IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
July 2016 Vol.:6, Issue:4

Formulation Development and Characterisation of Buccal Tablets of Irbesartan

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Ramyasree andol* , V.T.Iswariya , K. Sujitha

Department of Pharmaceutics , Omega College of Pharmacy, Hyderabad, India.

Submission: 10 July 2016
Accepted: 15 July 2016
Published: 25 July 2016

Keywords: Buccal Tablets, Mucoadhesive Polymers, Irbesartan, Formulation

ABSTRACT

The present study involved to formulate and evaluate buccal tablets of Irbesartan an anti-hypertensive drug that has low solubility, so buccal route is excellent for the systemic delivery, thereby rendering great bioavailability, by using different mucoadhesive polymers such as Carbopol 934, Sodium alginate and HPMC K4M in combination. The formulated buccal tablets were tested for surface pH, *in-vitro* drug release and moisture absorption. The prepared tablets also evaluated for mucoadhesive strength and drug permeation through porcine buccal mucosa. *In-vitro* bioadhesive strength and *in-vitro* release studies showed that formulation F8 containing 1:0.25 ratio combination of (Carbopol 934+ HPMC K4M) drug and polymer combination showed satisfactory bioadhesive and exhibited optimum drug release.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. It is also possible to administer drugs to patients who cannot be dosed orally via this route. Successful buccal drug delivery using buccal adhesive system requires at least three of the following

(a) A bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa.

(b) A vehicle to release the drug at an appropriate rate under the conditions prevailing in the mouth and

(c) Strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery stem promotes the residence time and act as controlled release dosage forms.

However, therapeutic potential of these compounds lies in our ability to design and achieve effective and stable delivery systems. Based on our current understanding, it can be said that many drugs cannot be delivered effectively through the conventional oral route.

The main reasons for the poor bioavailability of many drugs through conventional oral route are:

- Pre-systemic clearance of drugs.
- The sensitivity of drugs to the gastric acidic environment which leads to gastric irritation.
- Limitations associated with gastrointestinal tract like variable absorption characteristics.

Buccal mucosa composed of several layers of different cells. The Epithelium is similar to stratified squamous epithelia found in rest of the at least one of which is biological nature are held together by means of interfacial forces.[1]

Buccal drug delivery is a type of bioadhesive drug delivery especially it is a mucoadhesive drug delivery system is adhered to buccal mucosa.

Mucoadhesive drug delivery systems:

These may be defined as drug delivery systems which utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration.

The mucosal layer lines a number of regions of the body including gastrointestinal tract, urogenital tract, airway, ear, nose and eye. Hence mucoadhesive drug delivery system includes the following.

1. Buccal delivery system

2. Oral delivery system

3. Ocular delivery system

4. Vaginal delivery system

5. Rectal delivery system

6. Nasal delivery system

Buccal mucoadhesive drug delivery system:

These are the drug delivery system in which drug is delivered via the buccal mucosa which is present in oral cavity. Drug delivery via the membranes of the oral cavity can be subdivided as follows.

- Sublingual delivery, which is administration of the drug via the sublingual mucosa to the systemic circulation.

- Buccal delivery, which is administration of the drug via buccal mucosa (the linking of the cheek) to the systemic circulation.

- Local delivery for the treatment of conditions of the oral cavity, principally aphthous ulcers, fungal infections.

Types of buccal mucoadhesive dosage forms:[2]

Buccal mucoadhesive dosage forms can be categorized into 3 types based on their geometry.

 Type I is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss, due to swallowing.

 In type II devices, an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer, creating a double layered device and preventing drug loss from the top surface of the dosage form into the oral cavity.

 Type III is a unidirectional release device, from which drug loss in minimal since the drug is released only from the side adjacent to the buccal mucosa

Mainly the following types of buccal dosage forms are available in the market.

i. Buccal tablets

ii. Buccal patches

iii. Buccal films

iv. Buccal gels

v. Buccal ointments

Advantages of drug delivery through buccal mucosa:[3-5]

 The buccal mucosa is easily accessible, so dosage forms can be easily administered and even removed from the site of application

 It is a passive system and does not require activation.

 It can be easily removed in case of emergency.

 Therapeutic serum concentration can be achieved rapidly.

 For the patients suffering from nausea or vomiting and in state of unconsciousness, it is very much useful.

 Permits localization of drugs to the oral cavity for a prolonged period of time.

 A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.

Table 1: Comparison of gastrointestinal route and buccal mucosal route and nasal route for drug delivery

Parameter	Gastrointestinal	Buccal mucosal	Nasal
Accessibility	Poor	Good	Good
Permeability	Excellent	Good	Excellent
Reactivity	Good	Excellent	Poor
Surface area	Excellent	Excellent	Good
Surface environment	Poor	Excellent	Good
Vascular drainage	Excellent	Good	Excellent
First pass clearance	Poor	Excellent	Excellent
Patient acceptability	Good	Excellent	Good

Limitations: [6-7]

- Drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.
- Drugs that are impermeable to the buccal mucosa cannot be used.
- Surface area available for absorption is low.
- The buccal mucosa is relatively less permeable than small intestine, rectal etc.
- Only drugs with small dose requirements can be administered.
- Drugs which are unstable at buccal pH, cannot be administered by this route

Oral cavity as a site for drug delivery:

a) Physical description of oral cavity: The oral cavity can be divided into two regions; the outer oral vestibule which is bounded by lips and cheeks and the oral cavity itself. The borders being formed by the hard and soft palates, the floor of the mouth and the pillars of the face and tonsils. Virtually all of the membranes that line the oral cavity could potentially be used for systemic drug delivery.

b) Regional variations in the composition of oral mucosa pertinent to systemic drug delivery: Several membranes line the oral cavity and each offers different problems for its

utilization as a portal for drug entry into the systemic circulation. Both keratinized and non-keratinized tissues of varying thickness and composition are found in the oral cavity. In general, non-keratinized tissue, is considerably thicker than keratinized tissue, but the non-keratinized floor of the mouth is very thin (approximately 100µm). The keratinized layers of the oral mucosal epithelia from a protective surface, which is mechanically tough and resistant to physical insult and penetration by any foreign substance.

c) Blood supply to the oral mucosa:

The blood supply to the oral cavity tissue is delivering via the external carotid artery, which branches into the maxillary, lingual and facial arteries. Thus, delivery of drugs via the oral mucosa drains directly into the systemic circulation and thus avoids first-pass metabolism in the liver.

Documented values for blood flow through oral mucosa of Rhesus monkey as given in Table 2.

Table 2: Blood flow through buccal mucosa of Rhesus monkey

Site	**Blood flow (ml/min/cm^2)**
Buccal	2.40
Sublingual	0.97
Gingival	1.47
Palatal	0.89

d) Saliva:[8]

There are three major glands supplying saliva to the oral cavity. They are parotid, sublingual and submaxillary. Saliva is composed of 99% water and is a complex fluid containing organic and inorganic materials. The pH of saliva ranges from 6.0-7.5

Overview of the buccal mucosa[9-10]

a) Buccal mucosa structure and its suitability:

Buccal mucosa present as a lining of the buccal region which is a part of the mouth bounded anteriorly and laterally by lips and the cheeks, posteriorly and medially by the teeth and gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums.

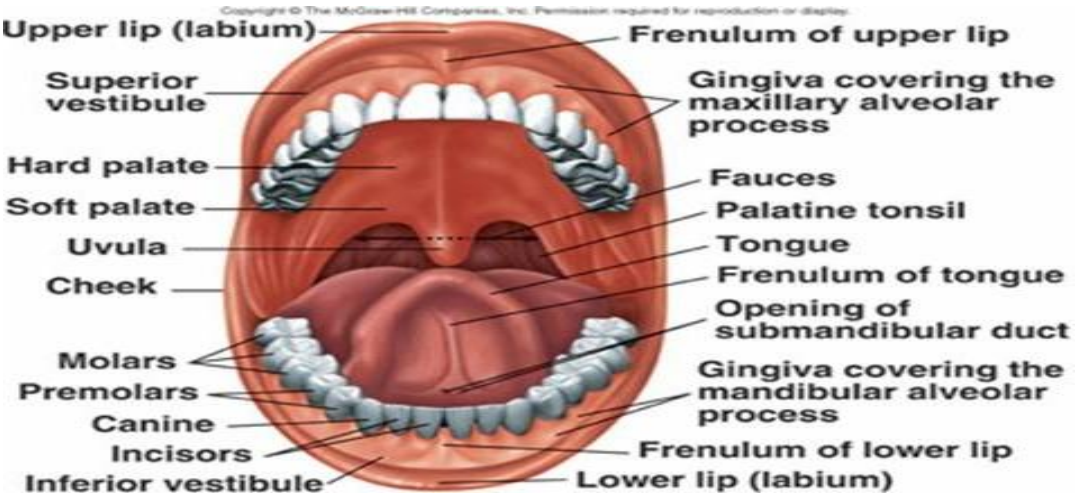

Figure 1: Buccal cavity and Cross section of buccal mucosa

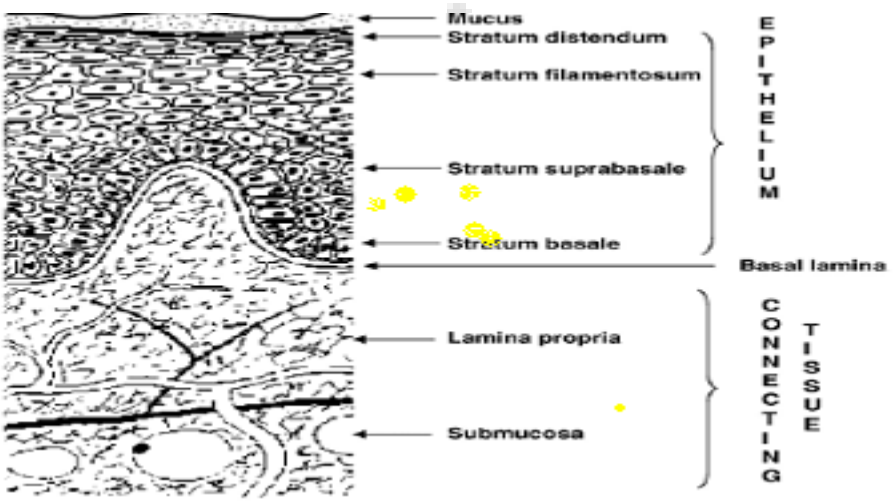

Figure 2: Transverse section of buccal mucosa

Buccal mucosa composed of several layers of different cells. In cross-section of mucosa mainly we can observe three layers like epithelium, basal lamina and connecting tissue which contains lamina propria and submucosa.

 The epithelium is similar to stratified squamous epithelia found in rest of the body and is about 40-50 cell layers thick. The primary function of buccal epithelium is protection of the underlying tissues. In non-keratinized regions, lipid based permeability barriers in the outer epithelial layers protect the underlying tissues against fluid loss and entry of potentially harmful environmental agents such as antigens, carcinogens, microbial toxins and enzymes from foods and beverages.

 Basal lamina also called basement membrane separates the epithelium and connective tissue.

 Connecting tissue which is present below the basal lamina consists of lamina propria and submucosa.

Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein.

Factors to be considered in buccal formulation design:

a. Drug characteristics: [12]

b. Drug release from the formulation:

c. Drug dissolution in the salivary film:

d. Partitioning into the superficial layers of the epithelium:

e. Ionization

f. Diffusion across the epithelial layer:[13]

g. Dependence of diffusivity on molecular size and weight:

h. Partitioning into and transport away by the blood:

i. Organoleptic properties:

j. Daily dose size:

k. Toxicity to buccal mucosa:

Buccal mucoadhesive polymers: [14]

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. Bioadhesive formulations use polymers as the adhesive component.

Ideal characteristics:

➢ Polymer and its degradation products should be non-toxic, non-irritant and free leachable impurities.

➢ Should have good spreadability, wetting, swelling and solubility and biodegradability properties.

➢ pH should be biocompatible and should possess good visco-elastic properties.

➢ Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.

➢ Should have optimum molecular weight.

➢ Should possess adhesively active groups.

➢ Should not aid in development of secondary infections such as dental caries.

b. Classification:

Mucoadhesive polymers in buccal delivery can be classified as below:

Table 3: Classification of polymers

Criteria	**Categories**	**Example**
Source	Semi-natural or natural synthetic	Agarose, Chitosan gelatin, Sodium alginate Cellulose derivatives like CMC, Sodium CMC,HPMC.; Poly (acrylic acid) based polymers like CP, PC etc.
Aqueous solubility	Water soluble Water insoluble	CP, HEC, HPS, HPMC, Sodium CMC, Sodium alginate etc. Chitosan, Ethylcellulose, CP etc.
Charge	• Cationic • Anionic • Non-ionic	Aminodextran, Chitosan trimethylated chitosan etc. Chitosan-EDTA, CP, CMC, Sodium alginate, Sodium CMC etc. Hydroxyethyl starch, HPC, HPMC etc.
Potential bioadhesive forces	• Covalent • Hydrogen bond • Electrostatic interaction	Cyanoacrylate CP, PC etc

New generation of mucoadhesive polymers:

The older generation of mucoadhesive polymers lack specificity and targeting capability. They adhere to the mucus non-specifically and suffer short retention times due to the turnover rate of the mucus.

There are three classes of new generation polymers. They are:

1. Thiolated mucoadhesive polymers
2. Target-specific, lectin mediated bioadhesive polymers
3. Bacterial protein polymers

1. Thiolated mucoadhesive polymers:

Through a covalent attachment between a cysteine (cys) residue and a polymer of choice, such as polycabophic, polyacylic acid and chitosan, a new generation of mucoadhesive polymers have been created. The mediated thiol bond, exhibit interaction, improved tensile strength, high cohesive properties, rapid swelling and water uptake behaviour.

2. Target-specific, lectin mediated bioadhesive polymers

Specific proteins or glycoprotein, such as lectins, which are able to bind certain sugars on the cell membrane, can increase bioadhesion and potentially improve drug delivery via specific binding and increase the residence time of the dosage forms. This type of bioadhesion should be more appropriately termed as cyto-adhesion. A site specific interaction with the receptor could potentially trigger intracellular signaling for internalization of the drug or the carrier system (endocytosis through cyto-adhesion) into the lysosomes or into other cellular compartments, such as the nucleus.

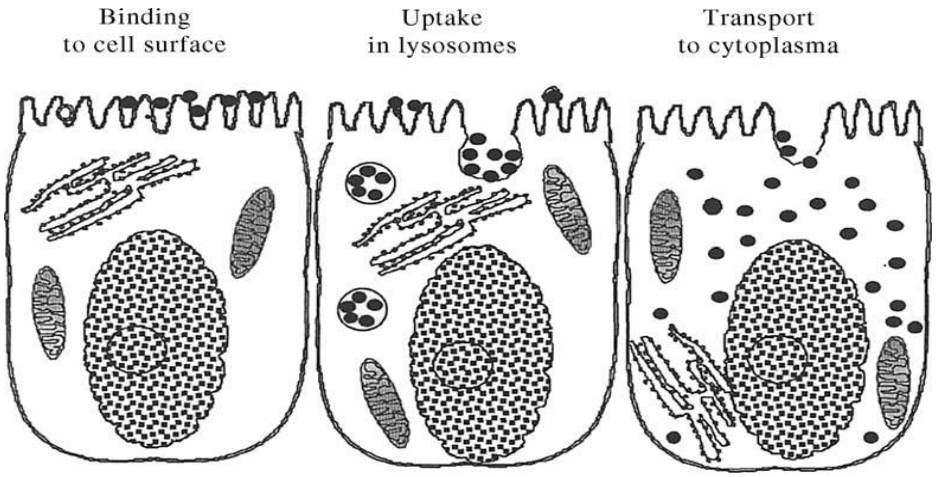

Figure 3: Different fates of lectin-mediated cyto-adhesive ligands or drug carrier systems upon specific binding to surface receptors on the epithelial cells

Although lectins are also found in bacteria, those from the plant kingdom still remain the largest group of this class lectin isolated from tomato fruit (*Lycopersicum esculentum*) has been reported to specifically and safely bind N-Acetylglucosamine (GluMAc) on this surface of several cell monolayer.

Technological advances in biomaterials and techniques have resulted in novel designs meeting the challenges of physicochemical properties of the drug and thus contributing to the therapeutic efficacy of Buccal drug delivery.[18]

3. Bacterial protein polymers:

The adhesive properties of bacterial cells, as a more complicated adhesion system, have recently been investigated. The ability of bacteria to adhere to a specific target is rooted from particular cell surface components or appendages, known as fimbriae, which facilitate adhesion to other cells or inanimate surfaces. The bacterial protein polymers are covalently attached to bioadhesive polymers. The attractiveness of this approach lines in the potential increasing the residence tome of the drug on the mucus and its receptor specific interaction similar to those of the plant lectins.

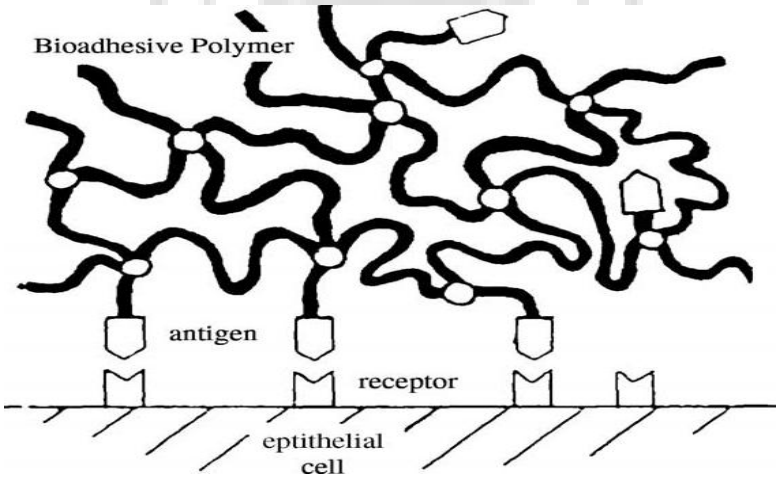

Figure 4: A diagram of covalently attached fimbrial protein (K99 from E.coli) to polyacrylic acid as a carrier system

MATERIALS AND METHODS

Irbesartan (IBS), Carbopol 934, Sodium alginate, HPMC K4M, Mannitol, Magnesium stearate, Talc, Potassium dihydrogen orthophosphate, Sodium hydroxide, Agar – agar powder, PEO's11

Methodology

Formulation of Buccoadhesive tablets:

Irbesartan was mixed manually in poly bags with different ratios of polyethylene oxides, sodium alginate and Methocel K4M (HPMC K4M) mixture or Carbopol 934 and HPMC K4M mixture as mucoadhesive polymers, and mannitol as diluent for 10 mins. The blend was lubricated with magnesium stearate for 3-5 mins and talc was added as glidant. Then mixed blend was compressed into tablets by direct compression using 8 mm punches. The tablets were compressed using a sixteen station rotary tablet punching machine.

Table 4: Formulation composition of Irbesartan buccal tablets

Formulation	Drug	Na Alginate	Carbopol 934	HPMC K4M	Mannitol	Mg stearate	Talc	Total
F1	100mg	25mg	-	10mg	43.00mg	1mg	1mg	180
F2	100mg	25mg	-	15mg	38.0mg	1mg	1mg	180
F3	100mg	25mg	-	20.0mg	33.0mg	1mg	1mg	180
F4	100mg	25mg	-	25mg	28.0mg	1mg	1mg	180
F5	100mg	25mg	-	30.0mg	23mg	1mg	1mg	180
F6	100mg	-	25mg	10mg	43.00mg	1mg	1mg	180
F7	100mg	-	25mg	15mg	38.0mg	1mg	1mg	180
F8	100mg	-	25mg	20.0mg	33.0mg	1mg	1mg	180
F9	100mg	-	25mg	25mg	28.0mg	1mg	1mg	180
F10	100mg	-	25mg	30.0mg	23mg	1mg	1mg	180

RESULTS AND DISCUSSION

Calibration curve of Irbesartan in pH 6.6 phosphate buffer:

Standard graph of Irbesartan, was plotted as per the procedure in experimental method and its linearity is shown in Table 5 and Figure 5 The standard graph of Irbesartan showed good linearity with R^2 of 0.9984 which indicates that it obeys "Beer-Lambert's" law.

Table 5: Standard graph of Irbesartan in pH 6.6 phosphate buffer

Concentration (µg/ml)	Absorbance at 246.4 nm
0	0
20	0.056
40	0.136
60	0.206
80	0.282
100	0.348
120	0.410
140	0.536
160	0.591
180	0.682
200	0.752

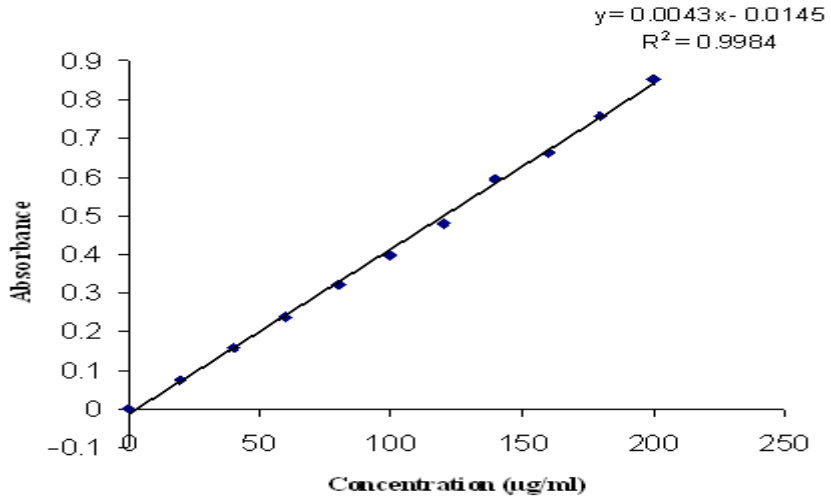

Figure 5: Standard graph of Irbesartan in pH 6.6 phosphate buffer

Table 6: Study of flow properties of powder blends:

Physical characters of blends	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Bulk density (W/V)	0.66	0.65	0.71	0.63	0.61	0.61	0.65	0.69	0.71	0.71
Taped density (W/V)	0.71	0.72	0.75	0.70	0.71	0.70	0.81	0.85	0.86	0.85
Angle of repose (in degrees)	23.5	23.8	23.3	24.4	23.6	28.8	28.1	28.5	27.2	28.4
Compressibility index	6.59	6.23	5.38	5.94	6.18	12.51	12.69	16.37	17.85	18.55

Evaluation of buccal tablets:

A) Characterization of physical properties of tablets:

a) Weight variation and thickness: The weight variation and the thickness of the tablets (Table 8) were within the limits of uniformity. The mass ranged from 199.50 to 200.76 mg with SD values 0.66–1.08. Thickness ranged between 3.90 and 4.06 mm with SD values of 0.01 to 0.03.

b) Friability and assay:

The drug content ranged from 100.9 ± 0.36 of formulation F1 to 100.6 ± 0.75 of formulation F5, 99.3 ± 0.36 of formulation F6 to 101.2 ± 0.36 of formulation F10 and the friability was ranged from 0.3 to 0.92. Friability and assay of all compressed tablets were within the limits as per USP.

Table 7: Characterization and properties of buccal tablets

Formulation	Mass (mg) Mean ± SD	Thickness (mm) Mean ± SD	Friability (%)	Assay (%)
F1	200.56 ± 1.05	3.90 ± 0.03	0.61	100.9 ± 0.36
F2	200.31 ± 0.66	3.98 ± 0.02	0.92	98.5 ± 0.47
F3	200.65 ± 0.69	3.97 ± 0.03	0.53	101.9 ± 0.59
F4	199.50 ± 0.79	3.97 ± 0.02	0.68	101.3 ± 1.01
F5	200.47 ± 1.04	4.06 ± 0.02	0.75	100.6 ± 0.75
F6	200.21 ± 0.89	4.01 ± 0.02	0.53	99.3 ± 0.36
F7	198.75 ± 0.85	3.99 ± 0.03	0.76	97.9 ± 0.48
F8	200.44 ± 0.99	3.97 ± 0.02	0.38	100.3 ± 0.36
F9	200.76 ± 1.08	3.98 ± 0.01	0.30	98.9 ± 0.27
F10	200.45 ± 0.72	3.97 ± 0.02	0.60	101.2 ± 0.36

B) *In-vitro* drug release:

The release of Irbesartan from buccoadhesive tablets (Figure: 6 and 7) varied according to the type and ratio of matrix forming polymers. The drug release was governed by the amount of matrix forming polymers. Formulations F1 and F2 released the drug completely within 5 hours, whereas formulations F3, F4 and F5 released within 6 hours. The drug release was extended beyond 8 hours in formulations F6 to F10. The most important factor affecting the rate of release from the buccal tablets was the ratio of drug and polymer mixture. In polymer mixture of all formulations HPMC K4M concentration was used increasingly from F1 to F5 and F6 to F10, whereas concentrations of sodium alginate and Carbopol 934 were maintained constant in formulations F1 to F5 and F6 to F10, respectively. The release of Irbesartan was decreased with increasing concentration of HPMC K4M. The possible reason for observed reduction in total drug release may be the interaction between two oppositely charged bioadhesive polymers i.e. sodium alginate (anionic) and HPMC K4M (nonionic) in formulations F1 to F5 or Carbopol 934 (anionic) and HPMC K4M in formulations F6 to F10.

It was observed that the matrix formation was more in formulations F6 to F10 as compared to formulations F1 to F5. The possible reason may be because of structure of Carbopol 934. It is highly cross-linked polymer that swells in water and do not disintegrate upon 24 hours.

Table 8: *In-vitro* release profiles of formulations F1 to F5

Time (hrs)	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	38.33±0.23	34.76±0.78	28.79±0.51	24.76±0.84	15.85±0.54
1	58.70±0.45	50.33±1.45	45.38±1.66	38.02±0.41	30.50±0.51
2	72.66±0.65	64.68±0.34	54.91±1.67	50.26±0.99	42.83±0.66
3	84.66±0.78	80.41±1.56	72.99±0.34	72.05±0.67	61.51±1.53
4	92.84±0.32	92.44±2.04	88.79±0.44	80.27±1.80	73.45±0.84
5	100.89±0.12	98.18±0.74	96.70±0.54	92.50±0.84	85.93±1.04
6	-	-	101.82±0.84	99.28±0.64	100.20±1.34

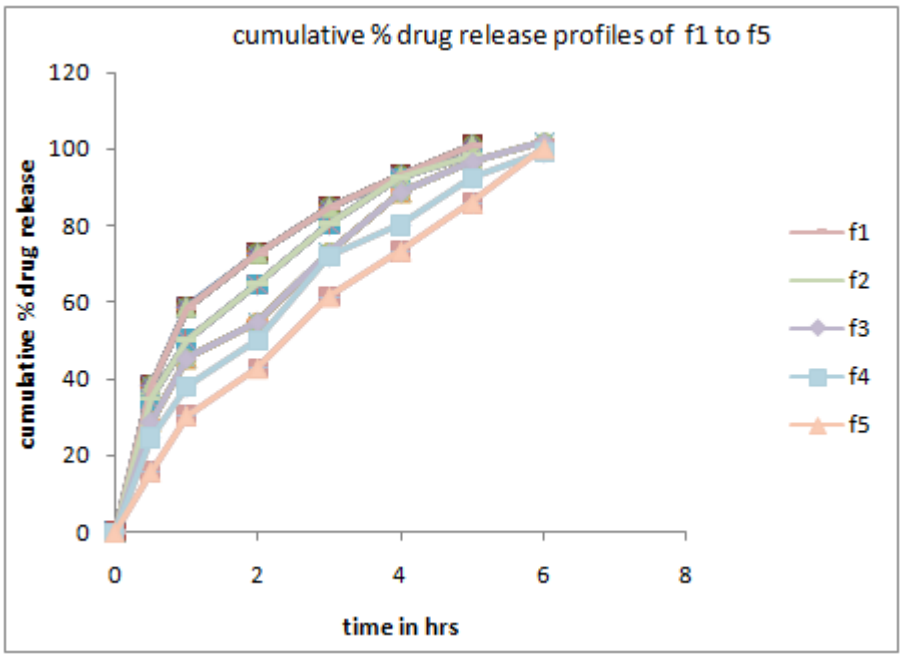

Figure 6: Comparison of dissolution profile of formulations F1 to F5

Table 9: *In-vitro* release profiles of formulations F6 to F10

Time (hrs)	F6	F7	F8	F9	F10
0	0	0	0	0	0
0.5	22.84 ± 0.74	20.89 ±0.56	15.54 ±0.22	12.60 ±0.43	9.81 ±0.24
1	28.33 ± 0.53	23.44 ±0.84	18.33 ±0.56	14.15 ±0.49	12.90 ±0.27
2	39.41 ± 0.22	32.37 ±0.76	24.31 ±0.09	18.42 ±0.21	15.30 ±0.45
3	40.21 ± 0.43	36.71 ±1.09	27.72 ±0.75	22.75 ±0.04	18.41 ±0.56
4	42.68 ± 0.54	40.12 ±0.84	31.90 ±0.45	28.57 ±0.84	26.47 ±0.76
5	51.75 ± 0.61	46.88 ±0.66	38.19 ±0.78	34.82 ±0.12	28.41 ±0.09
6	68.95 ± 0.84	50.83 ±0.45	50.19 ±0.88	43.38 ±0.56	37.73 ±0.67
7	74.39 ± 0.66	71.90 ±0.78	60.04 ±0.34	56.01 ±0.31	46.40 ±0.78
8	87.40 ± 0.32	82.37 ±0.67	78.33 ±0.21	66.57 ±0.80	61.19 ±0.91

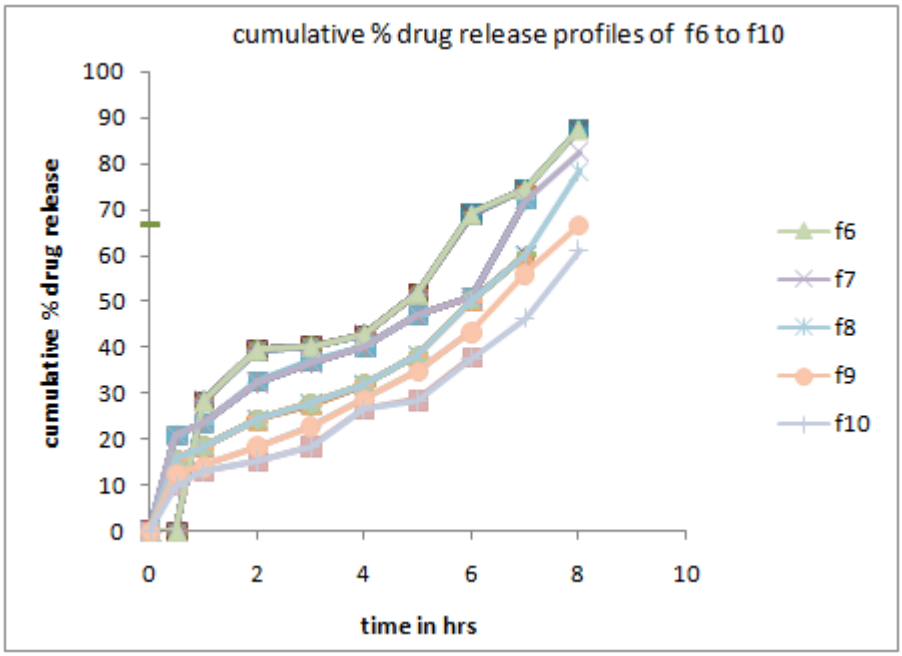

Figure 7: Comparison of dissolution profile of formulations F6 to F10

Table 10: Release kinetics of the formulations

Formulation R^2	Zero order R^2	First order R^2	Higuchi R^2	Peppas		Hixson-Crowell R^2
				n	R^2	
F1	0.8581	0.9513	0.9884	0.42	0.9892	0.9667
F2	0.9011	0.9409	0.9977	0.46	0.9982	0.9879
F3	0.9227	0.9523	0.9922	0.52	0.9848	0.9846
F4	0.9481	0.9799	0.9913	0.58	0.9929	0.9906
F5	0.9816	0.9759	0.974	0.71	0.9932	0.9931
F6	0.9412	0.9003	0.9463	0.44	0.9203	0.9346
F7	0.9393	0.8605	0.9177	0.47	0.905	0.9032
F8	0.9448	0.8518	0.8844	0.53	0.8976	0.8941
F9	0.9474	0.8759	0.8606	0.59	0.8838	0.9059
F10	0.9593	0.9088	0.8687	0.63	0.8955	0.9297

C) *In-vitro* mucoadhesive strength:

The values of the mucoadhesion strength of Irbesartan buccal tablets are given in Table 11. In all the formulations, as the polymer mixture concentration increased, the mucoadhesion was increased. The order of bio-adhesion of polymers used in the preparation, can be given as HPMC K4M < Sodium alginate < Carbopol 934. Buccal tablets formulated with a mixture of Carbopol 934 and HPMC K4M showed stronger mucoadhesion than that of Sodium alginate and HPMC K4M. Very strong bioadhesion could damage the epithelial lining of the buccal mucosa. The mucoadhesion strength for formulation F8 was optimum i.e. 21.12 ± 0.10 gm.

The force of adhesion was deduced using the following equation:

$$\text{Mucoadhesive Force (N)} = \frac{\text{Bioadhesive strength} \times 9.81}{1000}$$

Table 11: Mucoadhesive strength of buccal tablets

Formulation	Mucoadhesive strength (gm) Mean ± SD
F1	12.40 ± 0.14
F2	14.27 ± 0.11
F3	13.10 ± 0.20
F4	14.80 ± 0.10
F5	16.20 ± 0.10
F6	18.00 ± 0.11
F7	17.32 ± 0.13
F8	25.12 ± 0.10
F9	24.40 ± 0.32
F10	27.07 ± 1.17

D) Moisture absorption:

The moisture absorption studies give an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after moisture absorption. Moisture absorption was increased from formulations F1 to F5 and F6 to F10, The possible reason may be the increased concentration of polymer mixture from formulations F1 to F5 and F6 to F10. The moisture absorption was more in formulations containing Carbopol 934 and HPMC K4M when compared to formulations containing Sodium alginate and HPMC K4M. The order of moisture absorption capacity of polymers used in preparation can be given as HPMC K4M < Sodium alginate < Carbopol 934. This may be due to the more hydrophilic nature of Carbopol. Formulation F8 showed optimum moisture absorption i.e. 36.01 ± 0.15 %.

Table 12: Moisture absorption of buccal tablets

Formulation	Moisture absorption (%) Mean ± SD
F1	24.00 ± 1.21
F2	28.40 ± 1.70
F3	29.00 ± 1.20
F4	31.08 ± 1.40
F5	33.01 ± 1.30
F6	31.31 ± 0.08
F7	32.36 ± 0.20
F8	36.01 ± 0.15
F9	40.51 ± 0.22
F10	42.89 ± 0.15

E) *In-vitro* retention time:

The *in-vitro* retention time is one of the important physical parameter of buccal mucoadhesive tablets. Formulations F1 to F5 showed less retention time as compared to formulations F6 to F10. As increasing the concentration of polymer mixture in formulations, the retention time also increased. From the results, it can be said that the mixture of Carbopol 934 and HPMC K4M has better mucoadhesion than the mixture of Sodium alginate and HPMC K4M. Formulation F8 showed optimum retention time of 7 hrs 58 min.

Table 13: *In-vitro* retention time of Irbesartan buccal tablets

Formulation	*In-vitro* retention time
F1	3 hrs 35 min
F2	3 hrs 59 min
F3	4 hrs 25 min
F4	5 hrs 40 min
F5	6 hrs 24 min
F6	5 hrs 50 min
F7	6 hrs 35 min
F8	7 hrs 58 min
F9	More than 8 hrs
F10	More than 8 hrs

Table 14: Surface pH values (Mean ± SD) of formulations F1 to F5

Time (hrs)	F1	F2	F3	F4	F5
0.25	6.40±0.02	6.69±0.05	7.22±0.10	6.47±0.03	6.75±0.03
0.5	6.44±0.03	6.67±0.02	7.13±0.04	6.65±0.01	6.85±0.03
0.75	6.41±0.04	6.68±0.04	7.11 0.02	6.56±0.04	6.85±0.02
1	6.40±0.02	6.88±0.05	7.13±0.06	6.65±0.03	6.73±0.03
2	6.42±0.03	6.69±0.05	7.11±0.05	6.67±0.03	6.77±0.02
3	6.42±0.03	6.77±0.05	7.10±0.06	6.66±0.02	6.76±0.01
4	6.41±0.02	6.68±0.04	7.17±0.07	6.66±0.03	6.74±0.03
5	6.40±0.03	6.68±0.05	7.15±0.07	6.65±0.03	6.74±0.04
6	6.41±0.02	6.79±0.07	7.12±0.06	6.77±0.02	6.79±0.02
7	6.30±0.08	6.78±0.03	7.10±0.04	6.64±0.04	6.86±0.03
8	6.47±0.05	6.78 0.05	7.01±0.05	6.66±0.05	6.85±0.02

Table 15: Surface pH values (Mean ± SD) of formulations F6 to f10

T (hr)	F6	F7	F8	F9	F10	F7
0.25	6.83±0.02	6.66±0.02	6.98±0.02	7.120.03	6.76±0.02	6.67±0.02
0.5	6.88±0.03	6.65±0.04	6.95±0.03	7.03±0.02	6.62±0.01	6.68±0.04
0.75	6.67±0.03	6.66±0.03	6.84±0.02	7.07±0.02	6.66±0.03	6.56±0.03
1	6.67±0.05	6.67±0.02	6.87±0.03	7.17±0.02	6.85±0.03	6.73±0.02
2	6.76±0.03	6.77±0.03	6.89±0.03	7.07±0.03	6.64±0.03	6.66±0.03
3	6.68±0.01	6.55±0.02	6.98±0.02	7.43±0.03	6.65±0.02	6.75±0.02
4	6.47±0.02	6.66±0.03	6.91±0.02	7.07±0.03	6.65±0.02	6.77±0.03
5	6.12±0.03	6.68±0.05	6.94±0.01	7.12±0.01	6.87±0.03	6.87±0.05
6	6.78±0.02	6.67±0.03	6.96±0.02	7.08±0.04	6.76±0.03	6.66±0.03
7	6.78±0.04	6.75±0.02	6.95±0.05	7.19±0.02	6.64±0.03	6.65±0.02
8	6.77±0.03	6.85±0.02	6.86±0.04	7.14±0.02	6.55±0.02	6.90±0.02

G) *In-vitro* drug permeation:

Based on the *in-vitro* drug release, mucoadhesion strength, moisture absorption and *in-vitro* retention time of all formulations, the F8 formulation was selected as optimum and *in-vitro* permeation studies were conducted for this formulation. The buccal mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition.

Table 16: *In-vitro* permeation of Irbesartan from optimized formulation F8

Time (hrs)	*In-vitro* permeation (%)
0	0
0.5	19.01 ± 0.30
1	17.31 ± 0.33
2	28.15 ± 0.20
3	32.26 ± 0.20
4	33.00 ± 0.35
5	37.07 ± 0.24
6	36.02 ± 0.15
7	38.31 ± 0.23
8	39.70 ± 0.22

The results of drug permeation from buccal tablets through porcine buccal mucosa revealed that Irbesartan was released from the formulation and permeated through the porcine buccal membrane. The drug permeation was slow and steady (Figure 8)

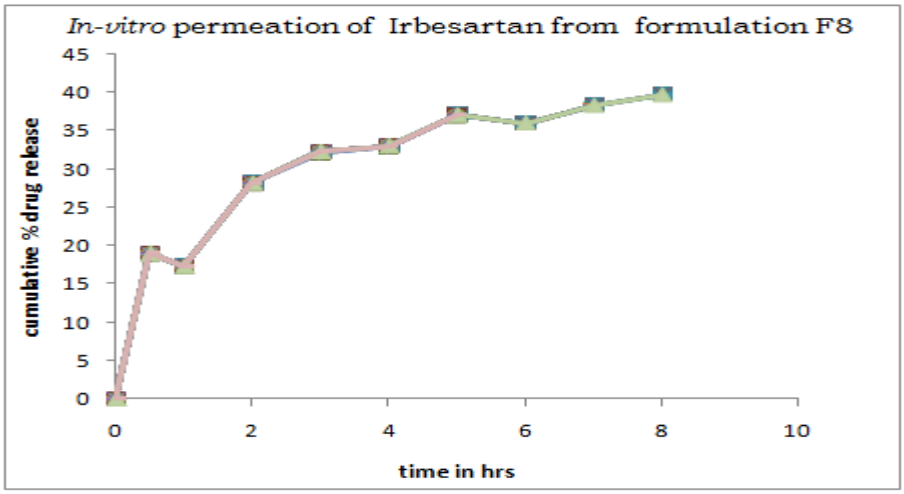

Figure 8: *In-vitro* permeation of Irbesartan from formulation F8

FTIR study:

FTIR study on the selected formulation prepared with different polymers combinations such as Carbopol-934, Sodium alginate, HPMC K4M. The spectrum peak points of the formulation were similar with that of the pure Irbesartan, this clearly indicating that there is no drug polymer interaction. The FTIR spectra of pure Irbesartan and formulation-f8 were shown in Figure 9 and 10.

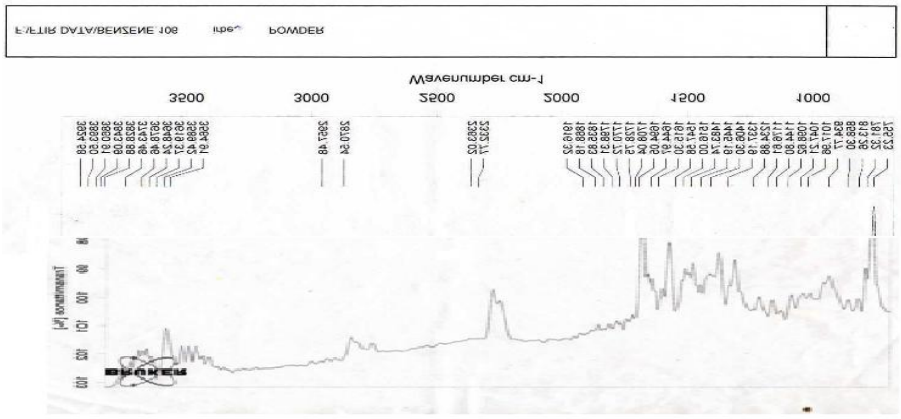

Figure 9: FTIR Spectrum of pure drug Irbesartan

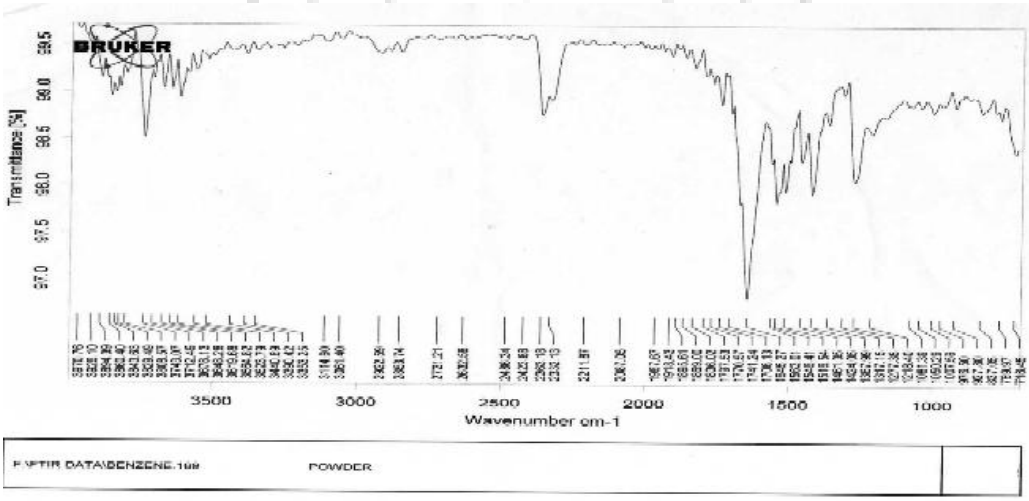

Figure 10: FTIR Spectrum of optimized formulation i.e F8

Differential scanning calorimetric study (DSC)

DSC study was conducted on selected formulation. DSC thermogram of pure Irbesartan shows sharp endothermic peak at 186.03°CSimilar endothermic peaks were obtained at 116.5°C for the formulation prepared with Carbopol 934-HPMC K4M.The DSC thermograms are shown in Figure 11 and 12. This clearly indicates that there is no drug-polymer interaction.

Table 17: DSC melting points of selected formulations

Formulations	DSC melting point in °C
Irbesartan	186.03°C
F8	116.5°C

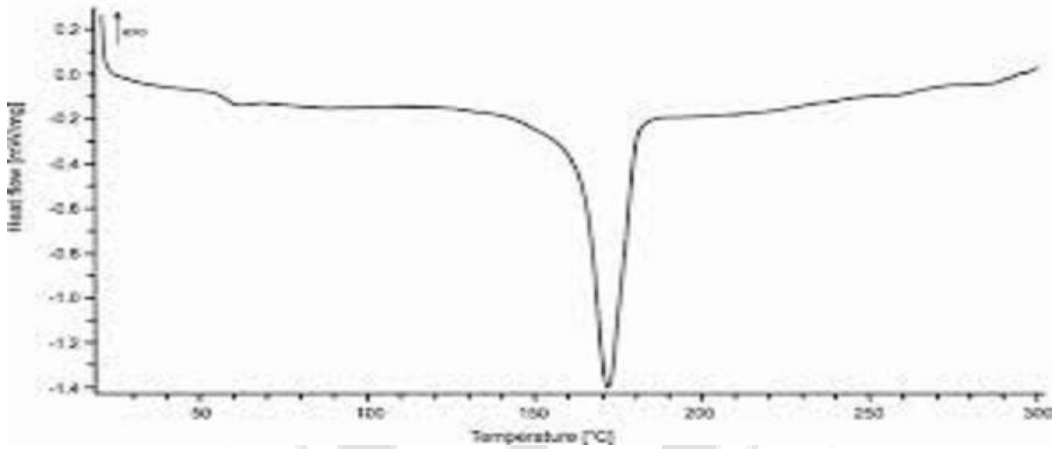

Figure 11: DSC thermogram of pure Irbesartan

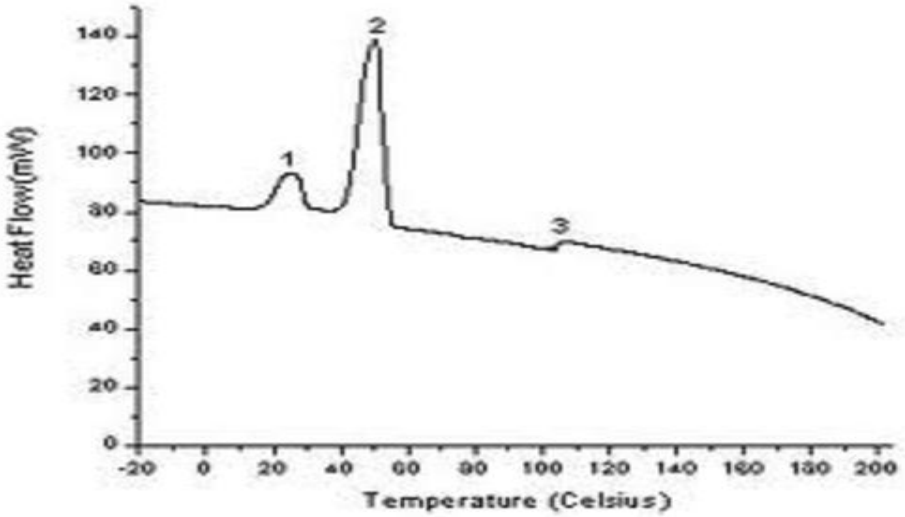

Figure 12: DSC thermogram of optimized formulation F8

CONCLUSION

A standard concentration of Irbesartan was prepared in pH 6.6 phosphate buffer and absorbance was measured at 246.4 nm. Irbesartan is showing good linearity between 20-100 µg/ml with a correlation coefficient of 0.9994. The formulations containing HPMC K4M only did not show

promising results, the drug release was poor, and the *in-vitro* retention time was also found to be less.

The release of Irbesartan was decreased with increasing concentration of HPMC K4M. The possible reason for observed reduction in total drug release may be interaction between two oppositely charged bioadhesive polymers i.e. Sodium alginate (anionic) and HPMC K4M (nonionic) in formulations F1 to F5 or Carbopol 934 (anionic) and HPMC K4M in formulations F6 to F10.

In-vitro release studies showed that formulation F8 containing 1:0.25 ratio combination of (Carbopol 934+ HPMC K4M) drug and polymer combination showed satisfactory bioadhesive and exhibited optimum drug release 78.33±0.21 after 12 hrs, Formulation F8 showed optimum moisture absorption i.e. 36.01 ± 0.15 %. DSC and FTIR study of pure Irbesartan and formulations showed that there is no drug polymer interaction.

REFERENCES

1) S.K.Gupta et al; Buccal adhesive drug delivery system: A review; *Asian Journal Of Biochemical and pharmaceutical research,* 1(2), 2011, 105-114.
2) Rajesh Mujoriya et al; A Review on study of Buccal Drug Delivery System, *Innovative systems Design and Engineering,* 2(3), 2011
3) Pankil A Gandhi et al; A Review article on Mucoadhesive Buccal Drug delivery system, *International Journal of Pharmaceutical Research and Development,* 3(5), 2011, 159-173.
4) Chinna Reddy p et al; A Review onBioadhesive Buccal Drug Delivery systems:Current Status ofFormulation andEvaluation Methods, *DARU,*19(6),2011,385-403.
5) J Thimmasetty et al; Design and *In vivo* Evaluation of Carvedilol Buccal Mucoadhesive patch *Pak.J.Pharmsci*21 (3), 2008, 241-248.
6) Gupta, S. Garg, R.K. Khar,Mucoadhesive buccal drug delivery system-A Review, Indian Drugs, 29(13) (1992) 586-593.
7) R.Khanna, S.P. Agarwal, A. Ahuja, Mucoadhesive buccal drug delivery -A potential to conventional therapy, Ind. J. Pharm. Sci., 60 (1) (1998) 1-11
8) Mamatha y et al; Buccal Drug delivery a Technical Approach,*Journal of Drug Delivery Therapeutics2* (2), 2012, 26-33
9) Bhaskara Jasti et al; Recent Advances in mucoadhesive Drug delivery system, *Business Briefing: Pharmatech* 2004, 194-196.
10) Naveet verma et al; Polymeric platform for Mucoadhesive Buccal Drug Delivery System: Review; *International Journal of Current Pharmaceutical Research*3 (3), 2011, 3-8
11) Chinnareddy palem et al, Development of Bilayered Mucoadhesive patches for Buccal Delivery of Felodipine: *In-vitro and ex-vivo* Characterization in Biotechnology and pharmacy, 4(2), 2010
12) C.Vijayraghavan, T.K. Ravi, Buccal delivery of Nifedipine using novel natural Mucoadhesive polymer as an excipients in buccal tablets, Indian Drugs, 41(3) (2004) 143-148.
13) M.S.Wani, S.R. Parakh, M.H. Dehghan, S.A. Polshettiwar, V.V. Pande, V.V. Chopade, Current Status In Buccal Drug Delivery. www.pharmainfo.net as on 28 April (2007)
14) M.Nappinnai et al, Formulation and Evaluation of Nitrendipine BuccalFilms, *Indian Journal of Pharmaceutical Sciences*70(5), 2008, 631-635.

15) A Semalty et al, Formulation and Evaluation of Mucoadhesive BuccalFilms of Enalapril maleate, *Indian Journal of PharmaceuticalSciences,72(5),2010,571-575.*
16) Anay R.Patel et al; Mucoadhesive Buccal Drug Delivery system, *International Journal of Pharmacy and Life sciences*, 2(6), 2011, 848-856.
17) Patel mitul et al; Buccal drug delivery system: The current Interest, *IJP*, 2(12), 2011, 4-11.
18) S.Velmurugan, B.Deepika, K.Naga Raju.Formulation and *in vitro* evaluation of buccal tablets of Piroxicam.International Journal of ChemTech Research, 2 (3):1958-1968, (2010).