FORMULATION, OPTIMIZATION AND EVALUATION OF TRIMETAZIDINE DIHYDROCHLORIDE BUCCAL TABLET

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Abstract

The prime objectives of this study was to develop buccal tablets of trimetazidine dihydrochloride using a direct compression procedure with various bioadhesive polymers. The aim was to enhance the in-vitro release and drug release of buccal tablets. Polyvinyl alcohol, polyvinyl pyrrolidone and carbopol 934P were utilized as bioadhesive polymers in different proportions to formulate the desired buccal tablets.

A total of nine formulations were prepared and optimized based on various characteristics of the buccal tablets. Compatibility studies were conducted to evaluate the compatibility between the polymers and between different formulations. A factorial design was employed with carbopol 934 and mannitol as independent variables and T50, drug release and swelling index as dependent variables. The buccal tablets were subjected to analyze for various physiochemical parameters including weight variation, friability, hardness, thickness, disintegration time, swelling studies and swelling index and in-vitro release. All these parameters were found to be within acceptable range.

The development and optimization of buccal tablets containing trimetazidine dihydrochloride using bioadhesive polymers demonstrated promising results. The formulation exhibited desirable physiochemical properties, including weight variation, hardness, swelling index, in-vitro drug release. These findings indicate the potential for the buccal tablets to effectively release of the drug and enhance its delivery. Further studies are warranted to evaluate their performance in vivo and assess their therapeutic efficacy.

Keywords: Buccal tablets, trimetazidine dihydrochloride, bioadhesive polymers, compatibility study, disintegration time.

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1. BACKGROUND

Among the various methods of delivering medications, the oral pathway is a commonly favoured option for both patients and medical professionals. Despite our present comprehension of all the biochemical and physiological factors related to absorption and metabolism, certain drugs cannot be suitably administered using this approach. The liver's pre-systemic clearance presents a notable obstacle, frequently resulting in a restricted connection between membrane permeability, absorption and the extent to which the drug remains active and available within the body [1].

In recent years, scientists and researcher in the field of drug development have been increasingly exploring an alternative routes for administration of drugs which helps to enhance the potency of approved drugs and to overcome the limitations associated with the oral route. These alternative routes include transdermal, buccal, nasal, sublingual, vaginal or rectal administration [2].

Drug delivery through transmucosal pathways, encompassing the mucosal linings of areas like the nose, rectum, vagina, eye, and mouth presents feasible alternatives for delivering drugs throughout the body. These routes offer potential benefits over perioral administration. These routes can help bypass pre-systemic elimination in the gastrointestinal (GI) tract and bypass the first-pass effect, depending on the characteristics of the drug being administered [3]. In the oral cavity, specific sites for medication administration include the sublingual region (floor of the mouth), buccal region (interior of the checks), and gingival region (gums) [4]. These locations in the oral cavity present opportunities for localized or systemic drug delivery, enabling improved bioavailability and therapeutic outcomes compared to traditional oral administration routes.

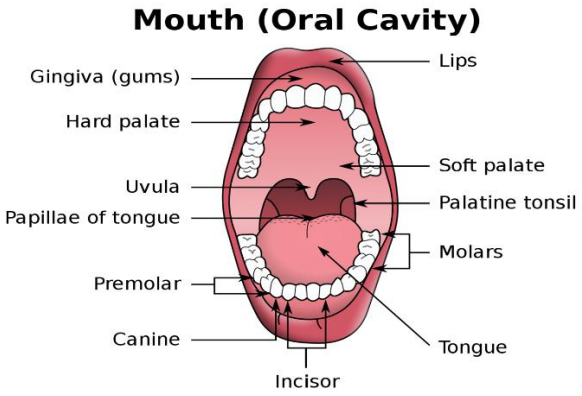

Figure 1: Diagram of oral cavity

The buccal routes offers potential routes for the administration of various types of pharmaceutical compounds, including small hydrophilic molecules, large and delicate proteins, oligonucleotides and complex sugars (polysaccharides). The oral cavity is widely preferred site for local and systemic distribution of drug. Ideally, for effective buccal drug administration, the drug compounds should have partition coefficient in the range 40-20000 and Pka values between 2 and 10 [5].

Buccal Tablet

Buccal bioadhesive tablets are solid forms of medication that require moistening prior to being to the buccal mucosa (inner cheek). These tablets are prepared by using bioadhesive polymers and additional ingredients to enhance their capability to stick to the mucous membrane effectively. Some buccal bioadhesive tablets are formulated as double or multilayered tablets, which may offer specific advantages such as controlled drug release or combination therapy.

The two buccal bioadhesive tablets are commercially available buccoadhesive in UK

are Bucastem (Nitroglycerine) and SuscardbuccaP (Prochloroperazine). Bucastem is indicated for the prevention and treatment of angina pectoris, while Suscard BuccaP is used for the treatment of severe nausea and vomiting. These buccal bioadhesive tablets provide localized drug delivery and are designed to adhere to the buccal mucosa, allowing for efficient drug absorption and therapeutic effects [6].

Figure 2: Buccal tablet in buccal mucosa [14]

Advantages of Buccal Tablet.

1. **Quick dissolution:** Buccal film has a wide surface area and has rapid dissolution in the oral cavity, facilitating the efficient systemic absorption of active pharmaceutical ingredients.
2. **No swelling or chewing required:** There is no need to swallow or chew the medication, making it convenient and easier to administer, especially for individual who have difficulty swallowing tablets or capsules.
3. **Choking risk minimized:** As the medication is not required to swallow, there is no possibility of choking, which is particularly advantageous for young children or patients with swallowing difficulties.
4. **Bypassing first-pass Metabolism:** By bypassing the The buccal film increases the medication's systemic bioavailability by facilitating hepatic first-pass metabolism, ensuring a higher concentration of the drug reaches the bloodstream.
5. **Protection from breakdown:** The acidic environment and GI enzymes present in the stomach and intestine are bypassed, which can protect drugs from being broken down and degraded, leading to better drug stability and effectiveness.
6. **Quick onset of action with fewer adverse effects:** medications administrated through the oral mucosa tend to have a faster onset of action, allowing for quicker relief from symptoms. Additionally, this route of administration can reduce the potential for adverse effects associated with gastrointestinal disturbances.
7. **Self-administration:** Buccal tablets can easily be self-administered by patients, providing them with greater control and convenience in taking their medications.
8. **Precise dosing:** oral mucosal drug delivery allows for more precise dosing compared to liquid dosages forms, offering better control over the amount of medication delivered.
9. **Good stability and mouth feel:** Oral drug delivery systems, such as buccal tablet can be designed to have good stability, ensuring that the medication remains intact and effective until administration [7].

Disadvantages of Buccal Tablet

1. **Sensitivity to moisture:** Buccal tablets may be sensitive to moisture, which can affect their stability and shelf life. Proper packaging and storage conditions are crucial to maintain their integrity.
2. **Local irritation:** The prolonged contact of buccal tablets with the oral mucosa can cause local irritation or discomfort in some individuals, leading to potential patient non-compliance.

3. **Limited permeability:** The permeability of the buccal mucosa is lower compared to other mucosal routes, such as sublingual or nasal routes. This can limit the absorption of certain drugs, especially those with low permeability properties [8].

2. MATERIALS AND METHODOLOGY

Table 1: list of materials used

S. No.	Materials	Source
1	Trimetazidine dihydrochloride	Prince Scientific
2	Carbopol-934P	Sample gifts from Nova Genetica PVT. LTD.
3	Polyvinyl alcohol	
4	Polyvinyl pyrrolidone	
5	Mannitol	
6	Magnesium Stearate	
7	Ethyl cellulose	
8	P-cyclodextrin	

Table 2: list of Equipments required

S. No.	Name of equipment	Company name
1	FT-IR spectrometer	Agilent Technologies Instruments
2	UV/Vis spectrometer	Shimadzu
3	Dissolution apparatus	Electro Lab
4	Digital balance	Denver
5	Electronic Digital Micrometer	SYATEK
6	Monsanto Hardness Tester	Harrisons
7	PH tester	OHAUS
8	Vernier Caliper	Berent
9	Friability Apparatus	Electro Lab

3. METHODOLOGY

Analytical Methods

A. Preparation of stock solution

A Sonicating 100 cc of water and 100 mg of trimetazidine for 20 minutes yielded a standard stock solution. To make 100 g/ml standard stock solution, 10 ml of the drug solution is diluted to 100 ml.

To get concentrations of 10, 20, 30, 40, and 50 g/ml, pipette 1, 2, 3, 4, and 5 ml of this solution into 10 ml volumetric flasks. Deionized water is then used to raise the total volume to 10 ml. A blank solution was also provided. The relationship between concentration (g/ml) and absorbance at 274 nm was plotted on a typical graph.

B. Preparation of buccal tablets of Trimetazidine Dehydrochloride

To prepare buccal tablets, the active pharmaceutical ingredient (Trimetazidine Dihydrochloride) and polymers were mixed together in a mortar and pistel, and combining them thoroughly. Other excipients such as diluents and lubricants are typically added to the mixture to enhance the tablet formulation. The mixture containing the drug, polymers, and excipients, was subjected to single punching machine for direct compression.This process involved applying to the mixture to compact it into tablet form.

Furthermore, to achieve unidirectional release, ethyl cellulose as a The buccal tablet's reverse was covered with a backing layer. It serves the propose of controlling release of the drug and promote its absorption via the buccal mucosa, while preventing the medication from being released into oral cavity.

FT-IR Compatibility studies

Prior to the development of any dosage forms, the compatibility investigation was conducted. The compatibility between the pure medication (trimetazidine dihydrochloride) and polymers utilized in the production of buccal tablets, such as Carbopol 934, PVP, PVA, and ethyl cellulose, is routinely examined using the Fourier Transform Infra-Red (FTIR) technique.

The peaks compared to the pharmacological spectrum's peaks. The key, distinct peaks connected to the drug and drug polymer's functional groups are seen [9, 10].

Optimization of buccal tablets

Optimization plays a crucial role in the development of any product, and factorial designs are commonly used to evaluate multiple factors simultaneously. By using factorial designs, interaction between different factors can be determined and analyzed. This allows for a comprehensive understanding of how different variables interact and impact the performance or outcome of the product being developed [11]

Design of experiment (DOE)

The experimental design was frequently a factorial design (2X3). The amount of Carbopol 934 (A1) and the amount of Mannitol were examined as the independent variables (A2). Table 6 lists the dependent variables, including time to release 50% of the drug (B1), drug release at 8 hours (B2), and swelling index (B3) which are shown in table 3.

Experimental design

To identify the elements involved in a process and assess their relative importance, a tool called a factorial design is utilised. It helps to make any potential interactions between the selected parameters clear. When developing a factorial design, careful consideration must be given to parameter and response choices. In this study, Designer Expert 11.0.1 (tat Ease Inc.) software is used to assess the full factorial technique. The dependent and independentand independent, were examined at three levels in a 32 full factorial design (table 7). Nine different formulations altogether of trimetazidine buccal tablet were prepared, encorporating various combination of the two variables as per 3^2 factorial evaluation. The result is analysed and evaluated and recorded.

Table 3. Factors and Factors levels investigated in factorial experimental design

Independent Variables	**Amount of drug (mg)**		
	-1	**0**	**+1**
Carbopol 934	40	80	120
Mannitol	30	60	90
Response	**Goal**		
Time taken to release 50% drug	Decrease		
Drug release at 8^{th} hour	Increase		
Swelling index	Increase		

Table 4. Composition of trimetazidine buccal tablet in mg

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Trimetazidine dihydrochloride	20	20	20	20	20	20	20	20	20
Carbopol 934	40	40	80	120	120	120	80	80	40
Mannitol	60	90	30	90	30	60	60	90	30
Polyvinyl pyrrolidone	10	10	10	10	10	10	10	10	10
Magnesium stearate	2	2	2	2	2	2	2	2	2
P-cyclodextrin	2	2	2	2	2	2	2	2	2
Ethyl cellulose	56	56	56	56	56	56	56	56	56

Evaluation Parameter for Buccal Tablets

1. Weight variation

Swallowing twenty pills was the weight variation test. Average tablet weight is used to compare tablet weights. The USP limit test is passed if no more than two tablets deviate by 5 mg or 10 mg [12].

Table 8: Limits of weight variation as per USP

Average weigh of tablet (X mg)	Maximum % difference allowed
130 mg or less	10
130mg to 324 mg	7.5
More than 324 mg	5

(WH-A/A) X 100 = maximum positive variation in percent
(WL-A/A) X 100 = minimal negative divergence in percent
WH is the heaviest milligram me.
WL is the lightest weight in milligrammes.
Average weight in milligrammes [13].

2. Drug content uniformity

Buccal pills with trimetazidine dihydrochloride were produced.

Method

10 pills, chosen at random from each batch, were ground into tiny, fine particles using the proper grinding equipment. A drug's standard solution is created using the appropriate concentration, and a reference solution is also created. Transfer the powder particles to a 100 ml volumetric flask after weighing them; they should weigh the same as one tablet. Shake the mixture in the flask to dissolve it after adding 20 ml methanol. Then add phosphate buffer PH 6.4.powder tablet has completely dissolved. The mixture should then be diluted to 100 ml and filtered through 0.45 m filter paper to remove any impurities. and. A UV-Visible Spectrophotometer should be used to detect the absorbance at 270 nm [60].

Calculation

$$\text{Drug content (mg)} = \frac{(\text{Absorbance X Slope} \pm \text{Intercept}) \text{ X Dilution factor [14]}}{1000}$$

3. Tablet thickness

Thickness of prepared tablet were evaluated with the help of Vernier caliper. From each batch, 3 tablets were randomly picked as a sample and average volume were determined [15]

4. Tablet hardness

Three tablets from each formulation are taken to measure the hardness of the tablet using a vernier calliper. For handling medications during manufacture, packaging, and shipping, tablets need to have a strong mechanical strength. Hardness testing is used to gauge a tablet's crushing powder [16].

5. Friability

The friability of a tablet is evaluated using the Roche friabilator. A plastic chamber that rotates up to 100 times at a speed of 25 rpm makes up the device. The pill is first put on a friabilator, where its weight is limited to 6.5 g. After taking out the tablet, the scales are reweighed. Appropriate tablet compressions are those that lose between 0.1 and 0.5 percent of the tablet's weight..

Percent friability = weight loss/starting weight multiplied by 100

Where,
Weight of tablets following a revolution = Initial weight – Final weight [17].

6. Swelling studies and swelling index

Three tablets from each batch were removed and weighed as a starting point (W1). Each tablet is individually placed in petri dishes with a 5 cc phosphate buffer at a pH of 6.8. Carefully remove the tablet from the petric disc at intervals of 1, 2, 4, and 8 hours. Use filter paper to drain any extra water. Calculate each tablet's percentage of hydration by reweighing the tablet as (W2) after it has been consumed.
Swelling Index (S.I.) = (W2-W1)/W1 [18, 19].

7. In-vitro dissolution studies

Dissolution apparatus USP type III rotating paddle method is employed for study of drug release from buccal tablets. Phosphate buffer having PH 6.8 is made as dissolution medium.

The dissolution apparatus are performed at 37°C ± 0.5°C, rotated at a constant speed of 50rpm. At a suitable time intervals, 5ml samples are withdrawn and the volume is replaced with fresh medium. The samples are analyzed in the UV spectrophotometer at a specified wavelength of nm [20].

8. Kinetic analysis of dissolution data

Trimetazidine Dehydrochloride release kinetics was evaluated based on four mathematical models such as Zero order kinetics, first order kinetics, Higuchi and Horsmeyer- Peppas.

Zero order Kinetics

$Qt = Q_0 + K_0t$

Where,

K_0 = zero order release constant

Qt = the amount of drug dissolved in time t,

Q_0 = the initial amount of drug in the solution

First order Kinetics

$Log\ Qt = Log\ Q_0 + K_1t/2.303$

Where,

K_1= the first order release constant

Higuchi method

$Qt = K_Ht^{½}$

Where, Qt = the amount of drug release in time t

K_H = the Higuchi dissolution constant

Korsmeyer-Peppas model

$Mt/ M\alpha = k.tn$

Where, $Mt/M\alpha$ = the fraction of drug release

K= the release constant

t = the release time

n= diffusional exponent for the drug release [21].

3. RESULTS

1. FT-IR Compatibility Studies

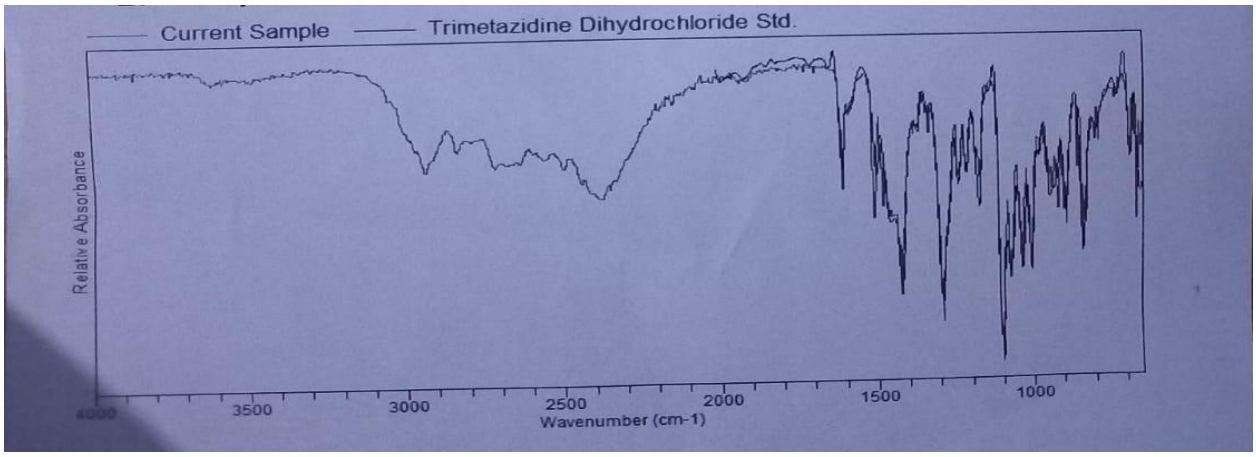

Fig 3: FTIR of pure drug

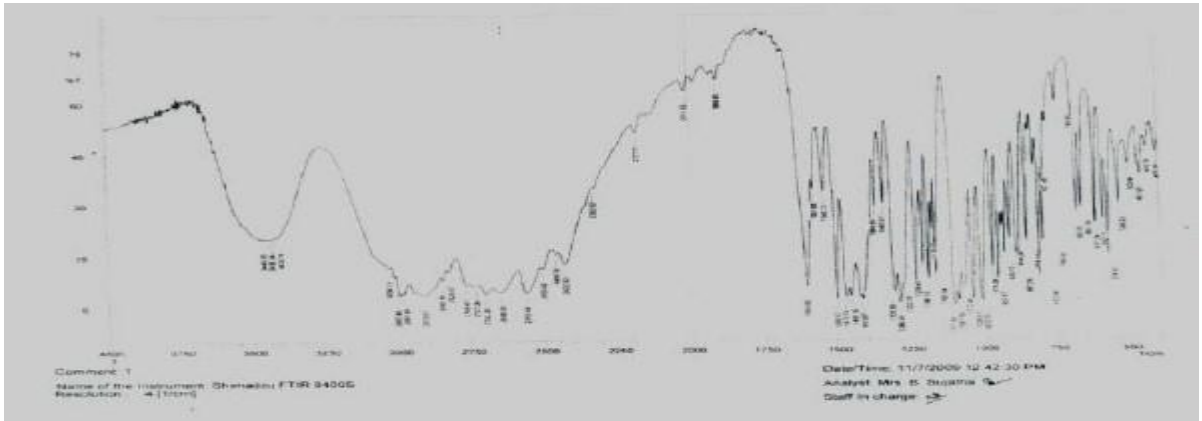

Fig 4: FTIR of compatibility studies of formulation

From the observation, it appears that there is no any characteristics peak in the FTIR spectra of drug and the polymers used. This suggests that there is no chemical interaction between the drug and the polymers. The presence of peaks within the expected range confirms that the authenticity of the materials used in the study, are genuine and do not exhibit any unexpected interactions.

2. Calibration Studies

Using phosphate buffer with a pH of 6.8, the trimetazidine dihydrochloride standard graph is built. It demonstrated a regression value of 0.9984, indicating that the linearity test was successful.

Table 5: Standard Graph of Trimetazidine Dehydrochloride

Concentration (µg/ml)	Absorbance at 274 nm
0	0.000
10	0.112
20	0.225
30	0.332
40	0.433
50	0.523

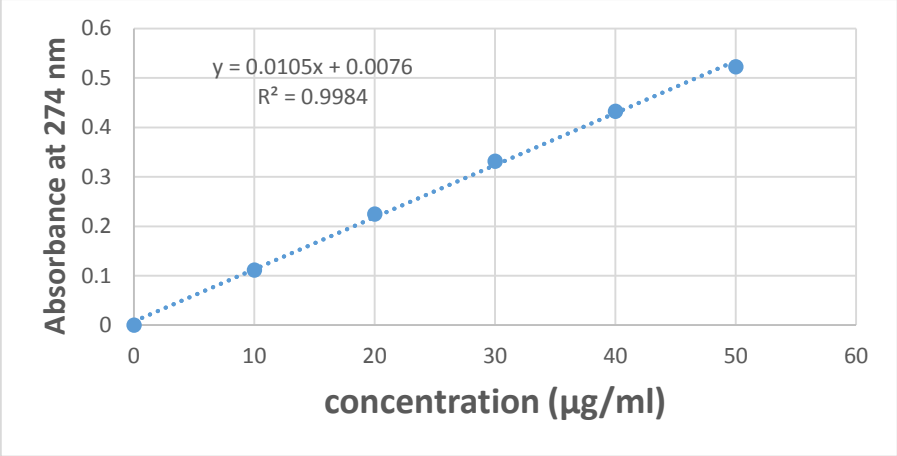

Figure 5: Standard Graph of trimetazidine Dehydrochloride

3. Evaluation parameters

The performed buccal tablet were evaluated and results are noted below:

1. Weight Variation

The weight of the prepared tablet ranges from 22 mg to 33 mg, depending on how it was produced. The outcomes were displayed in table 6.

2. Drug Content Uniformity

The performed buccal tablet of all batches consistently contain drug content ranging from 96.12±0.2% to 98.61±0.3% which indicates no drugloss during the preparation of buccal tablet**.** The result was shown in the table 6.

Table 6: Weight variation and drug content uniformity of formulated buccal tablet

Formulation	Weight Variation	Drug Content
F1	30±1.01	98.15±0.8
F2	33±0.57	97.21±0.3
F3	25±1.15	98.61±0.2
F4	31±0.45	96.12±0.9
F5	22±1.15	98.52±0.6
F6	28±2.09	97.14±0.9
F7	32±0.55	96.82±0.5

F8	29±1.21	97.31±0.8
F9	28±1.15	98.61±0.3

3. Tablet hardness

Monsanto hardness testers measured buccal medicament hardness. It was discovered that all formulations had hardness values ranging from 3.98±0.36 to 10.44±0.78 kg/cm^2. The result was shown in the table 7.

4. Tablet thickness

The tablet thickness of prepared tablet were observed and ranged from 0.226 to 0.996 mm and they are uniform. The result was shown in the table 7.

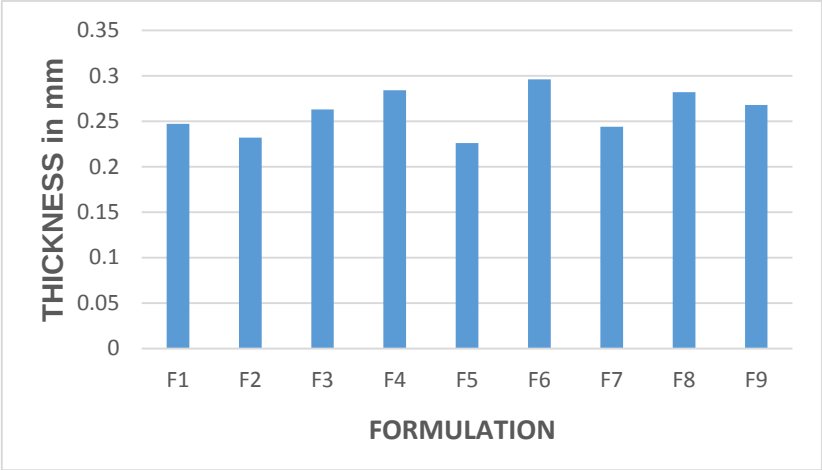

Figure 6: Thickness of buccal tablet

5. Friability

The tablet strength was tested by Roche Friabilator. The friability of all formulation were observed within the range of 0.13 to 0.78%. The values were given in table 7.

Table 7: Hardness, Thickness and Friability of formulated buccal tablet

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	0.247±0.02	6.47±0.28	0.48
F2	0.232±0.05	6.28±0.46	0.78
F3	0.263±0.03	10.44±0.78	0.38
F4	0.284±0.03	8.55±0.48	0.63
F5	0.226±0.02	5.88±0.38	0.13
F6	0.296±0.01	6.44±0.22	0.56
F7	0.244±0.03	4.85±0.45	0.35
F8	0.282±0.04	3.98±0.36	0.44
F9	0.268±0.05	6.75±0.27	0.52

6. Swelling studies

The swelling index is used to evaluate the behaviour of buccal tablets' swelling and moisture uptake. was calculated. The findings indicated that all of the pills had the appropriate swelling characteristics. It was discovered that when the concentration of carbopol 934 rises, so does the swelling index. Additionally, it grows via boosting mannitol concentration. The results were shown in table 8 and figure 7.

Table 8: Swelling index of Trimetazidine buccal tablet

Formulation	% Swelling index (n=3)
F1	35±1.51
F2	38±1.88

F3	40±2.44
F4	45±1.61
F5	50±1.21
F6	45±2.86
F7	37±1.76
F8	25±1.33
F9	30±1.86

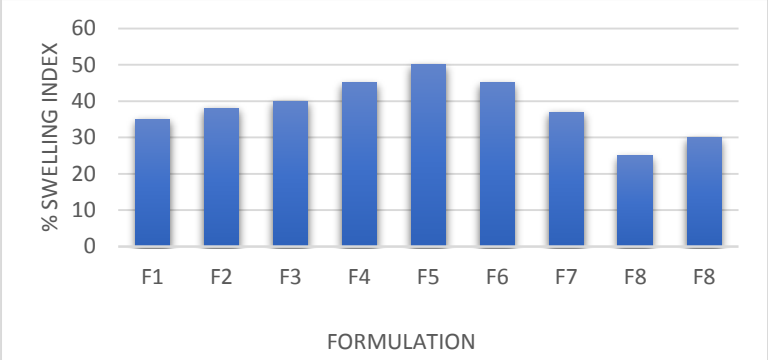

Figure 7: Swelling index of Trimetazidine buccal tablet

7. In-vitro drug release studies

Table 9: Cumulative percentage of drug release

Time (hours)	Cumulative percent drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	11.96	12.33	11.96	9.55	12.33	10.44	8.55	10.5	6.45
2	23.68	25.99	28.77	20.41	28.44	28.98	20.78	25.90	19.33
3	40.33	39.89	40.46	37.12	35.72	33.21	32.03	35.91	34.73
4	53.88	54.86	54.15	50.31	51.20	48.69	50.73	48.25	55.40
5	69.43	72.64	67.43	65.56	72.99	64.18	65.31	55.32	65.66
6	74.97	79.64	73.17	79.99	81.65	80.82	70.43	68.32	73.33
7	82.38	84.01	79.69	85.36	88.17	88.81	82.87	82.23	80.44
8	87.54	89.12	92.72	95.25	99.74	96.48	93.43	89.38	86.49

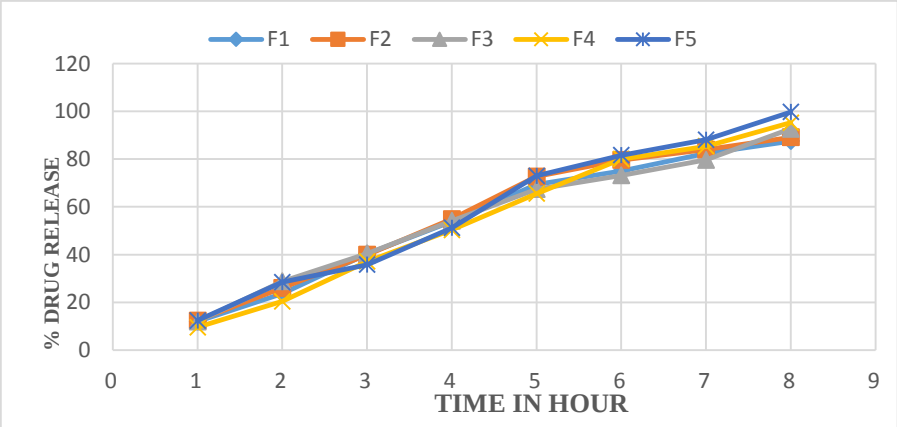

Figure 8: Dissolution profile of F1, F2, F3, F4 and F5

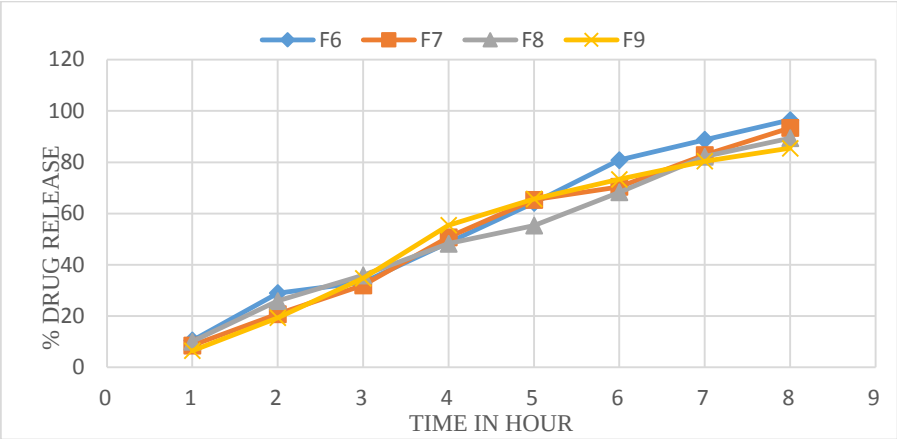

Figure 9: Dissolution Profile of F6, F7, F8 and F9

8 Release Kinetics

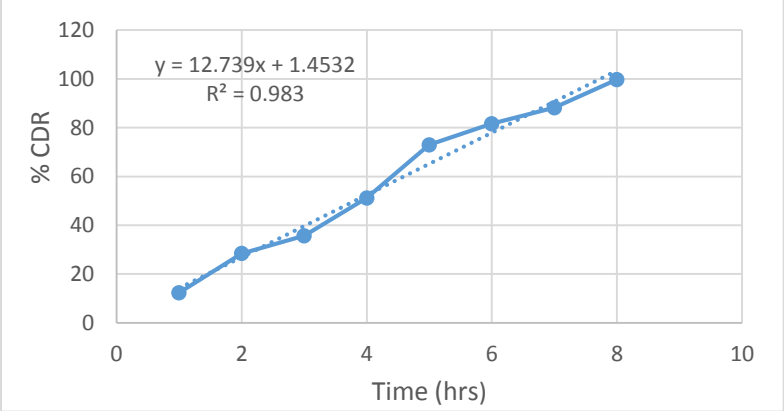

Figure 10: Zero order release kinetics

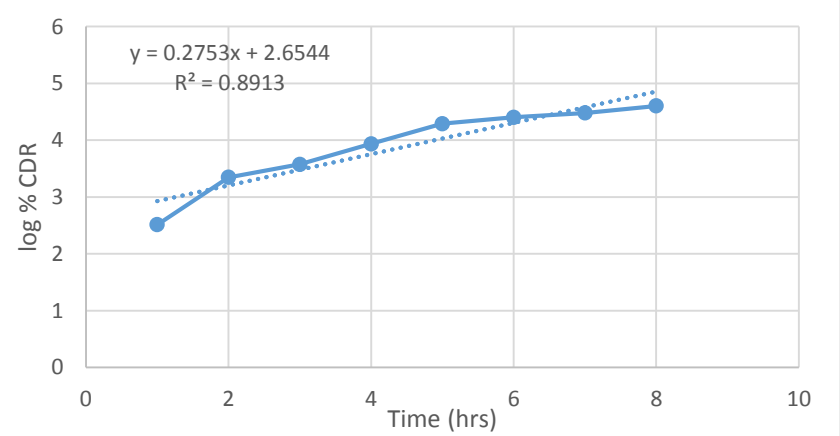

Figure 11: First order release kinetics

Optimization

The prepared tablets were optimized. The experiment was performed and responses were recorded in the table 10.

Table 10: Independent variables and corresponding dependent variables

Formulation	Factor 1	Factor 2	Response 1	Response 2	Response 3
	Carbopol 934	mannitol	50% drug release at time	Drug release at 8 h	Swelling index

F1	40	60	248	87.54	45
F2	40	90	250	89.12	50
F3	80	30	249	92.72	35
F4	120	90	240	95.25	50
F5	120	30	242	99.74	25
F6	120	60	237	96.48	30
F7	80	60	241	93.43	35
F8	80	90	236	89.38	30
F9	40	30	255	86.49	45

a. Time taken for 50% drug release

When Carbopol 934 concentration in a medication formulation rises, the time required for 50 % drug release is decreased. Similarly, increasing the concentration of mannitol, time for 50% drug release is also decreased, although lesser extent compared to Carbopol 934.

b. Drug release at 8 hour

When the concentration of Carbopol 934 increases in a drug formulation of trimetazidine buccal tablet, drug release at 8hour is increased as well as increasing the concentration of mannitol.

c. Swelling Studies

When it comes to mucoadhesive tablets, it has been observed that higher concentration of both polymers result in greater swelling index. Specifically, an increase in carbopol 934 concentration significantly enhances the swelling properties and extends the swelling index of the tablets.

4. DISCUSSION

The present work focused on formulation of trimetazidine buccal tablet through direct compression method. The formulation was developed using various excipients such as carbopol 934, mannitol, polyvinyl alcohol, polyvinyl pyrollidone, ethyl cellulose, and magnesium stearate. The results of the study demonstrated several important findings.

The compatibility between drug and polymers were confirmed through FT-IR studies, revealed no evidence of chemical interaction between the drug with a polymers, indicating their suitability for formulation. The calibration studies showed a high regression value(0.9984), indicate good linearity of the drug concentration and absorbance at 274nm. This suggests that the developed method for drug quantification is accurate and reliable.

The evaluation parameters of the buccal tablets, including weight variation, drug content uniformity, tablet hardness, thickness, and friability, were found to be within the acceptable range. These resullts indicate the successful formulation of buccal tablets with consistent physical characteristics.

The swelling studies demonstrated that the swelling index of the tablets increased with an increase in the concentration of Carbopol 934and mannitol. This suggests that these polymers play a significant role in enhancing moisture uptake and swelling behavior, which could contribute to better bioadhesion and drug release properties of the tablets.

In the in-vitro release studies, the cumulative drug release from the buccal tablets increased over time for all accumulations. The different formulations exhibited variations in the release profiles, indicating the influence of the polymer concentrations on the drug release kinetics. The kinetic release analysis using zero-order and first-order models further confirmed the controlled release pattern of the buccal tablets.

The optimization of the formulations based on the independent variables (Carbopol 934 and mannitol concentrations) and dependent variables(50% drug release time, drug release at 8hours, and swelling index) provided insights into the optimal formulation parameters. These findings can guide future research and development of buccal tablets for trimetazidine dihydrochloride.

5. CONCLUSION

This research project successfully developed and optimized and optimized buccal tablets of

trimetazidine dihydrochloride using bioadhesive polymers. The results indicate the suitability of the selected polymers, the achievement of desired physical characteristics, and the potential for controlled drug release. Further studies, including in-vivo evaluation, are warranted to assess the performance and drug bioavailability, improve patient compliance, and therapeutic efficacy of these buccal tablets.

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