	3	3	2	96.9±2.4	97.4±2.4	422±12
R21	3	3	1	86.4±2.8	74.6±2.2	402±14
R22	2	2	3	60.2±2.4	54.6±2.4	336±16
R23	1	2	1	68.6±2.8	65.8±2.6	366±14
R24	2	2	3	56.4±2.2	53.6±2.4	346±12
R25	1	3	2	58.8±2.0	54.2±2.2	302±16
R26	3	2	3	83.4±2.8	78.4±2.8	367±18
R27	2	1	2	74.6±2.6	68.8±2.6	294±16

Note: all values are expressed as mean±SD, n=3

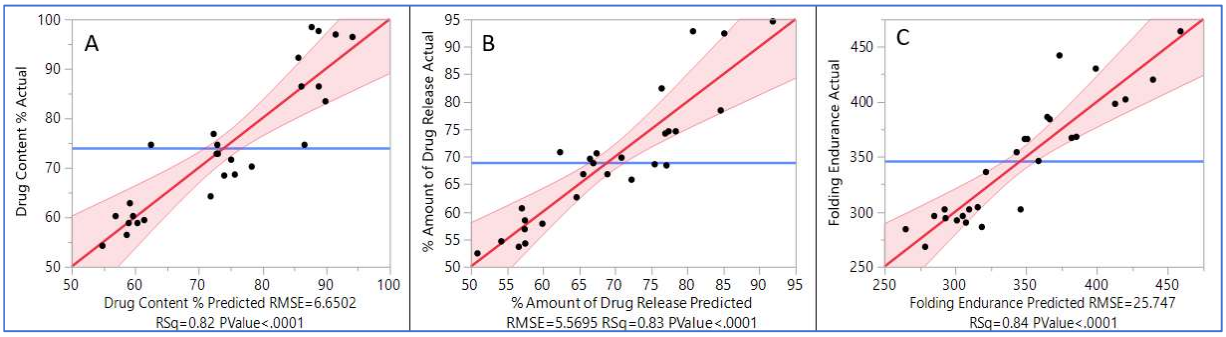

Fig. 1. Predicted plot of CMA vs. CQA: A – % drug content plot; B – % amount of drug release; C – folding endurance

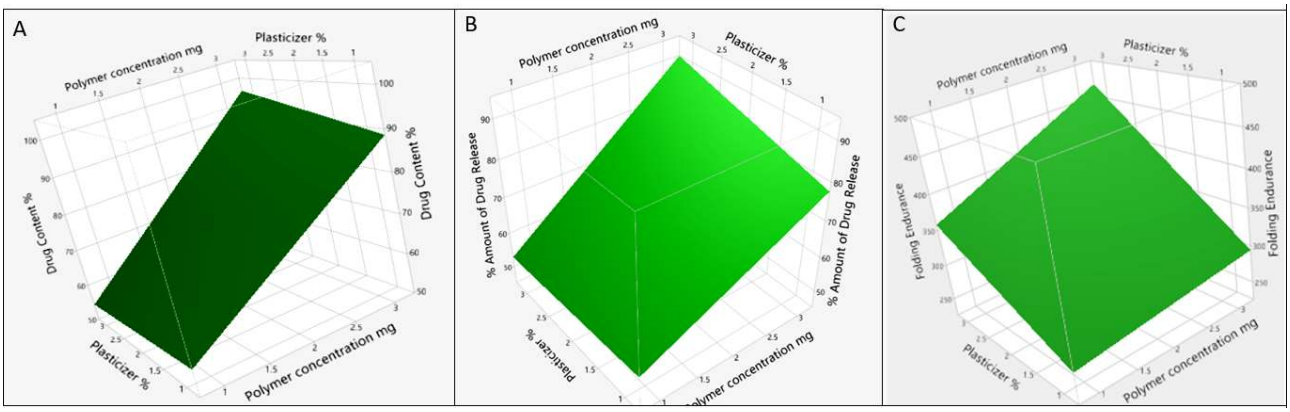

Fig. 2. Response surface profiler graph showing the relation between CMA vs. CQA: A – CMA vs. % drug content plot; B – CMA Vs. % amount of drug release; C – CMA Vs. folding endurance

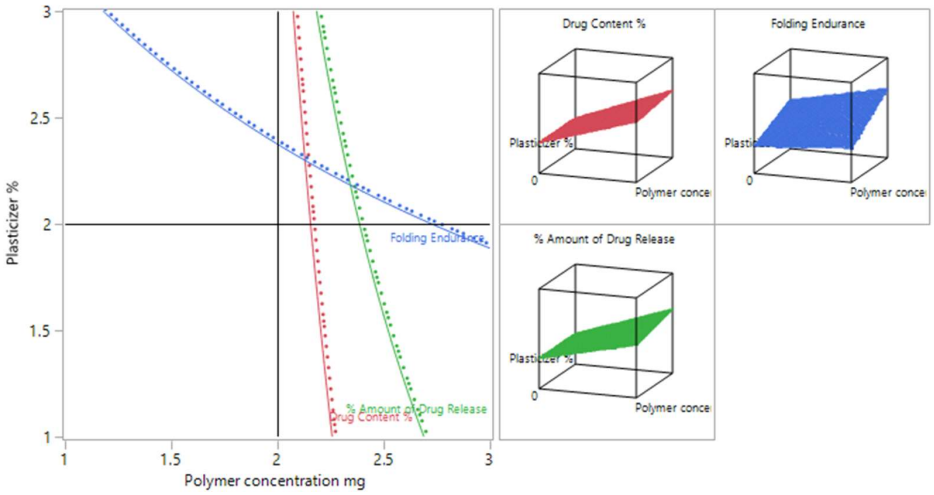

Fig. 3. Contour profiler graph showing the relation between CMA vs. CQA

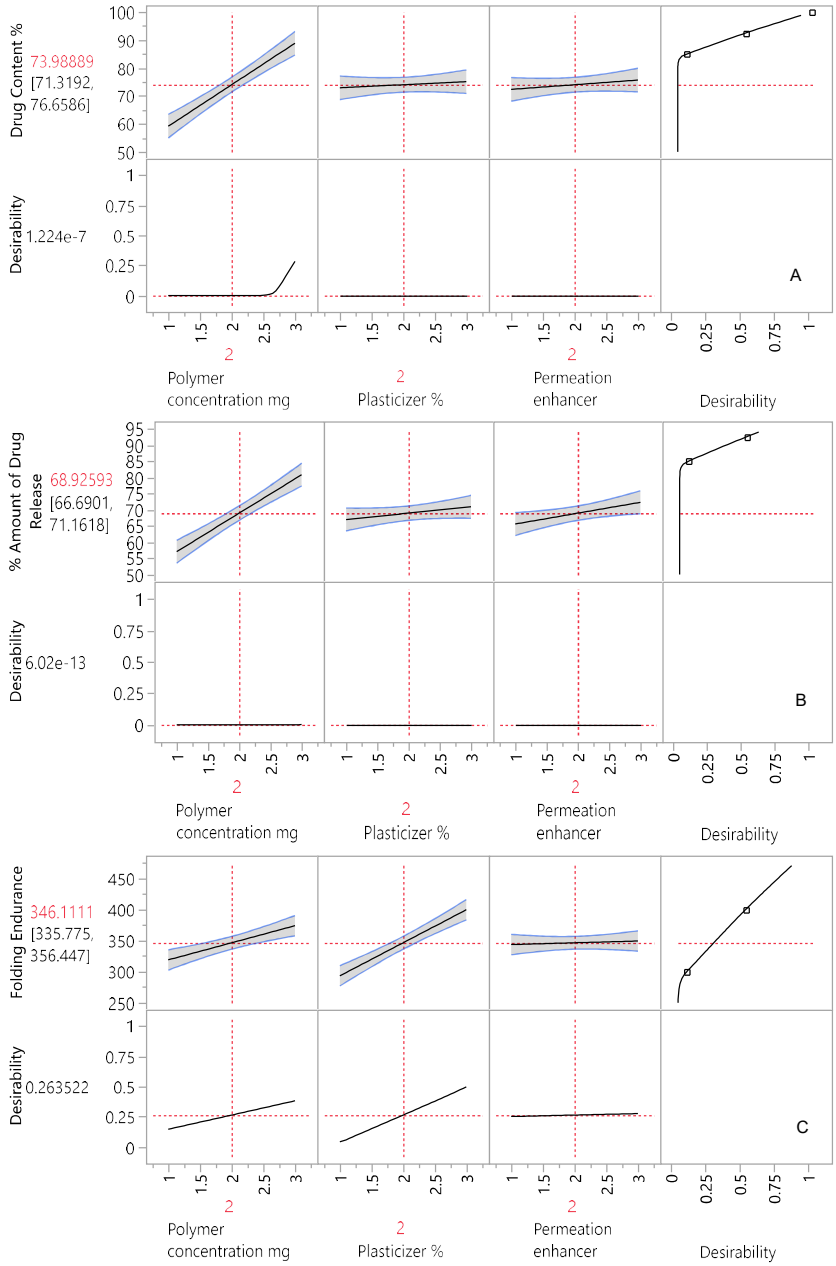

Fig. 4. Prediction profiler graph showing the relation between CMA vs. CQA: A – CMA vs. % drug content plot; B – CMA vs. % amount of drug release; C – CMA vs. folding endurance

4. 2. Response of CMA on % drug content (DC)

Table 4 presents the mean Drug Content (DC) values for all Carvedilol buccal film formulations, which range from 54.2±2.4 % to 98.4±2.2 %. The difference in DC is primarily attributed to the effect of the critical material attribute (CMA) of polymer concentration. Among the runs, R1, R14, R15, R16, R18, R20, and R21 exhibit DC values above 85 %, meeting the essential constraint. On the other hand, considering the acceptance constraint, formulation runs R16 (3 ml of $X1$ factor; 0.75 % of factor $X2$ and 1.5 % of factor $X3$) and R20 (3 ml of $X1$ factor; 0.75 % of factor $X2$ and 1 % of factor $X3$) show %DC values of roughly 96.9±2.4 % and 97.4±2.4 %, accordingly. The remaining formulations yield lesser DC percentages than predictable, highlighting the significant impact of polymer concentration on per cent DC. Statistical analysis by the F-test, p-value at 95 % confidence, and coefficient of determination confirm the meaningful fitness of the model to the data (p<0.05) with a sturdy regression (R^2) value. The ANOVA F-test indicates a significant influence of polymer concentration on per cent DC, with a p-value of 0.0000, as shown in Table 6. The observed values align closely with the expected values, as depicted in Fig. 4. Response Surface Profiler and Contour Profiler plots can be used to further analyze the relationship between CMA (polymer concentration) and CQA (per cent DC), as shown in Fig. 2 to 3. The following is the per cent DC polynomial regression equation:

$$Y1=38.81+14.83\ X1. \quad (1)$$

Table 5

Effect summary of CMA on % drug content

Source	Log worth	P-Value
Polymer concentration mg	8.098	0.0000
Permeation enhancer	0.522	0.3003
Polymer concentration mg*Plasticizer %	0.380	0.4168
Plasticizer %*Permeation enhancer	0.373	0.4240
Plasticizer %	0.307	0.4930
Polymer concentration mg*Permeation enhancer	0.117	0.7644

Table 6

Parameters Estimates of CMA response on % Drug Content

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	38.8111	5.5763	6.96	<0.0001*
Polymer concentration mg	14.8278	1.5646	9.46	<0.0001*
Plasticizer %	1.09444	1.5676	0.70	0.4931
Permeation enhancer	1.66666	1.5686	1.06	0.3003
(Polymer conc. mg-2)* *(Plasticizer %-2)	1.59166	1.9198	0.83	0.4168
(Polymer conc. mg-2)* *(Permeation enhancer 2)	–0.5833	1.9198	–0.30	0.7644
(Plasticizer %-2)* *(Permeation enhancer-2)	1.56666	1.9198	0.82	0.4241

4. 3. The CMA's reaction to the percentage of drug release (%ADR)

The average percentage of the amount of drug release (%ADR) for all Carvedilol buccal film formulations is shown in Table 4. The %ADR values range from 52.4±2.4 % to 94.6±2.2 %. The modification of critical material attributes (CMA), such as polymer content and permeation enhancer concentration, is principally responsible for the variations in %ADR. The runs R14, R16, and R20 of the formulation show %ADR values above 85 % as needed by the requirement. However, according to the acceptance constraint in Table 3, formulation runs R16 and R20 (3 ml of $X1$ factor; 0.75 % of factor $X2$ and 1.5 % of factor $X3$) show %ADR values of about 97.8±2.2 % and 92.4±2.4 %, accordingly, based on the other critical quality attribute (CQA) parameters. The remaining formulations exhibit lower %ADR values than desired. Consequently, both polymer concentration and permeation enhancer concentration have a significant impact on %ADR. The statistical analysis using the F-test, p-value at a 95 % confidence interval, and coefficient of determination confirms the meaningful fitness of the model to the data (p<0.05) with a strong regression (R^2) value. The ANOVA F-test reveals a significant effect of polymer concentration on %ADR with a p-value of 0.0000. The P-values for %ADR, as shown in Table 7, are all below 0.0001. The significant degree of closeness between the expected and observed values is seen in Fig. 4. The Response Surface Profiler and Contour Profiler plots shown in Fig. 2, 3 can be used to further examine the effects of CMAs (polymer concentration and permeation enhancer concentration) on CQA (%ADR). permeation enhancer ($X3$) and polymer concentration ($X1$) both show an increase in %ADR. The following is how to calculate the polynomial regression equation for %ADR:

$$Y2=34.62+11.85\ X1+3.34\ X3. \quad (2)$$

Table 7

Effect summary on CMA response on % amount of drug release

Source	Log worth	P-Value
Polymer concentration mg	7.768	0.00000
Permeation enhancer	1.717	0.01917
Plasticizer %*Permeation enhancer	1.055	0.08805
Plasticizer %	0.818	0.15191
Polymer concentration mg*Plasticizer %	0.813	0.15382
Polymer concentration mg*Permeation enhancer	0.120	0.75903

Table 8

Analysis of variance of CMA response on % amount of drug release

Source	DF	Sum of squares	Mean square	F ratio
Model	6	2971.0733	495.179	15.9638
Error	20	620.3785	31.019	Prob>F
C. Total	26	3591.4519	–	<0.0001*

Table 9

Parameters estimates of CMA response on % amount of drug release

Term	Estimate	Std error	*t* Ratio	Prob>|*t*|
Intercept	34.614815	4.672059	7.41	<0.0001*
Polymer concentration mg	11.855556	1.312735	9.03	<0.0001*
Plasticizer %	1.9555556	1.312735	1.49	0.1519
Permeation enhancer	3.3444444	1.312735	2.55	0.0192*
(Polymer conc. mg-2)*(Plasticizer %-2)	2.3833333	1.607766	1.48	0.1538
(Polymer conc.mg-2)*(Permeation enhancer 2)	0.5	1.607766	0.31	0.7590
(Plasticizer %-2)*(Permeation enhancer-2)	2.8833333	1.607766	1.79	0.0880

4. 4. Response of cmA on folding endurance (FD)

Table 4 presents the average folding endurance (FD) values for all formulations of carvedilol buccal film. The FD values range from 268±10 to 442±16. The deviation in FD is primarily attributed to the control of critical material attributes (CMA) such as polymer concentration and plasticizer concentration, which affect the % amount of drug release (%ADR). All formulation runs show good FD values above 350 % according to the given limitation. However, according to the acceptance constraint shown in Table 3 and based on the other critical quality attribute (CQA) parameters, formulation runs R16 (3 ml of *X*1 factor; 0.75 % of factor *X*2 and 1.5 % of factor *X*3), and R20 (3 ml of *X*1 factor; 0.75 % of factor *X*2 and 1 % of factor *X*3) show very good FD values of about 442±16 and 420±12 %. Accordingly, the remaining formulations display less favourable FD values. As a result, FD values are significantly influenced by both polymer and plasticiser concentrations. The statistical analysis of the data confirms the meaningful fitness of the model to the data (p<0.05) with a strong regression (R2) value, and the F-test, p-value at a 95 % confidence interval, and coefficient of determination were used for interpretation. The ANOVA F-test reveals a significant effect of polymer concentration on %ADR with a p<0.0000. The P-values for FD, as shown in Table 13, are all below 0.0001. Fig. 4 illustrates a close similarity between the expected and observed values. The impact of CMAs (polymer concentration and plasticizer concentration) on CQA (%ADR) can be further analyzed using response surface profiler and contour profiler plots as depicted in Fig. 2, 3. Among the CMAs, polymer concentration (*X*1) and plasticizer concentration (*X*2) show an improvement in FD. The polynomial regression equation for FD can be derived as:

$$Y3=179.66+27.38\ X1+53X2. \quad (3)$$

Table 10

Effect summary

Source	Log worth	P-Value
Plasticizer %	7.533	0.00000
Polymer concentration mg	3.673	0.00021
Polymer concentration mg*Plasticizer %	1.019	0.09561
Plasticizer %*Permeation enhancer	0.795	0.16049
Polymer concentration mg*Permeation enhancer	0.349	0.44820
Permeation enhancer	0.190	0.64563

4. 5. Physico-chemical evaluation of carvedilol buccal films

The evaluation of other physicochemical properties, including Mechanical Strength (kg/mm²), Thickness (mm), Weight (mg), Surface pH, % Swelling Index (S), Percentage Moisture Absorption (PMA), and Percentage Moisture Loss (PML), was conducted and the data are presented in Table 11. The mechanical strength of all Carvedilol buccal film formulations ranged from 5.24±0.24 to 15.64±0.46. The thickness of the formulations ranged from 0.20±0.01 to 0.78±0.02 mm. The weight of the buccal films varied between 101.17±1.70 and 164.12±1.16 mg. The pH of the buccal films ranged from 6.60±0.02 to 6.82±0.02. The % swelling of Carvedilol buccal film formulations ranged from 62.70±0.72 to 138.24±0.80 %. The PMA of all formulations ranged from 3.56±0.25 to 11.64±0.12, while the PML ranged from 0.94±0.10 to 1.88±0.02. Among the 27 formulations, R20 and R16 exhibited the best results in terms of desired constraints. R20 demonstrated a mechanical strength of 15.64±0.46, thickness of 0.78±0.02 mm, weight (mg) of 154.53±0.80, PMA of 124.2±0.99, and PML of 0.94±0.12. Similarly, R16 showed a mechanical strength of 15.42±0.46, thickness of 0.78±0.01 mm, weight (mg) of 156.72±0.02, PMA of 3.56±0.25, and PML of 1.84±0.08. Based on the data, it was concluded that R20 and R16 were the optimal formulations. Comparison of the percentage amount of drug release between commercialized Coreg ER and Carvedilol buccal film (R20 and R16) indicated that R20 exhibited the best performance, with a cumulative amount of drug release of 97.4±2.4 % at 24 hours. The in-vitro release kinetics of carvedilol buccal film (R20) were further analyzed by fitting the drug release data into various kinetic models (First Order, Zero Order, Higuchi, Hixson Crowell, and Korsmeyer-Peppas equations). The release kinetic data for the optimized R20 formulation followed a zero-order release pattern with high linearity (r^2=0.954). This indicated that R20 released the drug in a controlled and predetermined manner at a constant rate, making it an ideal formulation to achieve the required pharmacological effect while minimizing side effects. The drug release pattern also showed a good fit to the Higuchi model (r^2=0.936), suggesting diffusion as the underlying mechanism. The drug release exponent value (n) for R20 formulation, determined using Peppas equation fittings, was found to be 0.564, within the range of 0.45–0.89.

Table 11

Physico-chemical evaluation of carvedilol buccal films

Run	Mechanical strength (kg/mm²)	Thicknes (mm)	Weigh (mg)	Surface pH	% S	PMA	PML
R1	11.74±0.24	0.64±0.02	140.42±1.10	6.64±0.04	99.62±0.69	5.24±0.06	0.94±0.12
R2	5.54±0.64	0.24±0.01	102.45±1.10	6.60±0.02	67.50±0.65	7.32±0.10	1.14±0.72
R3	5.24±0.24	0.22±0.02	104.37±1.10	6.69±0.02	69.70±0.72	9.24±0.12	1.54±0.10
R4	5.46±0.34	0.20±0.01	102.94±1.60	6.72±0.02	71.62±0.62	10.32±0.14	1.14±0.20
R5	8.66±0.44	0.34±0.02	122.23±0.91	6.64±0.04	78.62±1.02	10.13±0.24	1.08±0.03
R6	8.62±0.46	0.38±0.01	120.37±0.60	6.66±0.04	82.64±1.12	5.21±0.12	1.18±0.02
R7	10.64±0.52	0.48±0.02	132.93±1.55	6.80±0.02	97.42±0.72	4.86±0.26	0.94±0.10
R8	10.47±0.64	0.46±0.01	132.18±0.91	6.72±0.04	92.53±0.62	5.18±0.28	0.98±0.08
R9	9.66±0.74	0.38±0.02	128.53±0.80	6.79±0.06	82.4±1.04	6.34±0.34	1.12±0.07
R10	9.54±0.88	0.36±0.02	130.31±0.58	6.71±0.02	80.4±1.04	6.12±0.22	1.06±0.06
R11	6.45±0.54	0.28±0.02	112.37±0.80	6.68±0.02	62.70±0.72	8.24±0.24	1.21±0.06
R12	6.56±0.66	0.26±0.01	112.17±1.70	6.72±0.04	63.70±0.72	10.02±0.23	1.10±0.08
R13	9.42±0.70	0.42±0.02	130.07±0.90	6.68±0.02	89.60±0.72	10.12±0.22	1.12±0.01
R14	15.23±0.46	0.70±0.01	166.12±1.12	6.66±0.04	104.9±0.90	3.66±0.10	0.98±0.02
R15	14.62±0.60	0.72±0.02	140.22±1.10	6.68±0.06	132.4±0.60	3.42±0.22	0.96±0.52
R16	15.42±0.46	0.78±0.01	164.12±1.16	6.70±0.02	138.24±0.80	3.44±0.12	0.98±0.08
R17	6.4±0.64	0.30±0.02	110.93±1.55	6.80±0.04	66.60±0.72	11.26±0.24	1.12±0.07
R18	10.42±0.56	0.59±0.01	134.18±0.91	6.72±0.04	118.4±0.26	4.56±0.25	0.98±0.08
R19	6.84±0.40	0.28±0.01	112.23±0.91	6.82±0.02	66.40±0.48	10.22±0.26	1.12±0.07
R20	15.64±0.46	0.78±0.02	154.53±0.80	6.72±0.02	124.2±0.99	3.56±0.25	0.98±0.72
R21	6.54±0.68	0.23±0.01	111.32±0.58	6.82±0.04	74.60±0.72	10.12±0.22	1.74±0.10
R22	5.76±0.50	0.25±0.01	101.37±0.80	6.78±0.02	64.60±0.72	11.32±0.26	1.06±0.06
R23	5.89±0.40	0.31±0.01	101.17±1.70	6.78±0.04	68.24±0.72	11.64±0.12	1.21±0.06
R24	5.76±0.56	0.26±0.02	102.35±1.10	6.80±0.04	66.54±0.72	11.48±0.16	1.84±0.08
R25	5.84±0.46	0.26±0.02	102.31±1.10	6.74±0.02	67.66±0.72	11.22±0.18	1.14±0.20
R26	12.64±0.36	0.74±0.02	144.34±1.10	6.68±0.04	114.2±0.99	4.56±0.22	0.98±0.03
R27	6.84±0.40	0.28±0.02	110.42±1.60	6.72±0.06	68.24±0.72	11.12±0.40	1.88±0.02

Note: all values are expressed as mean±SD, n=3

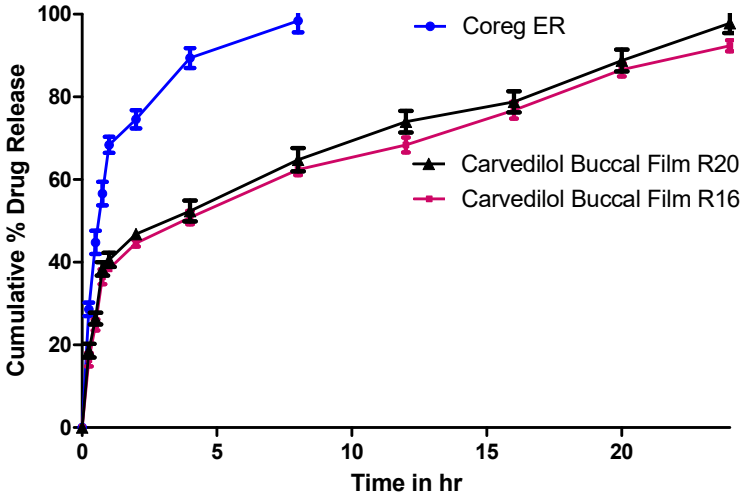

Fig. 5. Comparative *in vitro* drug release of Carvedilol buccal film vs. Coreg ER®

5. Discussion

Using different types and amounts of natural polymer mucilage derived from basil seeds, sweet basil, and purple basil, nine distinct buccal film formulations were created through screening trials. Among the trial formulations, formulation P3 with 1.5 mg of basil seed mucilage displayed the highest qualities, with a mucoadhesive strength (MS) of around 30.5±1.8 and a % drug content (%DC) of roughly 84.50±2.8 %. Based on these findings, 1.5 mg of basil seed mucilage was chosen as the naturally occurring polymer that could be further optimized inexpensively [7, 27].

The screening studies aimed to identify aappropriate natural polymer for the formulation of buccal films. The selection was based on the evaluation of % drug content (%DC) and mucoadhesive strength (MS) among the different trial formulations. Formulation P3, containing 1.5 mg of basil seed mucilage, demonstrated the highest %DC and MS values, indicating better drug content uniformity and mucoadhesive properties compared to other formulations [28, 29].

The choice of Basil seed mucilage as the selected natural polymer was driven by its favorable characteristics and cost-effectiveness. Basil seeds are readily available and can be extracted through a hydroalcoholic maceration process, making it an economically viable option for large-scale production [21].

The unsuitability of Tamarind and Purple basil as favorable polymers, as indicated by their lower %DC and MS values, suggests that these polymers may not possess the desired film-forming and mucoadhesive properties necessary for the buccal film formulation [21].

The screening studies provide valuable insights into the selection of the natural polymer for further optimiza-

tion. The chosen Basil seed mucilage formulation (P3) will serve as a starting point for subsequent optimization steps, including the adjustment of other formulation variables and the use of statistical tools to achieve the desired drug release profile, mucoadhesive strength, and overall performance of the buccal film [9–15].

The screening studies have successfully identified Basil seed mucilage as a promising natural polymer for the formulation of buccal films, laying the foundation for further optimization and development of cost-effective and efficacious carvedilol mucoadhesive buccal films.

In summary, the study investigated the influence of critical material attributes (CMA) on the critical quality attributes (CQA) of carvedilol buccal films. The CMAs considered were polymer concentration, permeation enhancer concentration, and plasticizer concentration. The findings regarding the response of CMAs on the % drug content (DC), % amount of drug release (%ADR), and folding endurance (FD) are as follows:

The %DC values were significantly impacted by polymer concentration. Formulations R16 and R20, which had 3 ml of factor $X1$, 0.75 % of factor $X2$, and 1.5 % and 1 % of factor $X3$, respectively, exhibited %DC values of approximately 96.9±2.4 % and 97.4±2.4 %. Statistical analysis confirmed the meaningful fitness of the model to the data, indicating a strong regression (R2) value and a significant influence of polymer concentration on %DC (p<0.05).

Both polymer concentration and permeation enhancer concentration significantly affected %ADR values. Formulations R16 and R20 demonstrated %ADR values of approximately 97.8±2.2 % and 92.4±2.4 %, respectively. Statistical analysis confirmed the meaningful fitness of the model to the data, indicating a strong regression (R2) value and a significant influence of polymer concentration on %ADR (p<0.05) [28–32].

Polymer concentration and plasticizer concentration had a significant impact on FD values. Formulations R16 and R20 exhibited very good FD values of approximately 442±16 % and 420±12 %, respectively.

Statistical analysis confirmed the meaningful fitness of the model to the data, indicating a strong regression (R2) value and a significant influence of polymer concentration on FD (p<0.05). The study demonstrated the critical role of polymer concentration in determining the % Drug Content, % Amount of Drug Release, and folding endurance of carvedilol buccal films. The findings provide valuable insights for the optimization and formulation of buccal films using natural polymers, aiding in the development of high-quality and effective drug delivery systems.

The physicochemical evaluation of carvedilol buccal films included the assessment of mechanical strength, thickness, weight, surface pH, % swelling index, percentage moisture absorption, and percentage moisture loss. Among the 27 formulations, R20 and R16 demonstrated the most desirable results within the specified constraints. R20 exhibited a mechanical strength of 15.64±0.46 kg/mm^2, thickness of 0.78±0.02 mm, weight of 154.53±0.80 mg, percentage moisture absorption of 3.56±0.25, and percentage moisture loss of 0.94±0.12. Similarly, R16 showed a mechanical strength of 15.42±0.46 kg/mm^2, thickness of 0.78±0.01 mm, weight of 156.72±0.02 mg, percentage moisture absorption of 3.56±0.25, and percentage moisture loss of 1.84±0.08. Based on these findings, R20 and R16 were identified as the optimal formulations. Furthermore, the comparison of the percentage amount of drug release between the commercialized Coreg ER and Carvedilol Buccal Film (R20 and R16) revealed that R20 demonstrated the highest cumulative amount of drug release (97.4±2.4 %) at 24 hours. The release kinetics of the optimized R20 formulation followed a zero-order release pattern, indicating controlled and constant drug release. The Higuchi model fitting suggested diffusion as the underlying mechanism, and the Peppas equation analysis yielded a drug release exponent value (n) of 0.564, indicating a non-Fickian release mechanism [12, 18, 20].

The optimized formulations, R20 and R16, exhibited favorable physicochemical properties and achieved the desired drug release profile. These findings support the potential of Carvedilol buccal films with Basil seed mucilage as a promising drug delivery system for efficient and controlled delivery of carvedilol while minimizing side effects.

Study limitations. There are several potential restrictions to take into account when undertaking research on the use of statistical tools for the development and optimization of carvedilol mucoadhesive buccal films utilizing natural polymers. The availability and sourcing of natural polymers utilized in buccal film formulation may vary. Due to differing suppliers or batches, some polymers may have a limited availability or may have varying qualities. The outcomes of the experiment may become variable as a result. Carvedilol can need certain natural polymers to be compatible with it. Carvedilol may not be sufficiently solubilized or stabilized by some polymers, which could compromise medication release and effectiveness. Natural polymers may be difficult to combine in the formulation due to limited compatibility.

Prospects for further research. Some potential areas for future investigation include:

Investigate new natural polymers to create buccal mucoadhesive films for carvedilol. Find out how blending natural polymers can improve film qualities. Examine the impact of excipients on the stability of the film and drug permeability. Utilize advanced techniques to comprehend drug-polymer interactions, create an accurate prediction of drug delivery and bioavailability in vivo, analyze the stability of films over time in various storage situations, comparing created buccal films to carvedilol commercial formulations identify production scaling issues while preserving film quality, examine the legal specifications needed for authorization and commercialization.

6. Conclusions

In conclusion, the screening studies successfully identified Basil seed mucilage as a suitable and cost-effective natural polymer for the formulation of buccal

films. The selected formulation, P3, containing 1.5 mg of basil seed mucilage, demonstrated the best characteristics in terms of % drug content and mucoadhesive strength. This lays the foundation for further optimization and development of carvedilol mucoadhesive buccal films. Additionally, the physicochemical evaluation of carvedilol buccal films highlighted the optimal formulations, R20 and R16, which exhibited favorable properties and achieved the desired drug release profile. These findings demonstrate the potential of Carvedilol buccal films as an effective and controlled drug delivery system.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available on reasonable request.

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