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Formulation And Evaluation Of Arginine Containing Mucoadhesive Buccal Tablet For Treatment Of Diabetes Mellitus

Dr. Sandip R. Pawar, Mr. Dhiraj S. Patil, Dr. Bharat V. Jain

Department of Pharmaceutics
Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda,
Maharashtra, India.

Mucoadhesive buccal drug delivery systems offer a promising approach for enhancing bioavailability and prolonging drug retention in the oral cavity, bypassing first-pass metabolism. This study focuses on the formulation and evaluation of Arginine-containing mucoadhesive buccal tablets for the effective management of Diabetes Mellitus. Arginine, a conditionally essential amino acid, plays a crucial role in glucose metabolism and insulin sensitivity, making it a potential therapeutic agent for diabetic patients. The tablets were prepared using direct compression and incorporated mucoadhesive polymers such as Hydroxypropyl Methylcellulose (HPMC), Carbopol, and Sodium Alginate to ensure optimal adhesion and controlled drug release. Various excipients were selected to enhance mechanical strength, swelling behavior, and drug permeation. The formulated tablets were evaluated for physicochemical properties, including weight variation, hardness, friability, surface pH, swelling index, and in vitro drug release studies. The optimized formulation demonstrated prolonged retention in the buccal mucosa, ensuring sustained drug release and improved therapeutic efficacy. Stability studies confirmed the integrity and effectiveness of the formulation over time. The findings suggest that Arginine-containing mucoadhesive buccal tablets could serve as a viable alternative for improving glycemic control in diabetic patients, enhancing patient compliance, and reducing dosing frequency.

Keywords: Mucoadhesive Buccal Tablet, Bioavailability, Controlled Drug Release, Buccal Drug Delivery.

INTRODUCTION: Mucoadhesive drug delivery systems (MDDS) utilize bioadhesive polymers to enhance drug retention at mucosal surfaces, improving bioavailability and therapeutic efficacy. These systems are particularly beneficial for drugs that require prolonged contact with mucosal tissues, bypassing first-pass metabolism and ensuring controlled drug release.MDDS can be applied across various routes, including buccal, sublingual, nasal, ocular, vaginal, and gastrointestinal drug delivery. The mechanism of mucoadhesion involves electrostatic interactions, hydrogen bonding, and van der Waals forces, ensuring strong adhesion between the drug formulation and mucosal surfaces.

Key Advantages:
Prolonged drug retention at the absorption site Improved bioavailability and therapeutic efficacy Targeted drug delivery for localized and systemic effects Reduced dosing frequency, enhancing patient compliance
Bypasses first-pass metabolism, minimizing drug degradation Types of Mucoadhesive Drug Delivery Systems:
Buccal and Sublingual Systems – Ideal for systemic drug absorption.
Nasal and Ocular Systems – Used for rapid drug delivery.
Vaginal and Rectal Systems – Suitable for localized treatment.
Gastrointestinal Systems – Enhances drug retention in the stomach.
Polymeric Materials Used:
Natural Polymers: Chitosan, Alginate, Gelatin
Synthetic Polymers: Carbopol, Polyvinyl Alcohol (PVA), Hydroxypropyl Methylcellulose (HPMC)
MATERIALS AND METHODS:
Method of Analysis
Pre-formulation Studies

Pre-formulation studies serve as a crucial step in dosage form development, involving the characterization of a drug's physical, chemical, and mechanical properties. These evaluations help in designing stable, safe, and effective formulations.

Identification and Characterization of the Drug
Description: The drug sample was examined for its physical state, appearance, color, and odor to ensure consistency in formulation.
Solubility Studies
The solubility of Arginine in phosphate buffer (pH 6.8) was determined using the phase equilibrium method.
An excess amount of drug was added to 10 ml of phosphate buffer in vials, sealed with rubber caps, and agitated for 24 hours at room temperature using a rotary shaker.
The resulting solution was filtered through 0.2 µm Whatman filter paper, and the solubilized drug content was estimated by measuring absorbance at 229 nm using a UV spectrophotometer.
Melting Point Determination
Melting point was determined using the capillary tube method.
A small quantity of drug was placed into a sealed capillary tube.
The tube was heated using a digital melting point apparatus, with the temperature recorded at the first signs of melting.
This process was repeated three times, and the average melting point was noted.
Determination of Wavelength (λmax)
A 10 mg drug sample was weighed accurately and dissolved in methanol in a 10 ml volumetric flask.

- A 0.1 ml aliquot was transferred into another 10 ml volumetric flask, diluted with ethanol, and scanned using a double-beam UV spectrophotometer to determine the wavelength of maximum absorption (λmax).

Drug-Polymer Compatibility Studies

- Compatibility between drug and excipients was assessed through Fourier Transform Infrared (FTIR) Spectroscopy.
- The potassium bromide (KBr) disc method was used, where powdered drug and excipient mixtures were blended with dry KBr powder.
- The mixture was compressed into transparent pellets under high-pressure (1000 psi), and characteristic peaks were analyzed.

Preparation of Mucoadhesive Buccal Tablets of Arginine
Mucoadhesive buccal tablets of Arginine were formulated using the direct compression method with a single-punch tablet press.
Formulation Process

- Drug, polymers, and excipients were weighed accurately.
- Multiple batches were prepared by varying the ratios of Carbopol 934, HPMC E15LV, sodium alginate, and xanthan gum (used as mucoadhesive polymers).
- Mannitol was used as a diluent, while magnesium stearate and talc acted as flow promoters.
- The prepared blend was compressed using a tablet punching machine.

Evaluation Parameters of Mucoadhesive Buccal Tablets
A thorough evaluation of mucoadhesive buccal tablets is conducted to ensure uniformity, stability, and effectiveness. These parameters are categorized into pre-compression and post-compression assessments.

I. Pre-Compression Parameters
Before tablet compression, the formulation blend undergoes various tests to determine its flow properties, particle characteristics, and compatibility.
1. Angle of Repose

- Determines the flowability of the powder blend.
- The fixed funnel method is employed where the powder is poured through a funnel onto a flat surface.

2. Bulk and Tapped Density

- **Bulk density** is calculated by dividing the mass of the powder by its volume before tapping.
- **Tapped density** is measured after mechanical tapping of the powder in a graduated cylinder.

3. Hausner Ratio

A lower value (<1.25) suggests good flowability, while higher values indicate poor flow.

4. Carr's Index (% Compressibility)

Carr's Compressibility Index (CI) measures the flow properties of a powder blend based on volume changes during tapping. It reflects the powder's ability to rearrange and pack efficiently.

II. Post-Compression Parameters

Once the tablets are prepared, they undergo rigorous evaluation to ensure mechanical integrity, uniformity, and optimal drug release. The following parameters are assessed:

1. Hardness

- Determines the mechanical strength of tablets.
- Measured using a Monsanto or Pfizer hardness tester.
- Ensures tablets withstand handling and transportation without breaking.

2. Friability

- Evaluates tablet resistance to abrasion.
- Conducted using a Roche friabilator, where tablets are rotated and subjected to impact.
- Acceptable friability is ≤ 1% weight loss.

3. Weight Variation

- Ensures uniformity in tablet weight.
- 20 tablets are randomly selected and weighed individually.
- The average weight is calculated, and deviations are checked against pharmacopeial limits.

4. Uniformity of Thickness

- Tablet thickness is measured using a digital Vernier caliper.
- Ensures consistent tablet dimensions for proper packaging and administration.

5. Drug Content Uniformity

- Confirms consistent drug distribution in tablets.
- 10 tablets are randomly selected, crushed, and analyzed using UV spectrophotometry or HPLC.
- Drug content should fall within 90-110% of the labeled claim.

6. Wetting Time

- Assesses tablet hydration rate, crucial for mucoadhesion.
- A tablet is placed on a wet filter paper, and the time taken for complete wetting is recorded.

7. In-Vitro Disintegration Time

- Determines tablet breakdown time in simulated conditions.
- Conducted using a disintegration test apparatus with phosphate buffer (pH 6.8).
- Ensures rapid disintegration for effective drug absorption.

8. In-Vitro Dissolution Study

- Evaluates drug release profile over time.
- Performed using a USP dissolution apparatus with simulated saliva or gastric fluid.
- Drug release is measured at specific time intervals using UV spectrophotometry.

9. Differential Scanning Calorimetry (DSC)

- Assesses thermal behavior of drug and excipients.
- Helps detect polymorphic changes, crystallinity, and interactions.
- Conducted using a DSC instrument, where heat flow is recorded.

10. Fourier Transform Infrared (FTIR) Spectroscopy

- Confirms chemical integrity and drug-excipient compatibility.
- FTIR spectra are obtained using the KBr pellet method.
- Characteristic peaks are analyzed to ensure no undesirable interactions.

RESULTS AND DISCUSSION

Characterization of Active Pharmaceutical Ingredient:

Table 1: Evaluation Parameter

Parameter	Observation
Color	White crystalline powder;
Odor	Odorless
Taste	Tasteless
State	Fine to granular powder.

Melting point:

Observation: The melting point of Arginine was found to be 180°C, confirming its thermal stability and purity.

Solubility studies:

Solubility of Arginine was determined in different solvent systems and buffers.

Table 2: Solubility of Arginine in different solvents

Sr. No	Solvents	Solubility
1	Distilled water	-
2	Methylene chloride	+
3	Acetone	+

Table 3: Concentraion of Arginine

Sr. No	Medium	Concentration
1	Phosphate 6.8 buffer	14.8
2	Phosphate 7.4 buffer	13.7
3	water	12.4

Preparation of PH 6.8 phosphate buffer:

A 1M phosphate buffer solution is prepared using potassium dihydrogen phosphate and disodium hydrogen phosphate, ensuring pH stability for various applications.

Table 4: Calibration curve of Arginine

S.No	Concentrations (µg/ml)	Absorbance at 330nm

1	0	0
2	2	0.197
3	4	0.356
4	6	0.484
5	8	0.622
6	10	0.790

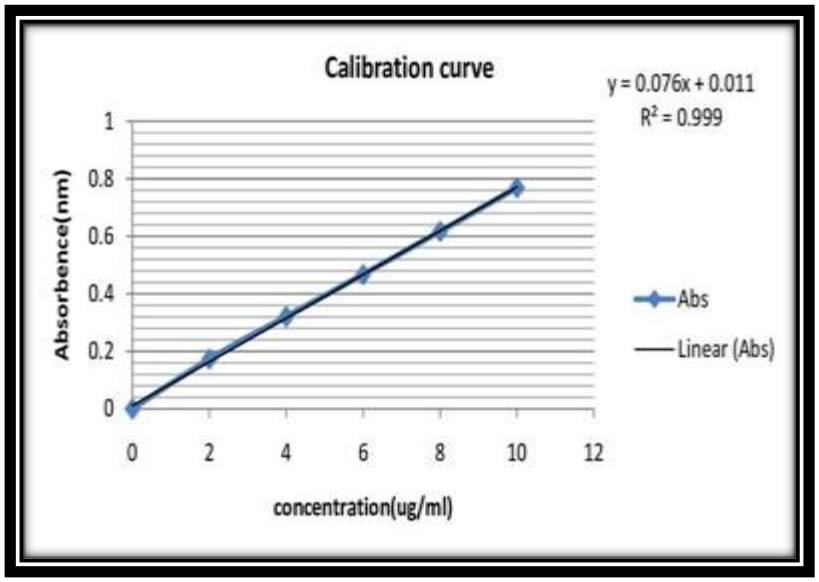

Fig. No 1: Calibration curve of Arginine

9.2. FTIR Compatability Studies:

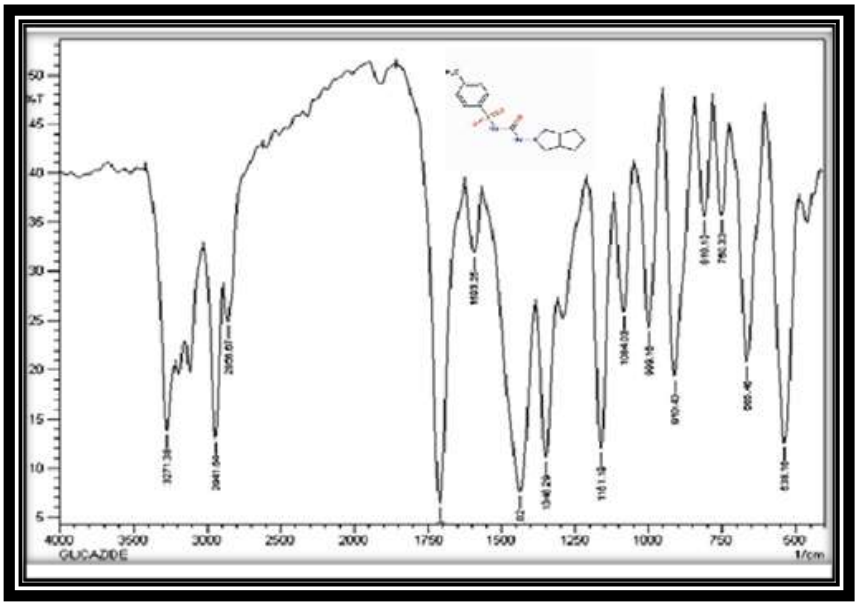

Fig. No.2: FTIR spectra of pure drug Arginine

Interpretation of FTIR

Table 5: Interpretation of FTIR peaks present in Arginine.

S.No.	Wave number in formulation (cm^{-1})	Characteristic Wave number range cm^{-1}	Bond nature and bond attributed
1	3447.78	3000-3700	N-H Stretching
2	1639.47	1600-1700	NH2 deformations
3	2870.17	2700-3300	C-H3asymetrical Stretching
4	1710.23	1600-1900	C-O Stretching
5	1466	1200-1500	O-H Bending
8	1596.55	1500-1800	C=C stretching
9	1348.07	1300-1490	c-c stretching
10	1164.24	1100-1200	C-N stretching

Precompression Parameter of Powder Blend:

Table 6: Precompression parameter of powder blend.

S.No	Formulation Code	Angle of repose (θ)*	Bulk Density* g/cm^3	Tapped Density* g/cm^3	Hausner's ratio*	Carr'sindex* %
1	H1	26.47±0.55	0.50±0.14	0.59±0.08	1.19±0.05	15.94±0.62
2	H2	25.28±0.97	0.48±0.19	0.56±0.04	1.17±0.03	15.63±0.86
3	H3	26.31±0.60	0.50±0.19	0.62±0.02	1.18±0.01	16.29±0.83
4	H4	27.26±0.70	0.49±0.18	0.60±0.01	1.18±0.02	15.43±0.63
5	S1	25.03±0.62	0.50±0.22	0.58±0.07	1.14±0.01	13.28±0.87
6	S2	25.98±0.66	0.50±0.23	0.57±0.08	1.17±0.01	14.74±0.41
7	S3	26.54±0.45	0.51±0.22	0.62±0.07	1.18±0.02	15.47±0.97
8	S4	25.03±0.55	0.50±0.24	0.58±0.06	1.17±0.01	13.31±0.62

9	G1	25.39±0.75	0.50±0.23	0.57±0.06	1.14±0.01	12.67±0.47
10	G2	26.43±0.50	0.50±0.21	0.58±0.05	1.16±0.01	13.73±0.89
11	G3	25.32±0.66	0.50±0.18	0.57±0.04	1.16±0.02	14.57±0.75
12	G4	25.44±0.68	0.41±0.14	0.59±0.02	1.19±0.01	15.64±0.89

***All values are expressed as mean ±SD, n=3**

Post Compression Parameters

Table 7: Results of Post-compression parameters

S.No	Formulation Code	Thickness* (mm)	Hardness* (kg/cm 2)	Friability (%)	Weight variation (%)
1	H1	3.32±0.15	5.16±0.40	0.85	0.073±0.43
2	H2	3.40±0.10	4.91±0.49	0.83	0.068±0.55
3	H3	3.44±0.41	5.41±0.37	0.84	0.047±0.46
4	H4	3.51±0.14	5.16±0.60	0.72	0.022±0.52
5	S1	3.25±0.15	5.33±0.51	0.65	0.068±0.48
6	S2	3.30±0.11	5.58±0.37	0.85	0.020±0.54
7	S3	3.17±0.09	5.50±0.54	0.65	0.020±0.65
8	S4	3.26±0.16	5.16±0.60	0.73	0.096±0.57
9	G1	3.23±0.12	5.25±0.41	0.52	0.068±0.57
10	G2	3.36±0.10	5.66±0.40	0.82	0.019±0.63
11	G3	3.28±0.12	5.50±0.44	0.75	0.020±0.16
12	G4	3.43±0.14	5.25±0.52	0.61	0.071±0.56

CONCLUSION: The development of mucoadhesive buccal tablets for Arginine offers an alternative route of administration, bypassing the first-pass metabolism and enabling prolonged drug release. These tablets can be formulated using Arginine in combination with Carbopol 940, HPMC K15 LV, sodium alginate, and xanthan gum in varying ratios.

A total of twelve formulations (H1-H4, S1-S4, G1-G4) were prepared and assessed for various physicochemical properties, including hardness, thickness, weight variation, friability, drug content percentage, surface pH, bioadhesive strength, swelling index percentage, in-vitro drug release, and in-vitro drug release kinetics.

Among the formulations, H4 demonstrated the most effective sustained drug release, achieving 71.70±0.53% release at the end of 8 hours with a drug-to-polymer ratio of 1:1. The in-vitro drug release kinetics analysis indicated that all formulations adhered to Peppas order kinetics, following a non-Fickian diffusion mechanism.

In conclusion, formulation H4 shows promise for buccal administration of Arginine, providing an effective means to bypass hepatic first-pass metabolism and enhance the bioavailability of the drug through the buccal mucosa

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