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Formulation and Evaluation of Mucoadhesive Buccal Tablet of Antianginal Drug

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Keywords: Trimetazidine Hydrochloride, Hydroxypropyl methylcellulose, sodium CMC, wet granulation method, buccal tablet, mucoadhesion.

ABSTRACT

The main objective of the study is to develop and evaluate the mucoadhesive buccal tablets of antianginal drug, Trimetazidine hydrochloride by wet granulation method using various polymer to avoid the first-pass metabolism, to reduce dosing frequency and to improve patient compliance with improved bioavailability. In this study, 11 formulations were prepared by wet granulation method using different polymers at varying ratios. Polyvinyl Pyrrolidone K30 used as granulating agent and lactose as diluent. Two different grades of Hypromellose (hydrophilic polymer) such as HPMC K100M, HPMC E5LV and sodium CMC (mucoadhesive polymer) were used for the formulation of Trimetazidine hydrochloride buccal tablet. The prepared mucoadhesive buccal tablets were evaluated for physicochemical parameters such as hardness, thickness, friability, weight variation, surface pH and content uniformity studies. The prepared buccal tablets were also evaluated for mucoadhesive strength, *ex vivo* residence time, *in vitro* drug release and drug permeation through the porcine buccal mucosa. The drug excipients compatibility was evaluated by FTIR studies. *Ex vivo* mucoadhesive strength, *ex vivo* residence time and *in vitro* release studies showed that formulation F7 showed satisfactory bioadhesion (0.25 N) and exhibited optimum drug release (94.25 % after 6hrs). The swelling index of formulation F7 was found to be 100%. The in vitro release kinetics studies revealed that all formulation fits well with first-order kinetics followed by Korsmeyer-peppas model and the mechanism of drug release is Fickian diffusion. Based on results of *ex vivo* mucoadhesive strength, swelling index and drug release studies formulation F7 was selected as optimized formulation and subjected for stability study. It was confirmed from stability studies that the optimized formulation remained stable at 40˚c and 75% relative humidity.

INTRODUCTION

Drug delivery system refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect[1]. Drug delivery is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination products.

Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Drug release is from diffusion, degradation, swelling, and affinity-based mechanisms[2]. Most common routes of administration include the preferred non-invasive peroral (through the mouth), topical (skin), transmucosal (nasal, buccal/sublingual, vaginal, ocular and rectal) and inhalation routes[3].

Among the various routes of drug delivery, the oral route is the most suitable and most widely accepted one by the patients for the delivery of the therapeutically active drugs. But, after oral drug administration, many drugs are subjected to presystemic clearance in the liver, which often leads to a lack of correlation between membrane permeability, absorption, and bioavailability[4-5]. Within the oral route, the oral cavity is an attractive site for drug delivery due to ease of administration and avoids possible drug degradation in the gastrointestinal tract as well as first-pass hepatic metabolism[6].

Buccal drug delivery system in which drug is delivered via the buccal mucosa which is present in the oral cavity. Buccal route of drug delivery is a good alternative, amongst the various routes of drug delivery. The oral route is perhaps the most preferred for the patients. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. However, oral administration of drugs has disadvantages such as hepatic first-pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Buccal routes of drug delivery offer distinct advantages over oral administration for systemic drug delivery. These advantages include a possible bypass of the first pass effect, avoidance of pre-systemic elimination within the GI tract, these factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery. Considering the low patient compliance of rectal, vaginal, sublingual and nasal drug delivery for controlled release, the buccal mucosa has a rich blood supply and it is relatively permeable.

Trimetazidine hydrochloride is an antianginal drug used for the treatment of angina pectoris. Trimetazidine is described as the first cytoprotective anti-ischemic agent developed. It is an anti-ischemic (anti-anginal) metabolic agent, which improves myocardial glucose utilization through inhibition of fatty acid metabolism, also known as a fatty acid oxidation inhibitor.

The main objective of the study is to develop and evaluate the mucoadhesive buccal tablets of antianginal drug, trimetazidine hydrochloride by wet granulation method using various polymer to avoid the first-pass metabolism, to reduce dosing frequency and to improve patient compliance with improved bioavailability.

MATERIALS AND METHODS:

MATERIALS:

Trimetazidine hydrochloride and Hydroxy Propyl Methyl Cellulose K100M have purchased from yarrow pharma Mumbai, Hydroxy Propyl Methyl Cellulose E5LV was obtained from Loba chemic Pvt. Ltd, Mumbai. Sodium CMC was from Powder pack chem, Mumbai. All chemicals and solvents used were a commercially available product of analytical or pharmaceutical grade.

METHODS:

Compatibility studies[7] using FT-IR Spectroscopy

The pure drug, drug, and polymer were prepared and scanned from 4000-400 cm^{-1} in FTIR spectrophotometer. The FT-IR spectrum of the obtained sample of drug and polymer were compared with the standard functional group frequencies of Trimetazidine hydrochloride, HPMC E5LV, HPMC K100M and Sodium CMC. The compatibility between the drug, polymer was evaluated using FTIR peak matching method.

Preparation of Standard Calibration Curve of Trimetazidine hydrochloride

Determination of wavelength of maximum amplitude (D2 value) of Trimetazidine HCL.

2.5 ml of the above solution was diluted to 100 ml with the same solvent to get a concentration of 25 µg/ml. The UV spectrum of the final solution was scanned in the range of 200 – 400 nm against distilled water as a blank. The λmax was found at 269 nm.

Preparation of a standard calibration curve of Trimetazidine hydrochloride

Trimetazidine HCL (100.0 mg) was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in 50 ml of distilled water. The volume was makeup to 100 ml using distilled water to obtain a standard stock solution of drug concentration of 1000 µg/ml. From the standard stock solution 0.5, 1, 1.5, 2 and 2.5 ml was pipette out and diluted to 100 ml with distilled water to give the final concentration of 5, 10, 15, 20 and 25 µg/ml respectively. The absorbances of resultant solutions were measured at 269 nm by UV spectrophotometer against distilled water without the drug as blank. A graph of concentration vs. absorbance was plotted.

FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLET[8]

The granules were prepared by wet granulation method as per formula is given in the Table. The drug trimetazidine hydrochloride, a hydrophilic polymer (HPMC K100M, HPMC E5), and mucoadhesive polymer sodium carboxymethyl cellulose were passed through sieve 40# separately and blended thoroughly. After proper mixing slowly add the binding solution containing PVP K-30 in IPA (Isopropyl alcohol) till fine uniform granules were obtained. The wet mass is now passed through sieve 10# and dried at 50 °C for 30 minutes to get the moisture content less than one. Then lubricate the dried granules with magnesium stearate and talc was added, which were already passed through sieve 40 #. Then lubricated granules were compressed on cadmach tablet punch machine for all formulations with 8 mm diameter.

Table 1: Formulations of Trimetazidine Hydrochloride Buccal Tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Trimetazidine hydrochloride	20	20	20	20	20	20	20	20	20	20	20
HPMC E_5LV	72	48	24	--	--	--	24	24	48	24	24
HPMC K_{100}M	--	--	--	72	48	24	24	48	24	24	24
Sodium CMC	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8	38.4	43.2
PVP K_{30}	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2
Lactose	50.4	74.4	101.6	50.4	74.4	101.6	74.4	50.4	50.4	64.8	60
Magnesium stearate	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
Talc	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total(mg)	200	200	200	200	200	200	200	200	200	200	200

EVALUATION OF TRIMETAZIDINE HYDROCHLORIDE MUCOADHESIVE BUCCAL TABLETS

Precompression parameters:

1. Bulk density:

The bulk density of a powder is the ratio of the mass of the powder sample to its volume including the contribution of the interparticulate void volume. The bulk density is expressed in grams per milliliter (g/ml) although the international unit is kilogram per cubic meter (1 g/ml = 1000 kg/m^3) because the measurements are made using cylinders. It may also be expressed in grams per cubic centimeter (g/cm^3)[9].

Apparent bulk density (ρ_b) was determined by An accurately weighed quantity of granules was transferred to a 50ml measuring cylinder and the volume occupied by the powder in terms of ml was recorded[10]. Bulk Density Calculated According To the Formula

$$\rho_b = M/V_b$$

Where Vb Is the Bulk Volume and M is the weight of the powder.

2. Tapped density:

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample.

The measuring cylinder containing a known mass of blend was tapped for 100 times on a plane hard surface and volume occupied in ml was noted[11, 12].

The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated by using formula.

$$\rho_t = M/V_t$$

3. Angle of repose

The angle of repose[13] is defined as the maximum angle possible between the surface of the pile of the powder and horizontal plane.it is used to determine the flow property of the powdered or granular material. The angle of repose can range from 0° to 90°.

The angle of repose was determined by using the funnel method. A funnel is fixed and is secured with its tip at a height (h) of 2 cm above graph paper which is placed on a horizontal surface. The powder is dropped and the radius (r) is measured.

The inverse tangent of this ratio is the angle of repose. The angle of repose (Θ) was calculated using the formula.

$$\Theta = \tan^{-1}(h/r)$$

Table 2: Flow Property Based On Angle of Repose as Per IP

The angle of Repose (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

4. Compressibility Index (I) [10, 13]

The Carr index or Carr's Compressibility Index is an indication of the compressibility of granule or powder. In pharmaceutics, it is an indication of flowability of the powder.

The Carr index is calculated by the formula

$$C = 100[1-(\rho_b/\rho_t)]$$

Where ρ_b is the freely settled bulk density of the powder and ρ_t is the tapped density of the powder.

5. Hausner ratio (H_R) [14]

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula.

$$H_R = \rho_t/\rho_b$$

Where ρ_b is the freely settled bulk density of the powder and ρ_t is the tapped density of the powder.

Table 3: Flow Property Based On Hausner Ratio & Compressibility Index as Per IP

Hausner ratio	Flow property	% Compressability index
1.00-1.11	Excellent	<10
1.12-1.18	Good	11-15
1.19-1.25	Fair	16-20
1.26-1.34	Passable	21-25
1.35-1.45	Poor	26-31
1.56-1.59	Very poor	32-37
›1.60	Very, very poor	>38

Post-compression parameters

1. Physical appearance:

The shape of the tablet can be dimensionally described, monitored and controlled.

2. Organoleptic properties[15]:

It includes the color and odor of the prepared tablet.

3. Weight variation:

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

Table 4: Weight variation specification as per IP

The average weight of the tablet	%deviation
80mg or less	±10
More than 80mg but less than 250mg	±7.5
250mg or more	±5

4. Hardness test[16]:

The hardness of the tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage, transportation, and handling before usage depends on its hardness.

The Pfizer tester compresses tablet between a holding anvil and a piston connected to a force-reading gauge when its plier-like handles are gripped.

The force required to break the tablets is measured in kilograms and a crushing strength of 4kg is usually considered to be minimum for satisfactory tablets. Oral tablets normally have a hardness of 4-10 kg, however hypodermic and chewable tablets are usually much softer (3kg) and some sustained-release tablets are much harder 10-20 kg.

5. Thickness[12, 17]:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using the filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. 10 tablets were randomly picked from each batch and their thickness and diameter were measured using a calibrated dial Vernier caliper. It is expressed in mm.

6. Friability[12]:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets has determined by using Roche friabilator. It is expressed in percentage (%). Previously weighed 10 tablets were taken in Roche friabilator and the friability was checked at 25 rpm for 4 minutes or run up to 100 revolutions. Then the tablets were dusted and reweighed and the percentage of powder eroded during 4 minutes was recorded. The resulting tablets were weighed and the percentage loss was calculated using the formula

$$F = [(W_i - W_f)/W_i] 100$$

Where; F= friability,

W_i= initial weight,

W_f= final weight

7. Surface pH

The surface pH of the buccal tablet was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible[18].

For the determination of the surface pH of the buccal tablets, a combined glass electrode is used. The bioadhesive tablet was allowed to swell by keeping it in contact with 1 ml distilled water in a petri dish for 2 hr at room temperature. The pH was identified by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrating for1 min[19].

8. Swelling index Buccal tablets were weighed individually; initial weight was considered as W1 and placed separately in Petri dishes containing 10 mL of phosphate buffer (pH 6.8) solution. At time intervals of 1 h, 2h, 3h, 4h, 5h and 6h, the buccal tablets were removed from the Petri dishes using coverslips and excess surface water was removed carefully using the Whatman filter

Paper. The swollen tablets were then reweighed (W2). This experiment was performed in triplicate. The degree of swelling (water uptake) was calculated according to the Following formula[20]

Degree of swelling = [(W2 – W1)/W1] x 100

Swelling index increases with increasing polymer concentration and thereby retarding the release of drug from the mucoadhesive buccal tablet.

9. Bioadhesive strength

Tissue Isolation[21]

Porcine buccal tissue was obtained from a freshly killed pig weighing about 50 kg. After removal, the tissue was stored in pH 6.8 phosphate buffer at 4°C and used within 3 hours. The epithelium was separated from the underlying connective tissue with a surgical technique making sure that the basal membrane was still present and the membrane was allowed to equilibrate for one hour in receptor buffer to regain lost elasticity. Slice thickness range from 2.1 to 2.5 mm.

Procedure[21, 22]:

A modified physical balance was used for determining the bioadhesive strength. The left pan was removed. The buccal tablet was then stuck to glass stopper using an adhesive (Feviquick). To left arm of the balance, the glass stopper along with the tablet was hanged. A clean glass beaker was placed below hanging glass stopper. The balance was so adjusted that right-hand-side was exactly 5 g heavier than the left. The fresh porcine buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied with the mucosal side upwards using thread over the disc, the disc was used because it gave strength to the buccal mucosa and it was not floating during the adhesion. The disc was then lowered into the glass beaker (250 ml), which was then filled with 200 ml phosphate buffer pH 6.8 kept at 37±0.5°C to keep mucosal membrane moist. This was then kept below the left-hand setup of the balance. The tablet to be tested for bioadhesion was then stuck with a little moisture. The 5 g weight on the right pan was removed. This lowered the tablet over the mucosa, with a force of 5 g. The balance was kept in this position for 3 minutes, and then the weight was added slowly to the right-hand pan until the tablet detached from the mucosal

surface. The detachments force gave the bioadhesive strength of the buccal tablet in gram. From the bioadhesive strength, a force of adhesion and then the averages of three determinations were calculated[23].

$$\text{Force of adhesion (F)} = (W \times g)/1000$$

Where g is the acceleration due to gravity (9.80665 m/seconds^2)

Figure 1: Modified physical balance

10. Residence time

The *ex-vivo* residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 900 ml (pH 6.8) of phosphate buffer maintained at 37±1°C. The porcine buccal mucosa was tied to the surface of a glass slab, vertically attached to the disintegration apparatus[24]. The buccal tablet was hydrated using phosphate buffer (pH 6.8) and the hydrated surface was brought in contact with the mucosal membrane by keeping the backing membrane outside. The glass slide allowed moving up and down and hence that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete displacement of the tablet from the mucosal surface was noted. The experiments were performed in triplicate (n = 3) and mean values were used to calculate the residence time[25].

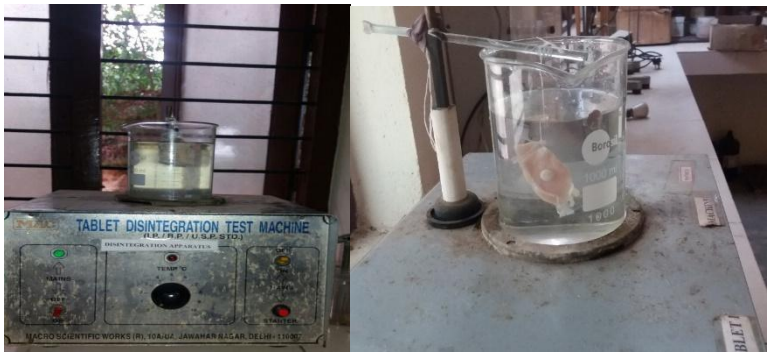

Figure 2: Modified disintegration apparatus

11. *Ex-vivo* permeation studies

Ex-vivo permeation study of Trimetazidine hydrochloride buccal tablet was carried out on a porcine buccal membrane using modified Franz diffusion cell with a diffusion area of 3.46 cm^2 and the acceptor compartment volume of 50 ml. A semi-permeable membrane (porcine buccal mucosa membrane) was clamped between the donor and acceptor compartments. The water in the acceptor compartment was continuously stirred at 100 rpm using a magnetic stirrer and maintained at 37±0.5 °C. The buccal tablet was placed in the donor compartment and was wetted with 1 ml of 6.8 phosphate buffer. The diffusion was carried out for 6 hrs. The amount of trimetazidine hydrochloride permeated through the membrane was determined by removing samples periodically and replaced with an equal volume of 6.8 phosphate buffer. These aliquots after filtration were diluted suitably and analyzed spectrophotometrically at 269 nm[26].

The experiments were performed in triplicate (n = 3) and mean values were used to calculate flux (J) and permeability coefficient (P).

$$J = (dQ/dt)/A$$

$$P = (dQ/dt)/\Delta CA$$

J is Flux ($mg.hrs^{-1}cm^{-2}$); P is permeability coefficient (cm/h); dQ/dt is the slope; ΔC, the concentration difference across the mucosa and A the area of diffusion (cm^2).

Figure 3: Franz diffusion cell

12. Content uniformity

10 tablets from each batch were randomly selected and weighed accurately and finely powdered. To a powder equivalent to 100 mg of Trimetazidine, HCl was added to 100 volumetric flasks, and volume was made up to the mark by adding distilled water. Mixed well and filtered. The absorbance of a resulting solution was measured at 269 nm. This test was conducted in triplicate. The concentration of the drug was calculated from the standard curve of trimetazidine hydrochloride. Percentage drug content was determined using the formula[27],

% drug content= (concentration of sample/concentration of standard) 100

13. *In vitro* dissolution studies

➢ **Procedure for dissolution [28] :**

The release rate of trimetazidine hydrochloride from mucoadhesive buccal tablets was determined using the United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of pH 6.8 phosphate buffer, at 37± 0.5 ^{0}C and 50 rpm. A sample (1ml) of the solution was withdrawn from the dissolution apparatus at 1, 2, 3, 4, 5 and 6 hrs. The samples were replaced with fresh dissolution medium of the same quantity. The absorbance of these solutions was measured at 269 nm using a Shimadzu UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Kinetics of In-vitro drug release[29]

The results obtained from *in-vitro* release studies were attempted to fit into various mathematical models as follows:

1) Cumulative percent drug released Vs. Time (Zero order kinetics)

2) Log cumulative percent drug retained Vs. Time (First order kinetics)

3) Cumulative percent released Vs. The square root of Time (Higuchi model)

4) Log cumulative percent drug released Vs. Log Time (Korsmeyer- Peppas model)

In this model, the value of 'n' characterizes the release mechanism of the drug as described in Table 5.

Table 5: Interpretation of diffusional release mechanism

Release exponent (n)	**Diffusion release mechanism**
<0.45	Quasi – Fickian diffusion
0.45	Fickian diffusion
0.45 <n<0.89	Anomalous(Non-Fickian) diffusion
0.89 - 1.0	Case II transport (Zero order release)
>1.0	Super case II transport

14. Stability studies[30]:

Stability testing plays a crucial role in the drug development process. The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of a variety environmental factors, such as temperature, humidity, and light to recommend shelf life for the drug product and recommended storage conditions. Stability studies were conducted according to ICH guidelines 40˚C ± 2˚C/ 75% ± 5% RH for 3 months to test the physical and chemical stability of the optimized formulations. Throughout the study, mucoadhesive buccal tablet formulation was stored in well-closed containers. The stored formulations were evaluated for physical appearance, hardness, drug content, residence time, mucoadhesive strength and *in vitro* drug release at a predetermined time interval.

RESULTS AND DISCUSSION:

Drug – Excipient Compatibility Study

FT-IR Spectroscopy of Trimetazidine Hydrochloride

The FT-IR spectrum of trimetazidine hydrochloride is shown in figure 4, which complies with standard functional group frequencies. The characteristic peaks due to pure Trimetazidine hydrochloride shows IR absorption at 1102.12 cm^{-1}(CH in-plane bend: 1225-950), 669.18 cm^{-1}(OCH_3 stretching: 900-660), 1416.46 cm^{-1}(C-N stretching: 1465-1405). All these characteristics peaks have appeared in pure drug (Figure 4) and drug-polymer combination (Figure 5). The IR spectrum indicates that there was no interaction between drug and studied excipients.

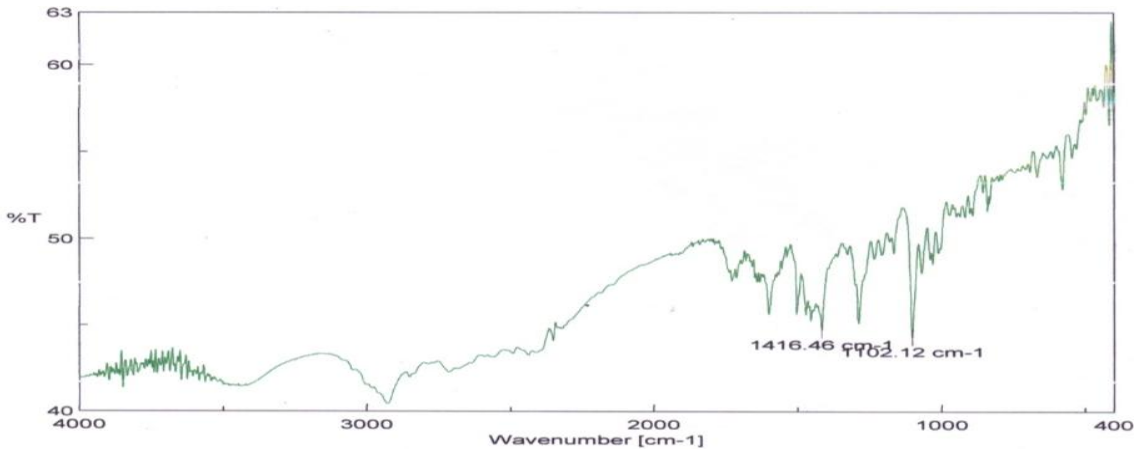

Figure 4: FT-IR spectrum of Trimetazidine hydrochloride

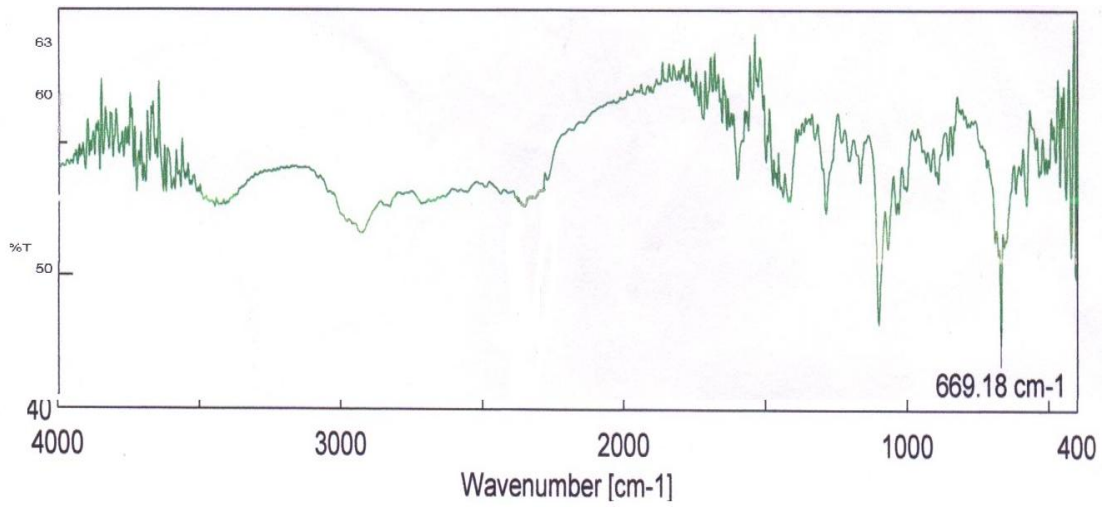

Figure 5: FT-IR spectrum of Trimetazidine hydrochloride+polymers

PREPARATION OF STANDARD CALIBRATION CURVE OF TRIMETAZIDINE HYDROCHLORIDE

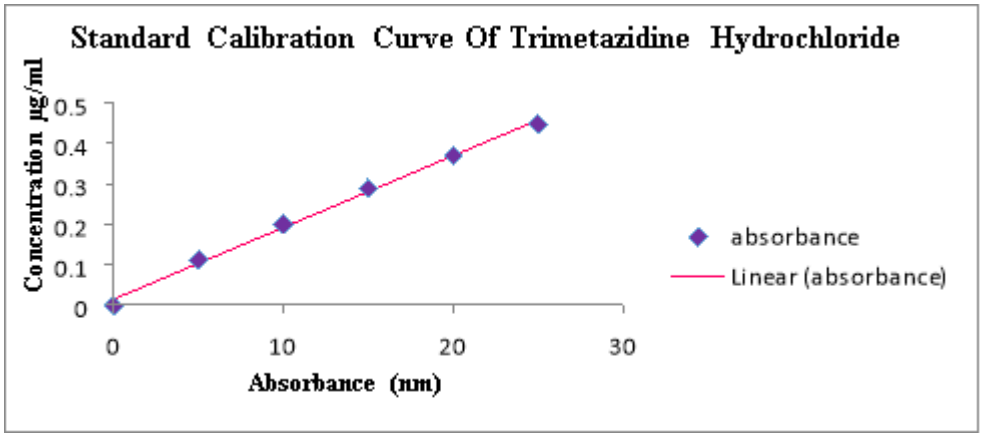

Figure 6: Standard calibration curve of trimetazidine hydrochloride

The UV spectrum of 25 µg/ml of stock solution was scanned in the range of 200 – 400 nm against distilled water as a blank. The λ max was found at 269 nm.

Figure 6 shows a standard calibration curve of Trimetazidine hydrochloride with slope, regression coefficient and intercept of 0.017, 0.996 and 0.015 respectively. The calibration curve was found to be linear in the range of 5-25 µg/ml at λ max 269 nm.

EVALUATION OF MUCOADHESIVE BUCCAL TABLETS

The granules were prepared by wet granulation method using various polymers such as a hydrophilic polymer (HPMC K100M, HPMC E5), and mucoadhesive polymer sodium carboxymethylcellulose. PVP K-30 in IPA (Isopropyl alcohol) used as a liquid binder.

Precompression parameters

Table 6: physical characteristic evaluation of granules (n=3)

Formulation code	Bulk density (g/cc) ± SEM	Tapped density (g/cc) ± SEM	Angle of repose (o) ± SEM	Compressability index (%)± SEM	Hausner ratio± SEM
F1	0.36 ± 0.005	0.40 ± 0.003	22.06 ± 0.003	9.11 ± 0.003	1.9 ± 0.003
F2	0.40 ± 0.003	0.44 ± 0.005	23.49 ± 0.015	9.95 ± 0.005	1.10 ± 0.005
F3	0.34 ± 0.003	0.44 ± 0.005	23.64 ± 0.008	22.7 ± 0.005	1.29 ± 0.005
F4	0.33 ± 0.003	0.38 ± 0.005	22.06 ± 0.005	12.30 ± 0.005	1.14 ± 0.005
F5	0.29 ± 0.005	0.36 ± 0.005	25.96 ± 0.005	18.61 ± 0.005	1.22 ± 0.008
F6	0.38 ± 0.005	0.42 ± 0.005	26.31 ± 0.031	9.17 ± 0.005	1.10 ± 0.005
F7	0.24 ± 0.003	0.26 ± 0.003	22.08 ± 0.005	7.90 ± 0.005	1.08 ± 0.005
F8	0.30 ± 0.003	0.33 ± 0.005	24.28 ± 0.005	6.96 ± 0.005	1.07 ± 0.005
F9	0.30 ± 0.003	0.34 ± 0.005	24.96 ± 0.018	9.97 ± 0.005	1.11 ± 0.005
F10	0.31 ± 0.003	0.34 ± 0.005	23.96 ± 0.005	9.01 ± 0.005	1.09 ± 0.005
F11	0.30 ± 0.003	0.34 ± 0.005	24.94 ± 0.008	12.46 ± 0.018	1.14 ± 0.005

Post-compression parameters

Physical appearance and organoleptic properties

All the prepared tablet were Round and standard convex in shape with white color.

Table 7: Physicochemical Evaluation of Trimetazidine Hydrochloride Buccal Tablet

Formulation code	Average Weight (mg) ± SEM	Average Hardness (kg/cm^2) ± SEM	Thickness (mm) ± SEM	Diameter (mm) ± SEM	Friability (%)± SEM	Content uniformity (%)± SEM	Surface pH± SEM
F1	199 ± 0.33	4.2 ± 0.05	3.1 ± 0.05	8.0 ± 0.03	0.45 ± 0.003	98.76 ± 0.02	7.14 ± 0.003
F2	203 ± 1.00	4.1 ± 0.03	4.0 ± 0.03	8.1 ± 0.03	0.48 ± 0.003	101.26 ± 0.02	7.20 ± 0.057
F3	200 ± 0.57	4.1 ± 0.03	4.1 ± 0.03	8.1 ± 0.03	0.47 ± 0.003	108.76 ± 0.01	7.17 ± 0.050
F4	201 ± 0.33	4.4 ± 0.05	3.6 ± 0.05	8.0 ± 0.03	0.48 ± 0.003	102.51 ± 0.02	6.45 ± 0.01
F5	202 ± 0.66	4.3 ± 0.03	2.8 ± 0.05	8.0 ± 0.03	0.48 ± 0.005	111.26 ± 0.03	6.63 ± 0.008
F6	206 ± 0.57	4.8 ± 0.03	3.6 ± 0.05	8.2 ± 0.06	0.48 ± 0.005	101.26 ± 0.01	6.81 ± 0.005
F7	197 ± 0.33	4.8 ± 0.03	3.5 ± 0.03	8.0 ± 0.00	0.47 ± 0.005	112.51 ± 0.02	6.95 ± 0.005
F8	199 ± 0.33	4.1 ± 0.03	3.6 ± 0.03	8.0 ± 0.05	0.96 ± 0.003	96.19 ± 0.03	6.55 ± 0.032
F9	198 ± 0.57	4.6 ± 0.03	3.2 ± 0.05	7.9 ± 0.05	0.94 ± 0.005	100.00 ± 0.04	6.60 ± 0.057
F10	200 ± 0.57	4.2 ± 0.03	3.2 ± 0.05	8.0 ± 0.03	0.48 ± 0.008	98.76 ± 0.01	6.85 ± 0.072
F11	198 ± 0.33	4.3 ± 0.03	3.2 ± 0.08	8.0 ± 0.03	0.51 ± 0.005	97.38 ± 0.02	6.50 ± 0.033

20 tablets were randomly selected from each formulation and evaluated. The values are almost uniform and were within the specifications. Thus all the formulations passed the test for weight variation. The values of hardness for tablets are ranged from 4.1 to 4.8 kg/cm^2 which indicates that the hardness of all the formulations was almost uniform and possess good mechanical strength with sufficient hardness. The thickness of tablets was determined using Vernier calipers. Tablet thickness is almost uniform in all the formulations and the values obtained are from 2.8 to 4.1 mm. Tablet diameter ranges from 7.9 to 8.2 mm. The friability values ranged from 0.45 to 0.96 %. All the values are below 1% indicating that the tablets of all formulations are having good friability property. The content uniformity of the prepared formulations was mentioned in 5.23 Table. The values ranged from 96.19 to 112.51%. The surface pH of the formulation depends on the nature of the polymer. Surface pH of the formulations was found to be 6.4-7.2 (near to neutral pH). It was suggesting that the neutral pH of the formulation does not cause any irritation and biocompatible to the buccal mucosa.

Swelling Index:

Table 8: Swelling Index of Formulations F1-F11

Formulation code	**% Swelling index**					
	1hr	**2hr**	**3hr**	**4hr**	**5hr**	**6hr**
F1	15	35	50	65	70	75
F2	25	30	45	50	55	65
F3	10	15	20	30	35	45
F4	20	25	45	50	80	85
F5	20	25	35	55	70	75
F6	10	20	30	40	50	55
F7	40	50	65	75	90	100
F8	60	80	90	95	100	115
F9	65	85	95	100	105	110
F10	80	95	105	115	120	125
F11	**75**	**85**	**95**	**100**	**110**	**135**

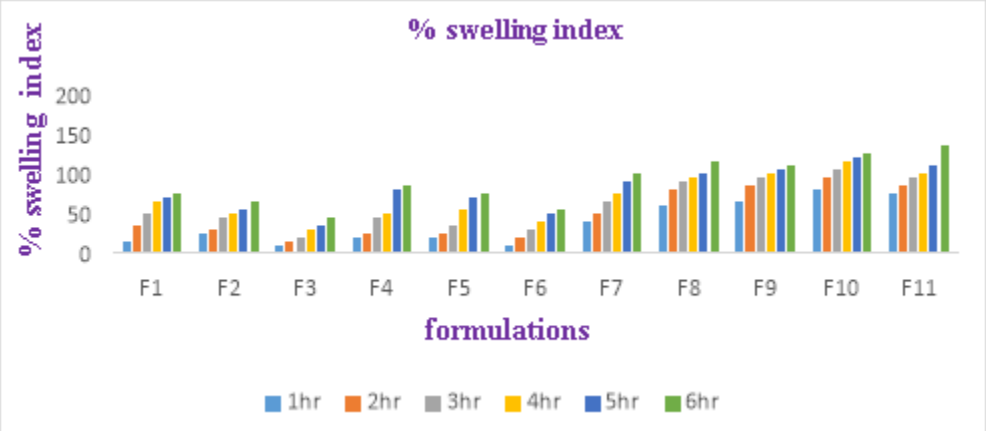

Figure 7: Swelling index of formulation F1-F11

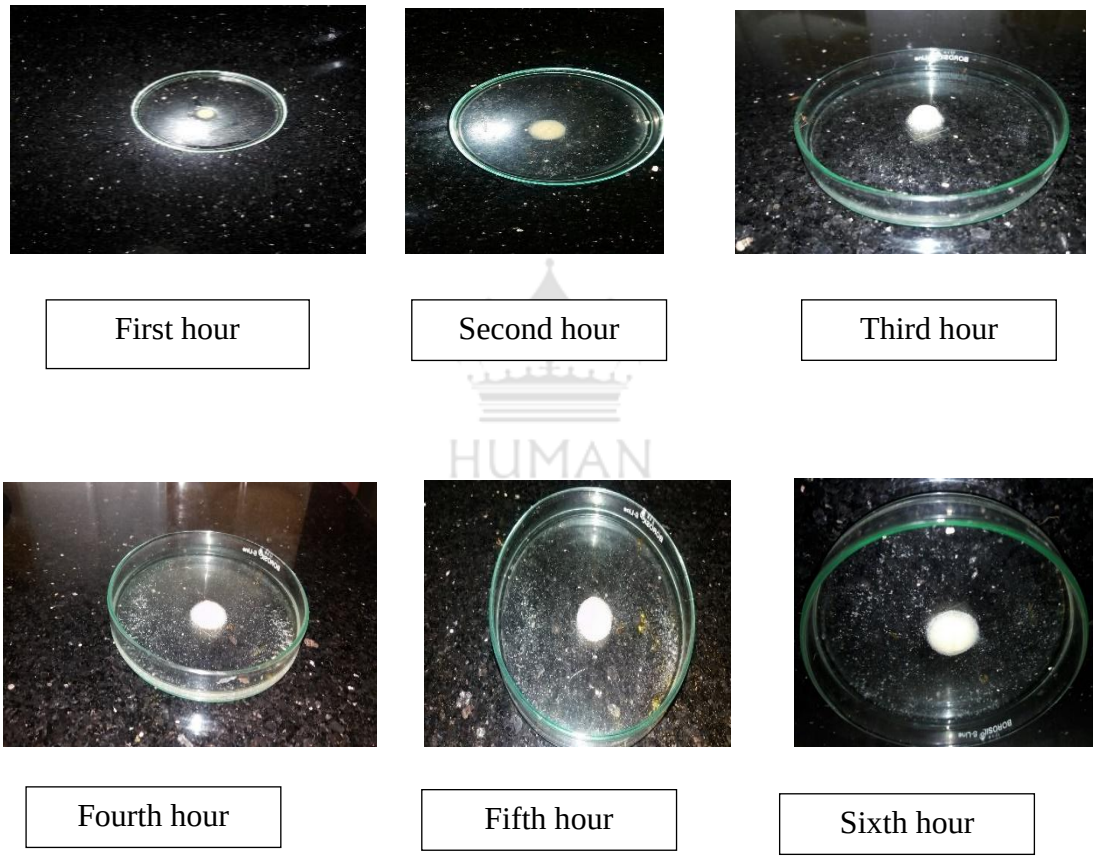

Figure 8: swelling index of prepared buccal tablet

The swelling properties of all the formulations were studied, and its results indicate that all the formulations possess good swelling indices. The maximum swelling was attained in 5 hrs after which polymers started eroding slowly in the swelling medium. The swelling index of formulations containing HPMC K100M and HPMC E5LV was increased with increasing the amount of that polymer respectively. A formulation containing sodium CMC have the more swelling index.

Ex-vivo Mucoadhesive Strength

The bioadhesive strength was influenced by the type and ratios of bioadhesive polymers. In all the formulations, as the polymer concentration increased, the mucoadhesive strength increased

Table 9: *Ex-vivo* Mucoadhesive Strength of Formulations F1-F11

Formulation code	Mucoadhesive strength (g) ± SEM	Force of adhesion (N) ± SEM
F1	24 ± 0.05	0.235 ± 0.005
F2	20 ± 0.05	0.196 ± 0.05
F3	19 ± 0.05	0.186 ± 0.05
F4	25 ± 0.05	0.245 ± 0.05
F5	24 ± 0.05	0.235 ± 0.05
F6	22 ± 0.04	0.215 ± 0.04
F7	26 ± 0.05	0.255 ± 0.05
F8	29 ± 0.05	0.284 ± 0.05
F9	27 ± 0.05	0.264 ± 0.05
F10	30 ± 0.05	0.294 ± 0.05
F11	32 ± 0.05	0.313 ± 0.05

Ex-vivo Residence Time

Table 10: *Ex-vivo* residence time of formulations F1-F11

Formulation code	Residence time (hour) ± SEM
F1	6.30 ± 0.01
F2	5.52 ± 0.01
F3	5.20 ± 0.03
F4	6.48 ± 0.01
F5	6.26 ± 0.02
F6	6.15 ± 0.04
F7	7.10 ± 0.01
F8	7.55 ± 0.02
F9	7.35 ± 0.03
F10	> 8 h ± 0.02
F11	> 8 h ± 0.03

The *Ex-vivo* residence time was determined by using a specially designed apparatus (modified physical balance). As the concentration of mucoadhesive material increased, the retention time increased. This test reflects the adhesive capacity of polymers used in formulations. The results revealed that sodium CMC containing formulations showed better bioadhesion than other formulations and F7 shows lower retention time compared to formulation contains combination of polymers.

***In vitro* dissolution studies:** *In vitro* dissolution studies of all formulations were carried out in dissolution test apparatus using phosphate buffer pH 6.8 as the dissolution medium for 6 hours. Percentage cumulative drug release at each time interval as shown in the table and the data represented graphically.

Table 11: Percentage cumulative drug release data for Formulations F1-F11

Time in hours	% Cumulative Drug Release										
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
0	0	0	0	0	0	0	0	0	0	0	0
1	24.77	37.84	40.54	21.23	33.30	37.39	47.89	42.01	45.90	39.19	34.23
2	39.64	41.89	50.21	34.59	40.54	48.20	54.51	50.32	53.07	45.92	45.50
3	41.89	46.40	63.07	39.48	59.16	58.34	68.67	61.80	64.12	54.41	48.65
4	45.95	59.91	69.15	42.25	64.42	60.81	76.28	70.17	73.82	62.16	56.76
5	49.36	65.32	72.08	67.53	70.58	81.09	88.74	83.26	85.89	68.02	59.81
6	57.21	75.68	89.19	75.23	81.94	88.29	94.25	90.04	92.10	69.37	64.42

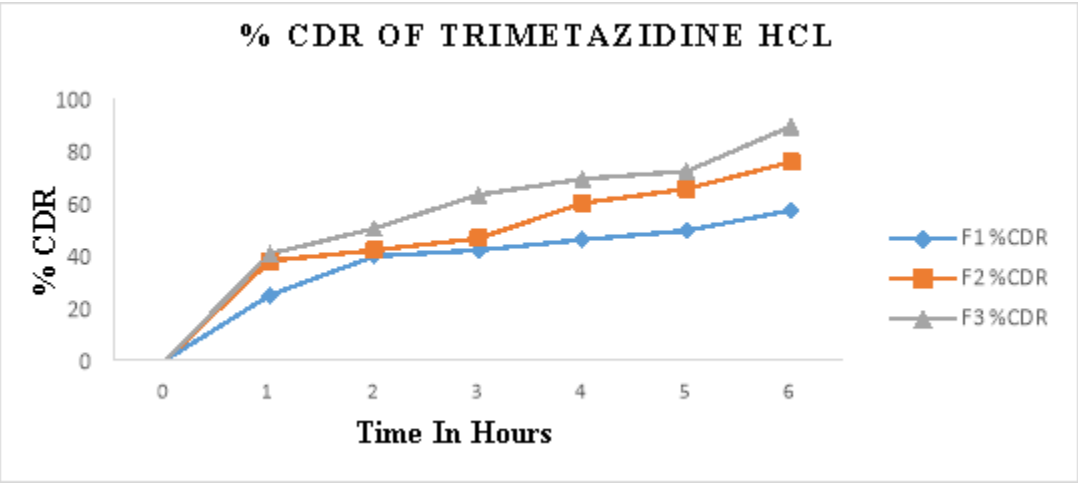

Figure 9: Percentage cumulative drug release profile of Formulations F1-F3

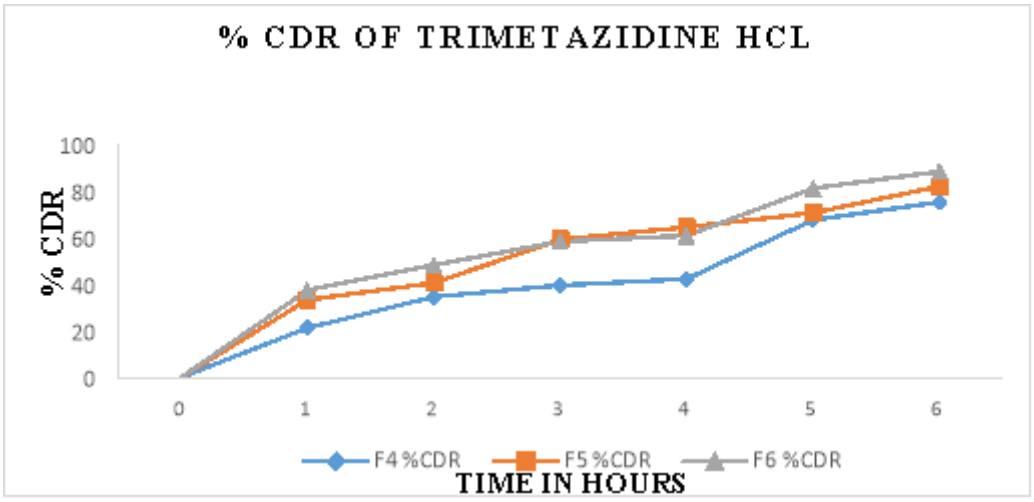

Figure 10: Percentage cumulative drug release profile of Formulations F4-F6

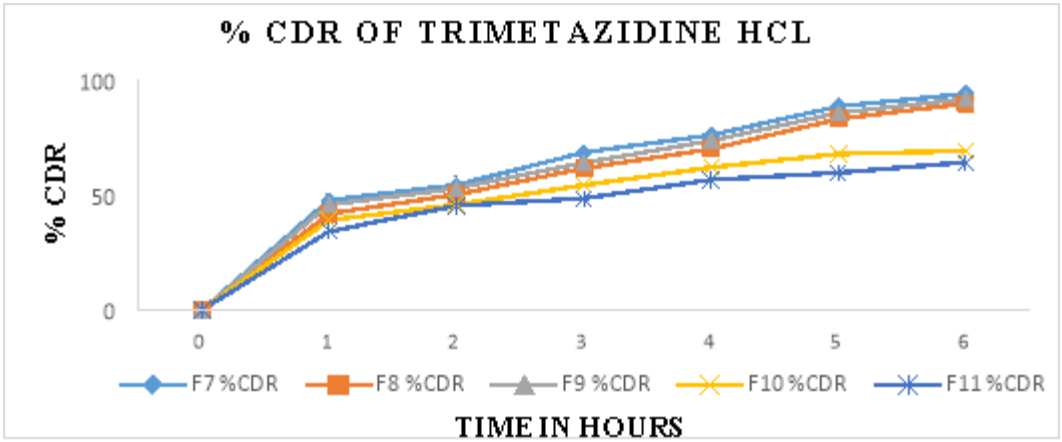

Figure 11: Percentage cumulative drug release profile of Formulations F7-F11

Kinetics of *In vitro* drug release

The results obtained from *in vitro* release studies were attempted to fit into various mathematical models.

Table 12: Kinetic study of formulations F1-F11

Formulation code	Release Kinetics				
	Zero-order R^2	First order R^2	Higuchi R^2	Peppas	
				R^2	N
F1	0.841	0.913	0.948	0.949	0.422
F2	0.882	0.952	0.973	0.893	0.389
F3	0.875	0.916	0.983	0.967	0.415
F4	0.916	0.951	0.918	0.928	0.672
F5	0.919	0.975	0.989	0.967	0.512
F6	0.914	0.936	0.979	0.949	0.476
F7	0.899	0.961	0.995	0.988	0.454
F8	0.873	0.959	0.989	0.960	0.396
F9	0.882	0.963	0.989	0.960	0.403
F10	0.815	0.930	0.975	0.981	0.341
F11	0.809	0.914	0.974	0.988	0.345

The *in-vitro* drug release data was subjected to the goodness of fit by linear regression analysis, according to zero order, first-order kinetic equation, Higuchi and Korsmeyer models to ascertain the mechanism of drug release. The result of linear regression analysis of data including the regression coefficient is summarized in table 12. When the regression coefficient 'R^2' values of zero order and first order plots were compared, it was observed that the 'R^2' values of first order was higher than that of zero order plots which indicate that the drug release from the formulations is more likely to follow first-order kinetics as the 'R^2' values of first-order kinetics was found to be close to unity.

Based on the values of the regression coefficient, it was concluded that the formulation F7 strictly follows first-order kinetics compared to other formulations.

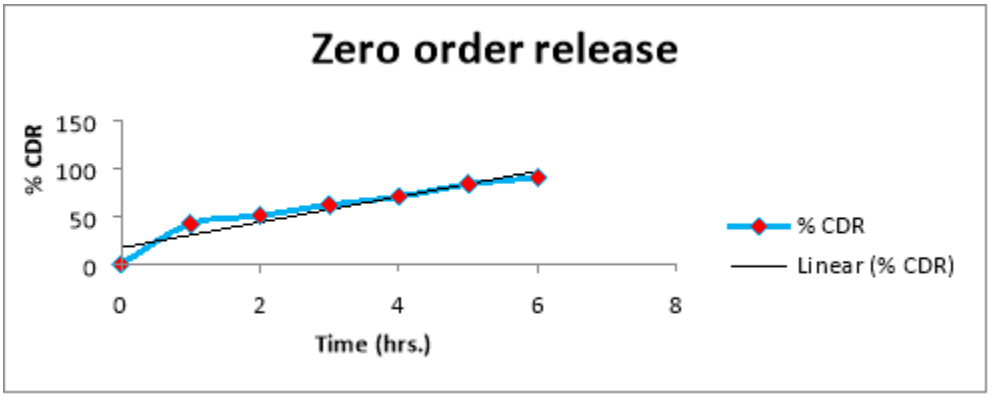

Figure 12: Zero order plot of F7

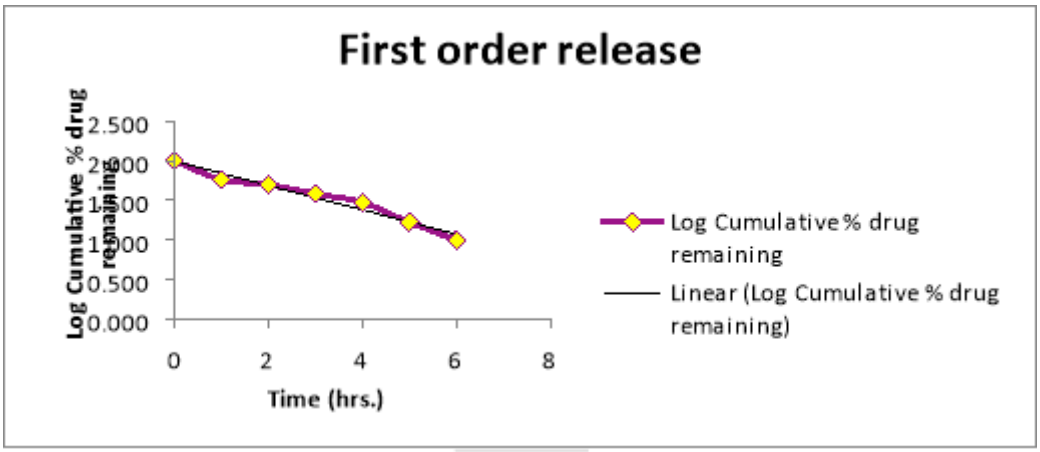

Figure 13: First order plot of F7

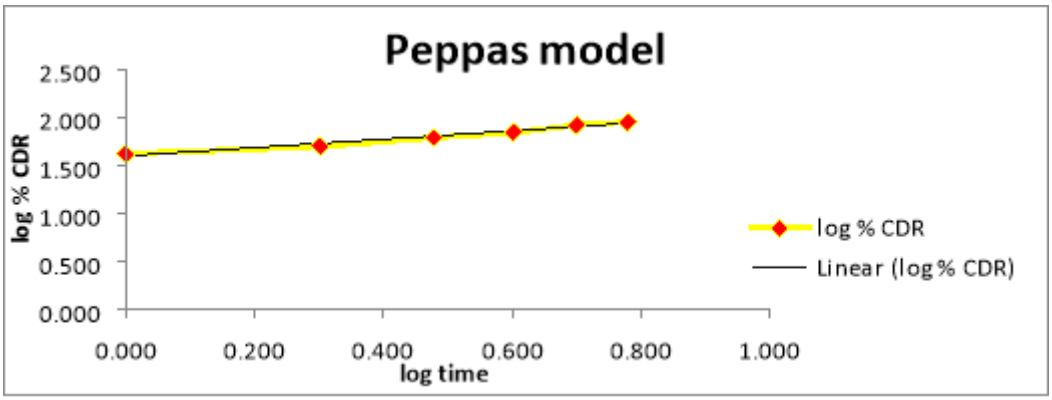

Figure 14: Peppas plot of F7

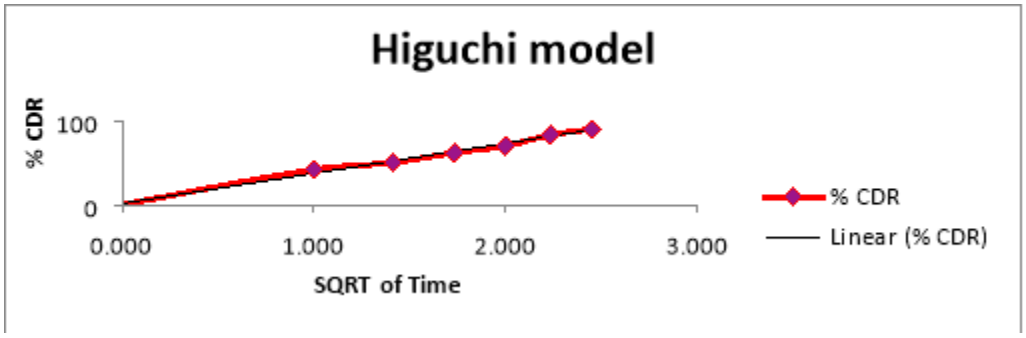

Figure 15: Higuchi plot of F7

***Ex -vivo* permeation study**

Table 13: *Ex-vivo* permeation study of formulation F7

Time in hours	%CDR
1	43.24
2	59.74
3	63.54
4	73.42
5	86.75
6	93.68

From the results, it was found that optimized formulation shows good permeability. This may be due to the adsorption and fusion of drug molecules onto the surface, resulting in the high thermodynamic activity gradient of the drug at the interface, which is the driving force for drug permeation.

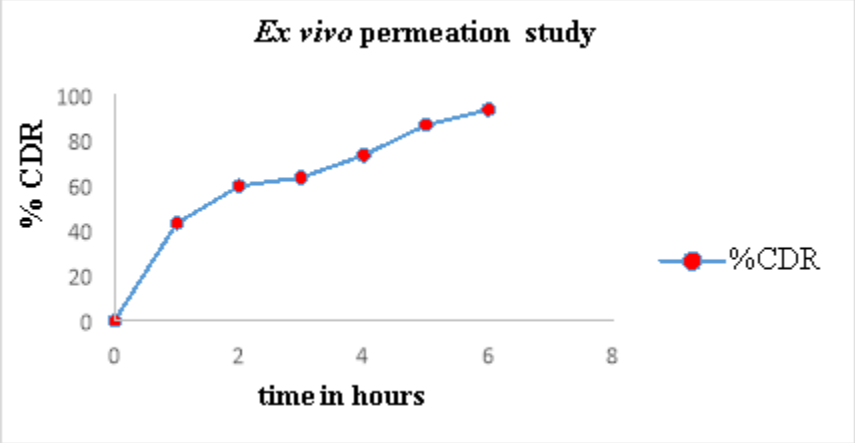

Figure 16: *Ex-vivo* permeation study of formulation F7

Stability studies

Stability studies were carried out on formulation F7 for a period of 3 months and comparison of the parameters before and after stability studies was represented in table 14.

Table14: Comparison of parameters before and after stability

Parameters	Before stability studies	After stability studies
Physical changes	White, Round, standard convex	No changes
%drug content	112.51 ± 0.02	110.83 ± 0.01
Residence time	7 hour 10 min ± 0.01	7 hour 8 min ± 0.02
Mucoadhesive strength	26 ± 0.05	25 ± 0.05
% CDR	93.25	92.94

The stability of the optimized formulation was known by performing stability studies for 3 months at accelerated conditions of 40 ^{0}C ± 75 % RH. The formulation was found to be stable with no physical changes and shows a slight decrease in residence time and mucoadhesive strength also shows a slight decrease in drug content and *in-vitro* drug release pattern after the stability period. From the stability studies, it was confirmed that the formulation remains stable at accelerated stability conditions.

CONCLUSION

In this study, 11 formulations were prepared by wet granulation method using different polymers at varying ratios. Polyvinyl Pyrrolidone K30 used as granulating agent and lactose as diluent. Two different grades of Hypromellose (hydrophilic polymer) such as HPMC K100M, HPMC E5LV and sodium CMC (mucoadhesive polymer) were used for the formulation of Trimetazidine hydrochloride buccal tablet.

The compatibility of the drug in the formulation was performed by FTIR spectroscopy.FTIR spectroscopy studies indicated that there were no drug-excipient interactions. Each batch of the formulations was subjected to Precompression and post-compression evaluation techniques and stability study of the optimized formulation. The prepared tablets were in the acceptable range of weight variation, hardness, thickness, friability, drug content as per pharmacopoeial specifications. Surface pH of the formulations was found to be 6.4-7.2 (near to neutral pH). It was suggesting that the neutral pH of the formulation does not cause any irritation and biocompatible to the buccal mucosa.

The swelling properties of all the formulations were studied, and its results indicate that all the formulations possess good swelling indices. The maximum swelling was attained in 6 hrs after which polymers started eroding slowly in the swelling medium. The swelling index of formulations containing HPMC K100Mand HPMC E5LV was increased with increasing the amount of that polymer respectively. A formulation containing sodium CMC have the more swelling index i.e. 135%.

Based on the evaluation data, the present study concluded that the formulation F7 containing equal amounts of HPMC K100M and HPMC E5LV was found to be optimized one because it has exhibits desired bioadhesive property according to its minimum detachment force about 0.25 N and minimum stretching at the detachment point and F7 shows lower retention time about 7 hours 10 minute compared to formulation contains combination of polymers. From the results of *ex vivo* permeability studies it was found that optimized formulation shows high permeability about 93.68 % at 6 hours.

The % drug content values ranged from 96.19 to 112.51%. From the results of *ex vivo* permeability studies, it was found that optimized formulation shows high permeability, i.e. 93.68 % at 6 hours.

Based on the values of regression coefficient and n value from Peppas model, it was concluded that the formulation F7 strictly follows first order kinetics with Fickian release.

The stability of the optimized formulation was known by performing stability studies for 3 months at accelerated conditions of 40^0C ± 75 % RH. The formulation was found to be stable with no physical changes and shows the slight decrease in residence time and mucoadhesive strength time and also shows the slight decrease in drug content and *in vitro* drug release pattern after the stability period. From the stability studies, it was confirmed that the formulation remains stable at accelerated stability conditions.

Thus the study revealed that the Trimetazidine hydrochloride buccal tablets showed good mucoadhesion time with the optimum release of drug for more than 6 hours. The optimized formulation also showed satisfactory surface pH and physical parameters, effective *in vitro* permeation, satisfactory stability and comfortability in the oral cavity. From the results of the present investigation, it can be concluded that Trimetazidine hydrochloride can certainly be administered through the oral mucosa and by providing faster release and better patient compliance.

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REFERENCES:

1. M. N. V. Ravi Kumar, Handbook of Particulate Drug Delivery (2-Volume Set), American Scientific Publishers 2008.
2. Wang, NX. Von Recum, HA, Affinity-Based Drug Delivery- MacromolBiosci. 2011; 321–332.
3. Bertrand N, Leroux JC, The journey of drug carrier in the body. The. Journal of Controlled Release. 161 (2): 152–163.
4. Prasad B Kadam, Remeth J Dias, Kailas K Mali1, Vijay D Havaldar1 and Niranjan S Mahajan. Formulation and evaluation of buccoadhesive tablets of Atenolol. J Pharm Res. 2008; 1(2): 193-199.
5. Noha Adel Nafee, Fatma Ahmed Ismail, Nabila A Boraie. Mucoadhesive Delivery Systems. I. Evaluation o f Mucoadhesive Polymers for Buccal Tablet Formulation. Drug Dev Ind Pharm. 2004; 30 (9): 985- 993.
6. M.S.El- Samaligy, N.N. Afifi, E.A. Mahmoud. Increasing bioavailability of silymarin using a buccal liposo mal delivery system: preparation and experimental design investigation.international journal of pharmaceutics. 2006; 308:140-148.
7. H. Kaur; instrumental methods of chemical analysis, eleventh edition; 199-238.
8. Burak Celik, Optimization of piribedil mucoadhesive tablets for efficient therapy of Parkinson's disease: physical characterization and *ex vivo* drug permeation through the buccal mucosa. Journal Of Drug Development and Industrial Pharmacy, 2017 ;(11), 3355-3365.
9. World Health Organization; Bulk density and tapped density of powder; Final Text for addition to the IP; Mar 2012; 1-6.
10. Rakhi B Shah, Mobin A Tawakkul, Mansoor A Khan; Comparative Evaluation of Pharmaceutical powders and granules; Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2976911
11. Amira, Mucoadhesive buccal tablets containing silymarin Eudragit-loaded nanoparticles: formulation, characterization and ex vivo permeation, 2017, 34(5):463-474.
12. Lachman L, Lieberman H, Kanig J. The theory and practice of industrial pharmacy. Varghese publication house. 3rd edition, 2009, 297-303.
13. S. Z. Chemate *et al*, Formulation and Evaluation of Losartan Potassium Bi-Layer Buccal Tablet Using Mucoadhesive Polymer, SJR (2017)
14. Hausner ratio- Wikipedia; Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2976911/
15. Sana Hanif et al, Computer Aided Formulation, and Characterization of Propranolol HCl Buccal Tablet Using Polymeric Blend the Open Conference Proceedings Journal, 2017, 8, 1-13.
16. The Anonymous, Hardness or Crushing strength, Pharmainfo.net. 2008.
17. Majid Saeedi *et al*, Evaluation of carbomer, CMC and HPMC on dissolution and bio adhesion of buccoadhesive Cinnamaldehyde tablets, 2018; 27(157):70-82 ·
18. Swati Mittal and Shalaka Pawar, design and evaluation of buccal mucoadhesive tablets of pantoprazole sodium, ejpmr, 2018; 5(02), 514-522.
19. C.c.patil, formulation, and evaluation of mucoadhesive buccal tablets of ondansetron hydrochloride, 2018; 2(11), 581-586.
20. Hiral koradia *et al*,formulation and evaluation of mirtazapine, 2018;1(4),155-157
21. Brunella Cappello, Giuseppe De Rosa, LuciaGiannini, Maria Immacolata La Rotonda,
22. Kashappa Goud H. Desai and T.M. Pramod Kumar, Preparation and Evaluation of a Novel Buccal Adhesive System, AAPS Pharm Sci Tech.,2004;5(3): 1-9.
23. Han-Gon Choi, Chong-Kook Kim, Development of omeprazole buccal adhesive tablets human saliva; J. Control. Rel., 2000; 68: 397– 404.

24. Gazzi S, Kumar CK, Gonugunta CSR, Kumar BV, Veerareddy PR. Formulation and evaluation of Bioadhesive buccal drug delivery of tizanidine hydrochloride tablets. AAPS Pharm Sci Tech. 2009; 10(2): 530-9.
25. Singh B and Ahuja, N, Development of controlled released buccoadhesive hydrophilic matrices of Diltiazem hydrochloride: Optimization of bioadhesion, dissolution and diffusion parameters, Drug Dev. Ind. Pharm., 2002; 28 (4): 431-442.
26. Nakhat PD, Kondawar AA, Babla IB, Rathi LG, and Yeole PG. Studies on buccoadhesive tablets of terbutaline sulfate, Ind. J. Pharm. Sci., 2007; 505.
27. Ankarao A, Rao CB, Devanna K. Formulation and evaluation of buccoadhesive bilayered tablets of carvedilol. Int. J. Adv. Pharm. Sci. 2010; 1(1): 71-6.
28. Rajkumar M, Kiran JP, Vidya Sager CH, Venkateswara Reddy B, *et al*. "Formulation and evaluation of controlled release matrix tablets of Trimetazidine dihydrochloride", J.Chem. Pharm. Res., 2012, 2 (3), 746-753.
29. Abdul Malik *et al*, freeze-dried buccal tablet of naloxone 2017; 67(3): 217-223.
30. Kim Huynh-Ba. Chapter 1-Introduction. Handbook of stability testing in Pharmaceutical development. 1st edition, 2011: 1-2.