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FORMULATION AND EVALUATION OF ESOMEPRAZOLE MUCOADHESIVE BUCCAL TABLETS

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ABSTARCT

Esomeprazole pellets containing mucoadhesive tablets were developed by direct punch method. Three mucoadhesive polymers namely hydroxypropylemethylcellulose K 100 M, Carbopol 934, HPMC K 15 M, were used for preparation of tablets which intended for prolong action may be due to the attachment with intestinal mucosa for relief from active duodenal ulcer. The prepared tablets were evaluated for different physical parameters and dissolution study were performed in two dissolution mediums like pH 6.8 and pH 7.4 phosphate buffer solution. The release mechanism of all formulation was diffusion controlled confirmed from Higuchi's plot. Thus, the present study concluded that, carbopol-934P containing mucoadhesive tablets of omeprazole pellets can be used for local action in the ulcer disease.

KEYWORDS: Mucoadhesion, esomeprazole, direct compression, ulcer.

INTRODUCTION

The concept of mucosal-adhesive or mucoadhesive was introduced into the controlled drug delivery in the early 1980's. Bioadhesive polyacrylic acid nanoparticles are an example of a novel drug delivery system designed for mucosal drug delivery. Mucoadhesive polymers are synthetic or natural polymers, which interact with the mucus layer covering the mucosal epithelial surface and mucin molecules constituting a major part of mucus. They render the treatment more effective and safe, not only for local action but also for systemic problems. These dosage forms are self-administrable, cheap and have superior patient compliance[1]. With the right dosage form design, local environment of the mucosa can be controlled and manipulated in order to optimize the rate of drug dissolution and permeation.

The buccal delivery is defined as the drug administration through the mucosal membranes lining the cheeks (buccal mucosa). The main impediment to the use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and erratic oral absorption. The future challenge of pharmaceutical scientists is to develop effective non-parenteral delivery of intact proteins and peptides to the systemic circulation. Based on our current understanding of biochemical and physiological aspects of absorption and metabolism of many biotechnologically produced drugs, they cannot be delivered effectively through the conventional oral route.

Advantages[2]

- Among the various transmucosal routes, buccal mucosa has the excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms.
- Direct access to the systemic circulation through the internal jugular vein bypasses drugs from hepatic first pass metabolism leading to high bioavailability.
- Low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa, painless administration, easy drug withdrawal, facility to include permeation enhancers.
- Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery.

Disadvantages

- The low permeability of the buccal membrane
- specifically when compared to the sublingual membrane and a smaller surface area.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately, the involuntary removal of the dosage form.
- In addition to the swallowing, there is another inconvenience of such dosage form during drinking and eating by the patient.

Mucoadhesive buccal drug delivery systems[3-5]

The oral cavity is an attractive site for drug delivery due to ease of administration, avoidance of possible drug degradation in the gastrointestinal tract, and first-pass metabolism. Within the oral mucosal cavity, delivery of drugs is classified into three categories:

- **Sublingual delivery**, which is administration of the drugs via mucosal membranes lining the floor of the mouth i.e., sublingual mucosal to the systemic circulation.
- **Buccal delivery**, which is administration of the drug via mucosal membranes lining the cheeks i.e., buccal mucosa to the systemic circulation.
- **Local delivery,** for the treatment of conditions of the oral cavity, principally Aphthous Ulcers, fungal conditions and Periodontal diseases by the application of the bioadhesive system either to the palate, the gingiva or the cheek.

Buccal mucoadhesive dosage forms[6-9]

Buccal mucoadhesive dosage forms can be categorized in to 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 in to 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. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.

Types of buccal mucoadhesive drug delivery system

Buccal tablets, Buccal patches, Buccal films, Buccal hydrogels, Buccal gels & ointments, Buccal pellets.

Table 1: Comparison of some routes for systemic drug delivery

Parameter	Gastro intestinal	Buccal mucosal	Nasal
Accessibility	+	+ +	+ +
Permeability	+ + +	+ +	+ + +
Reactivity	+ +	+ + +	+
Surface environment	+	+ + +	++
Vascular drainage	+ + +	+ +	+ + +
First pass clearance	+	+ + +	+ + +
Patient acceptability	+ +	+ + +	+ +

Key: + Poor; + + Good; + + + Excellent

Table 2: Various factors affecting systemic absorption of drugs through the oral mucosa

Biological factors	Drug factors	Formulation factors
	Taste	Feel of delivery system
	Discolouration of teeth	Properties excipient
Area	Solubility	Visibility
Thickness	Partition coefficient	Release characteristics
Structure of oral mucosa	pk_a	Retentive properties
pH of environment	Biological half-lfe	Protection from saliva
Saliva flow rates	Retention	Mobility of backing layer
Composition of saliva	Rate of absorption	Delivery system
	Drug stability	Size and shape
	Diffusion coefficient	Texture

General criteria for candidate's drug

Other than dose considerations, the following properties will make the drug suitable candidate for buccal delivery:

- Relatively short biological half-life[10] :- Drugs with biological half-life 2-8 hr will in general be good candidates for sustained release dosage forms
- The maximal duration of buccal delivery is approximately 4–8 hr.
- Drug must undergo first pass effect or it should have local effect in oral cavity.

Buccal mucosal structure and its suitability

Buccal region is that part of the mouth bounded anteriorly and laterally by the lips and the cheeks, posteriorly and medially by the teeth and/or gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums. Maxillary artery supplies blood to buccal mucosa and blood flow is faster and richer ($2.4mL/min/cm^2$) than that in the sublingual, gingival and palatal regions thus facilitate passive diffusion of drug molecules across the mucosa.

Buccal mucosa composed of several layers of different cells as shown in Fig 1. The outermost layer is stratified squamous epithelium; below this lies a basement membrane, a lamina propria followed by the sub mucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in rest of the body and is about 40–50 cell layers thick. The epithelium, as a protective layer for the tissues beneath and is divided into

a) ***Non- keratinized epithelium***

This present in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, vestibule, lips and cheeks.

b) ***Keratinized epithelium***

This is found in the hard palate and non-flexible regions of the oral cavity. The keratinized epithelia contain neutral lipids like ceramides and acyl ceramides, which are associated with the barrier function. These epithelia are impermeable to water. The non-keratinized epithelia do not contain acylceramides and only have small amounts of ceramides and also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosylceramides. Basement membrane, lamina propria followed by the submucosa is present below the epithelial layer. Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein. The primary function of buccal epithelium is the protection of the underlying tissue.

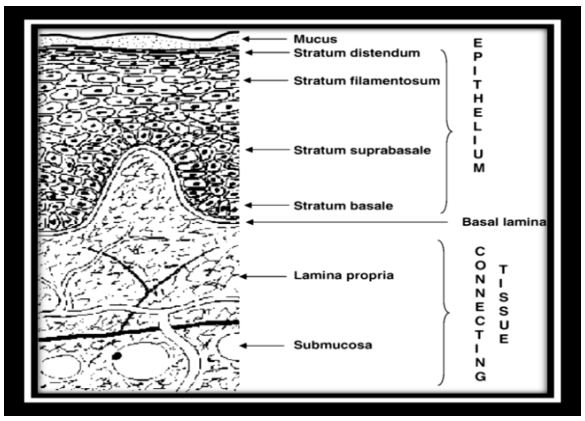


Fig.1. Cross-section of buccal mucosa.

The basement membrane forms a distinct layer between the connective tissues and the epithelium. The innermost layer is the sub mucosa, which secretes a gel like secretion known as mucus. The membranes of the internal tracts of the body including GIT, buccal cavity, eye, ear, nose, vagina and rectum are covered with a gel like structure known as mucin. The tissue layer that is responsible for the formation of adhesive interface is mucus.

Mucus layer

The target for interactions of most of bioadhesive polymers is the mucus. In higher organisms epithelia are covered by a protective gel layer defined as mucus. Mucus is translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. Goblet cells produce, store and secret mucus The composition of mucus varies widely depending on animal species, animal location, normal or physiological state of organism. The main component of mucus secretion is the glycoprotein fraction, which is responsible for its gel like characteristics. Mucus has the following general composition.

Table 3: General Composition of Mucus

S.No	Composition	Percentage
1	Water	95%
2	Glycoproteins & Lipids	0.5-5%
3	Mineral salts	1%
4	Free proteins	0.5-1%

Functions of Mucus layer:

Protective role, Barrier role, Adhesion role, Lubrication role.

Mechanism of Bioadhesion[11]

The mechanism of bioadhesion can be described in three successive steps: Steps involved in the process of bio/mucoadhesion are as follows

1. Wetting and swelling of polymer to permit intimate contact with biological tissue.
2. Interpenetration of bioadhesive polymer chains and entanglement of polymer andmucin chains.
3. Formation of weak chemical bonds between entangled chains.

STEP 1: The wetting and swelling of the polymer

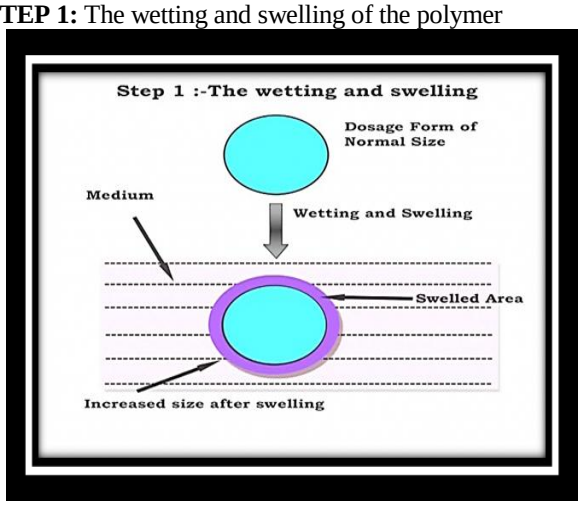


Fig.2: **Wetting and swelling of polymer**

STEP2: Inter penetration between the polymer chains and the mucosal membrane and their entanglement.

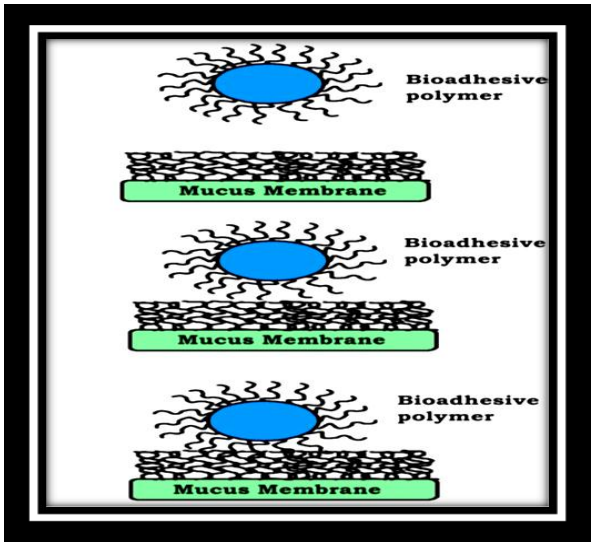


Figure.3 Interdiffusion and Interpenetration of Polymer and Mucus

STEP3: Formation of Chemical bonds between the entangled chains**.**

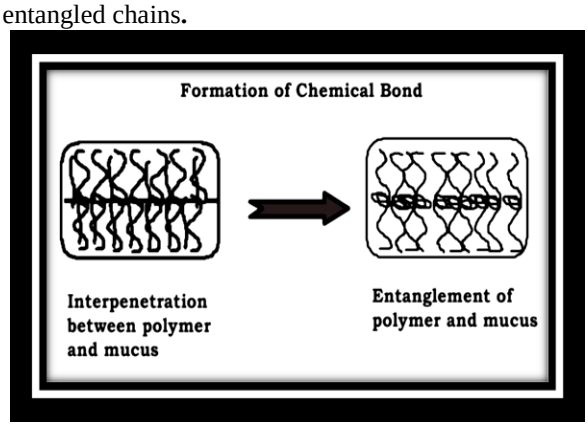


Fig.4.Entanglement of Polymer and Mucus by Chemical bond

Formulation design

An ideal buccal adhesive system must have the following properties:

- Should adhere to the site of attachment for a few hours,
- Should release the drug in a controlled fashion,
- Should provide drug release in an unidirectional way towards the mucosa,
- Should facilitate the rate and extent of drug absorption,
- Should not cause any irritation or inconvenience to the patient and
- Should not interfere with the normal functions such as talking, drinking etc.

Table 4: Mucoadhesive Polymers used in Buccal drug delivery

Criteria	Categories	Examples
Source	Semi-natural /natural	Agarose, chitosan, gelatin, Hyaluronic acid Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate)
	Synthetic	**Cellulose derivatives** [CMC, sodium CMC, HEC, HPC, HPMC, MC, hydroxyethylcellulose]
		Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly (methylvinylether-co-methacrylic acid), poly (2-hydroxyethyl methacrylate), poly (alkylcyanoacrylate), copolymer of acrylic acid and PEG]
		Others Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm) PVA, PVP, thiolated polymers
AqueousSolubility	Water-soluble	CP, HEC, HPC, HPMC (cold water)
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, trimethylated chitosan
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP
Potential bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylatedmetacrylate, poly (metacrylic acid)], CP, PC, PVA
	Electrostatic force	Chitosan

Bioadhesive polymers.
Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond forming groups, flexibility for interpenetration with mucus and epithelial tissue and visco-elastic properties

Ideal characteristics[12]
- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.

Permeation enhancers
The goal of designing penetration enhancers.[13] with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the effect induced in the membrane and of course, the mechanism of action. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients.

Table 5: Mucosal penetration enhancers and mechanisms of action[14-17]

S. no	Classification	Examples	Mechanism
1	Surfactants	**Anionic:** Sodium lauryl sulphate **Cationic:**Cetylpyridinium Chloride, cetyltrimethyl ammonium bromide **Nonionic:**Poloxamer, Brij, Span, Myrj, Tween **Bile salts:** Sodium glycodeoxycholate, Sodiumglycocholate, Sodium taurodeoxycholate, Sodium taurocholate, Azone	Perturbation of intercellular lipids, protein domain integrity
2	Fatty acids	Oleic acid, Caprylic acid, Lauric acid, Propylene glycol, Methyloleate, Phosphatidylcholine	Increase fluidity of phospholipid domain
3	Cyclodetrins	α, β, γ, Cyclodextrin, methylated β-cyclodextrins	Inlusion of membrane compounds
4	Chelators	EDTA, Citric acid, Sodium salicylate, Methoxy salicylates.	Interfere with Ca^{2+} Polyacrylates
5	Positively charged polymers	Chitosan, Trimethyl chitosan	Ionic interaction with negative charge on the mucosal suface
6	Cationic compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal suface

Research on buccal adhesive drug delivery systems
Several buccal adhesive delivery devices were developed at the laboratory scale by many researchers either for local or systemic actions. They are broadly classified in to
- ❖ Solid buccal adhesive dosage forms
- ❖ Semi-solid buccal adhesive dosage forms
- ❖ Liquid buccal adhesive dosage forms.

MATERIALS AND METHODS
HPMC K 100 M, Carbopol 934, Guar gum, HPMC K 15 M, PVP K 30, MCCP 101, Magnesium stearate, Aerosol, Esomeprazole, Sodium hydroxide, Potassium dihydroxide ortho phoaphate, Sodium chloride, Phenol red.

METHODOLOGY
Preformulation studies: *Drug-excipient compatability studies.*

Fourier Transform Infrared spectroscopic studies
A Fourier Transform – Infra Red spectrophotometer was used to study the non-thermal analysis of drug-excipient (binary mixture of drug:excipient 1:1 ratio) compatibility. The spectrum of each sample was recorded over the 450-4000 $cm^{-1.}$ Pure drug of Esomeprazole, Esomeprazole with physical mixture (excipients) compatibility studies were performed.

Evaluation of final blend
The final blend of all formulations was evaluated for Angle of repose, Compressibility index, Hausner ratio, Angle of repose, Hausner ratio.

Standarad graphs
Standard graph of Esomeprazole in Phosphate buffer pH 6.8
100 mg of Esomeprazole was dissolved in small amount of phosphate buffer and make the volume up to 100mL with phosphate buffer pH 6.8, from this primary stock (1mg/mL), 10 mL solution was transferred to another volumetric flask made up to 100 mL with Phosphate buffer pH 6.8. From this secondary stock 0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, mL was taken separately and made up to 10 mL with phosphate buffer pH 6.8 to produce 1, 2, 4, 6, 8, 10, 12 µg/mL respectively. The absorbance was measured at 302 nm using a UV spectrophotometer.

Standard graph of Esomeprazole in phosphate buffer pH 7.4

100 mg of Esomeprazole was dissolved in small amount of phosphate buffer and make the volume up to 100mL with phosphate buffer pH 7.4, from this primary stock (1mg/mL), 10 mL solution was transferred to another volumetric flask made up to 100 mL with phosphate buffer pH 7.4. From this secondary stock 0.1, 0.2, 0.4, 0.6, 0.8, 1.0,1.2 mL was taken separately and made up to 10 mL with phosphate buffer pH 7.4, to produce 1, 2, 4, 6, 8, 10.µg/mL respectively. The absorbance was measured at 302 nm using a UV spectrophotometer.

Solubility Studies

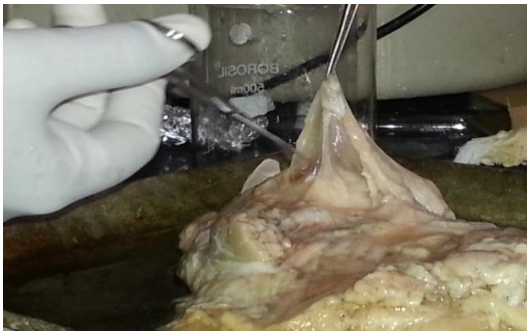
The solubility of Esomeprazole in phosphate buffer solution pH 6.8, pH 7.4 and water was determined by phase equilibrium method. An excess amount of drug was taken into 20 ml vials containing 10 mL of phosphate buffers (pH 6.8, and pH 7.4). Vials were closed with rubber caps and constantly agitated at room temperature for 24hrs using rotary shaker. After 24hrs, the solution was filtered through 0.2µm Whatman's filter paper. The amount of drug solubilized was then estimated by measuring the absorbance at 302 nm using a UV spectrophotometer. The standard curves for Esomeprazole were established in phosphate buffers (pH 6.8 and 7.4) and from the slope of the straight line the solubility of esomeprazole was calculated. The studies were repeated in triplicate (n = 3) and mean was calculated.

***Ex-vivo* permeation studies through Porcine buccal mucosa**

The aim of this study was to investigate the permeability of buccal mucosa to Esomeprazole. It is based on the generally accepted hypothesis that the epithelium is the rate-limiting barrier in the buccal absorption.

Tissue permeation

Buccal tissue was taken from Pigs slaughter-house. It was collected within 10 minutes after slaughter of pig and tissue was kept in Krebs buffer solution. It was transported immediately to the laboratory and was mounted within 2hrs of isolation of buccal tissue. The tissue was rinsed thoroughly using phosphate buffer saline to remove the adherent material. The buccal membrane from the tissue was isolated using surgical procedure. Buccal membrane was isolated and buccal epithelium was carefully separated from underlying connective tissue. Sufficient care was taken to prevent any damage to the epithelium.



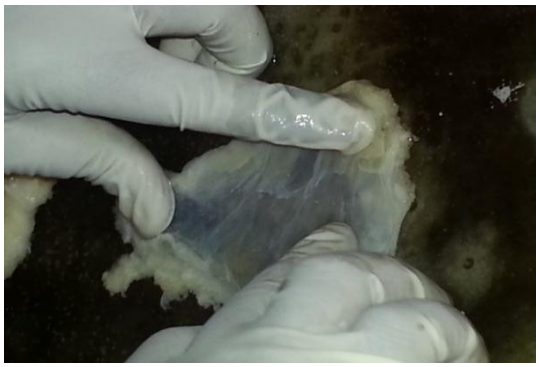


Table 6: Composition of Tyrode solution (Krebs buffer)

Ingredients	Quantity(gm)
Sodium chloride	8.0
Potassium chloride	0.2
Calcium chloride dehydrate	0.134
Sodium bicarbonate	1.0
Sodium dihydrogen orthophosphate	0.05
Glucose monohydrate	1.0
Magnesium chloride	0.1
Distilled water up to	1.0Litre

Formulation and preparation of tablets

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. ESOMEPRAZOLE was mixed manually with different ratios of HPMC K 15M, K100M, PVP K 30 and Guar gum, carbopol934 as mucoadhesive polymers and MCCP101 as diluent for 10 min. The blend was mixed with Magnesium stearate for 3-5 min and then compressed into tablets by the direct compression method using 6mm flat faced punches. The tablets were compressed using a sixteen station SISCO rotary tablet-punching machine. The mass of the tablets was determined using a digital balance (SHIMADZU) and thickness with digital screw gauge. Composition of the prepared bioadhesive buccal tablet formulations of Esomeprazole were given in Table 7.

Table 7: Composition of Esomeprazole buccal tablet
(Each tablet weight 100mg). (0.6% of aerosol was present in each tablet)

S.no	API(Drug) (mg)	Polymers (mg)				MCCP101	PVPK30	Mg.sterate
		Guargum	Carbopol934	HPMCK 15 M	HPMCK100M			
F1	20	10	-	10	-	53.8	5	0.6
F2	20	20	-	10	-	43.8	5	0.6
F3	20	30	-	10	-	33.8	5	0.6
F4	20	10				53.8	5	0.6
F5	20	20	10	-		43.8	5	0.6
F6	20	30	10	-		33.8	5	0.6
F7	20	-	10	10		53.8	5	0.6
F8	20	-	20	10		43.8	5	0.6
F9	20	-	30	10		33.8	5	0.6
F10	20	-	10	-	10	53.8	5	0.6
F11	20	-	20	-	10	43.8	5	0.6
F12	20	-	30	-	10	33.8	5	0.6

F1-F3 Indicates the formulation containing GUAR GUM + HPMC K 15M
F4- F6 Indicates the formulation containing GUAR GUM + HPMC K 100M
F7- F9 Indicates the formulation containing CARBOPOL 934P + HPMC K 15M
F10-F12 Indicates the formulation containing CARBOPOL 934P + HPMC K 100M

EVALUATION OF BUCCAL TABLETS

1. Physicochemical characterization of tablets

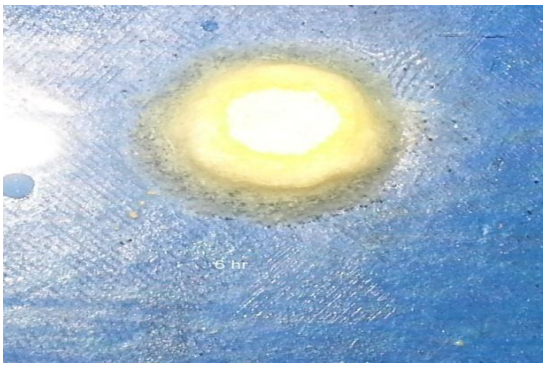
The prepared Esomeprazole buccal tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Swelling Studies

Buccal tablets were weighed individually (designated as W_1) and placed separately in Petri dishes containing 15 mL of phosphate buffer (pH 6.8) solution. At regular intervals (0.5, 1, 2, 3, 4, 5 and 6hrs), the buccal tablets were removed from the Petri dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W_2**)** *(Ritthidej et al., 2002).* This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Eq**.**

Swelling index = (W2 – W1)/W1* 100

0 hr



5 hr

Fig: 5: Swelling studies of Esomeprazole tablets

***Ex-vivo* bioadhesion strength:** The work of adhesion was determined from the area under the force distance curve.

The peak detachment force was maximum force to detach the tablet from the mucosa.

Force of adhesion = Bioadhesion strength x 9.8

$$\text{Bond strength} = \frac{\text{Force of adhesion}}{\text{surface area}} \times \frac{1}{1000}$$

Moisture absorption

Agar (5% m/V) was dissolved in hot water. It was transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface of the agar and incubated at 37°C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula

% Moisture Absorption = $\frac{\text{Final weight – Initial weight}}{\text{Initial weight}}$ x 100/

***Ex-vivo* residence time**

The *Ex-vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablet. The adhesive tablet was pressed over excised pig mucosa for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 500 ml of phosphate buffer, pH 6.8, at 37^0C. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm (Fig 6). The time for complete erosion or detachment from the mucosa was recorded.

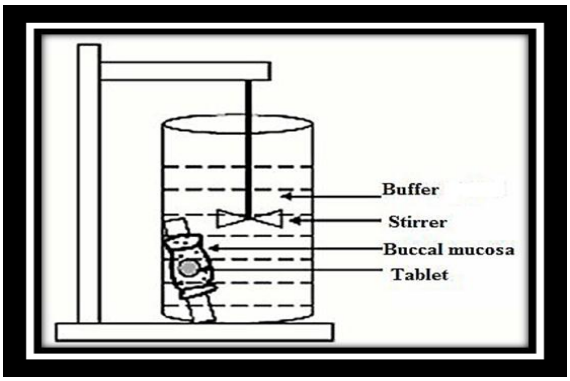


Fig 6: Schematic representation of *Ex-vivo* residence time study

***Ex-vivo* permeation of buccal tablets**

Stability studies

a) Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (BRUKER). Pure drug and optimized formulations were subjected to FTIR study. About 2-3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disc. The KBr disc is then subjected to FTIR studies. The samples were scanned from 400 to 4000cm-1.

Table 8: stability studies of optimized formulations

Stability studies	
Optimized formulations	**Accelerated Storage Conditions(45 days)**
F3	40°C±5°C/ 75% RH ±5%RH
F5	40°C±5°C/ 75% RH ±5%RH
F8	40°C±5°C/ 75% RH ±5%RH
F10	40°C±5°C/ 75% RH ±5%RH

RESULTS AND DISCUSSION

Esomeprazole is used to treat dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD/GERD) and Zollinger-Ellison syndrome. Esomeprazole has the very low biological half life of about 1.5 hr. Therefore formulating bioadhesive tablets in oral cavity is going to extend the release upto 6-7 hrs and also going to avoid the acidic environment in which the is unstable.

Esomeprazole tablets were prepared by direct compression technique, using natural polymers like guargum, hydrophilic polymers like HPMC K 100M and HPMC K 15M, Carbopol 934 P.

Determination of absorption maximum values

The UV-Visible Spectrum of Esomeprazole (10µg/ml) in 6.8 pH phosphate buffer was shown in fig 7. The maximum absorbance was observed at 302 nm.

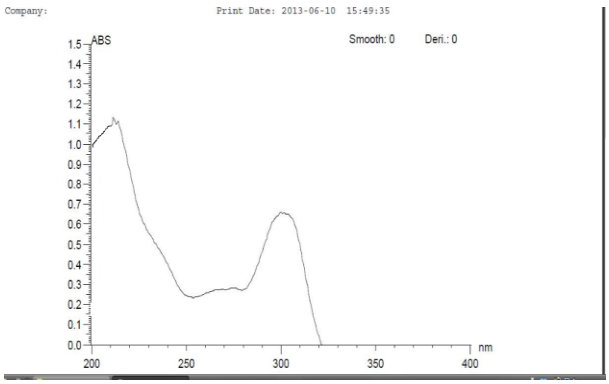


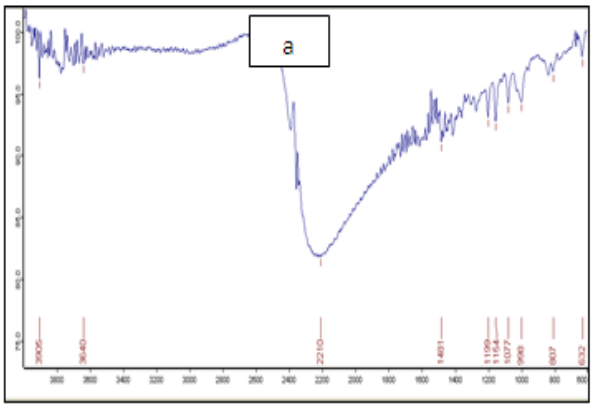
Figure 7: UV absorption spectrum of Esomeprazole in 6.8 pH phosphate buffer

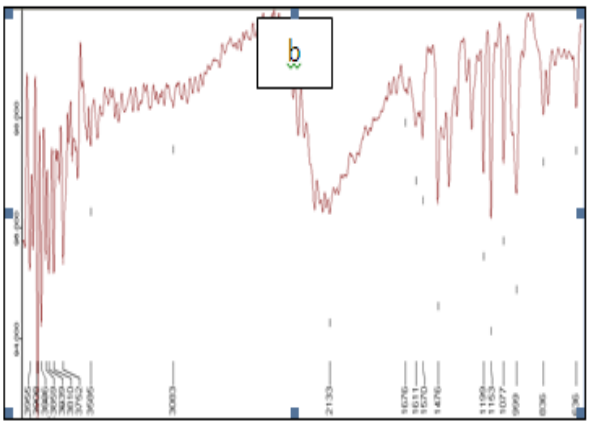
Preformulation study

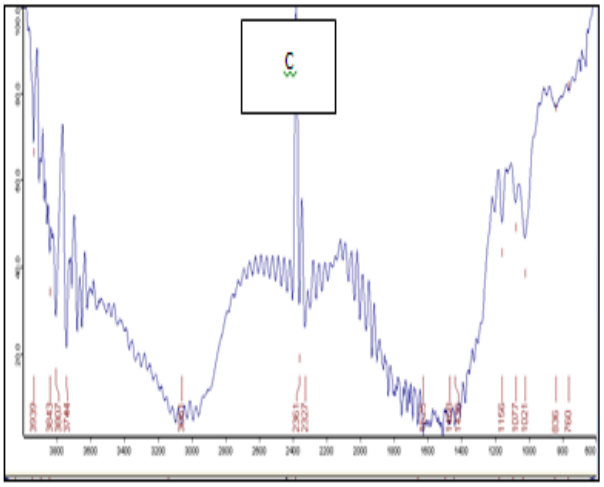
Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

FTIR Compatibility Studies

In the FTIR spectra of pure drug and formulation with other ingredients (different polymers) it is observed that the peaks of major functional groups of Esomeprazole, which are present in spectrum of pure drug, are observed. It means that there are no interactions between drug and other ingredients in a physical mixture and drug is compatible with other ingredients.







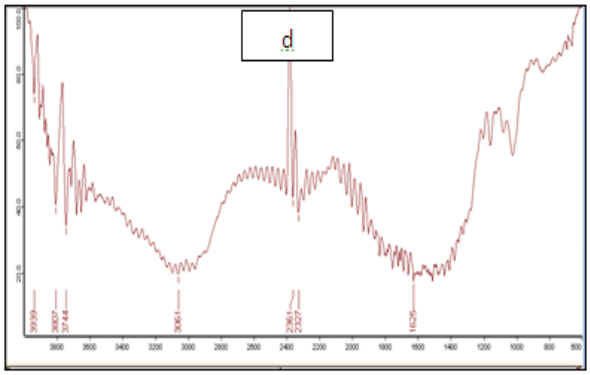


Figure 8: FT-IR spectra of

a) Esomeprazole,
b) F3 formulation (GUAR GUM +HPMC K 15 M),
c) F8 formulation (CARBOPOL 934P+HPMC K 15M),
d)F10 formulation (CARBOPOL 934 P +HPMC K100M).

Standard graph in phosphate buffer pH 6.8 (λ_{max} 302nm)

Standard graph of Esomeprazole was plotted as per the procedure in experimental method and its linearity is shown in **table 21 and fig 10.** The standard graph of Esomeprazole showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Table 9: Standard graph of Esomeprazole in phosphate buffer pH 6.8

Concentration(µg/mL)	Absorbance
0	0
1	0.0435
2	0.0728
4	0.1390
6	0.205
8	0.269
10	0.3301
12	0.390
14	0.454
16	0.511
18	0.571
20	0.632
22	0.715
24	0.800

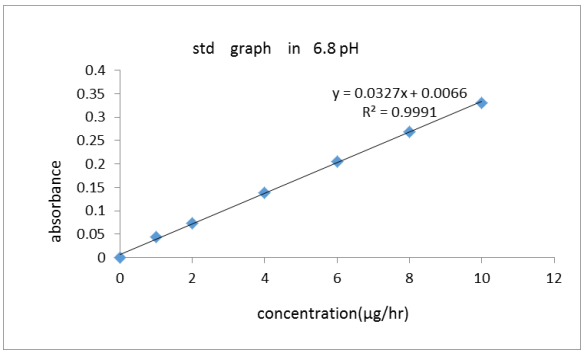


Fig 9: Standard graph of Esomeprazole in phosphate buffer pH 6.8

Standard graph in phosphate buffer pH 7.4 (λ_{max} 302nm)

Standard graph of Esomeprazole was plotted as per the procedure in experimental method and its linearity is shown in **Table 10 and Fig 10**. The standard graph of Esomeprazole showed good linearity with R^2 of 0.9972, which indicates that it obeys "Beer- Lamberts" law.

Table 10: Standard graph of Esomeprazole in phosphate buffer pH 7.4

Concentration (µg/mL)	Absorbance
0	0
1	0.074
2	0.115
4	0.205
6	0.283
8	0.375
10	0.454
12	0.545
14	0.644
16	0.721
18	0.825
20	0.906
22	0.965

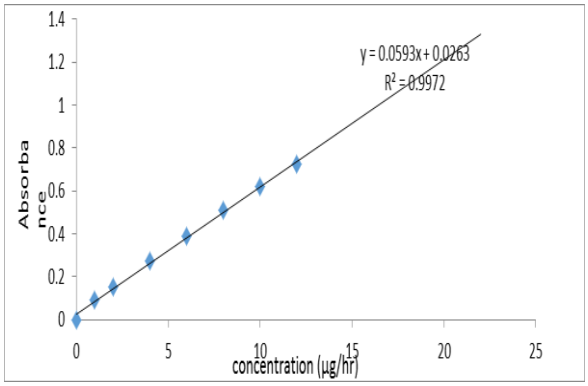


Fig 10: Standard graph of Esomeprazole in phosphate buffer pH 7.4

***Ex-vivo* permeation of drug solution through the porcine bucccal mucosa**

Ex-vivo permeation study of Esomeprazole drug solution through the porcine buccal mucosa was performed using Franz diffusion cell.

Table 11: *Ex-vivo* permeation of Esomeprazole drug solution through the porcine buccal mucosa

Time (hrs)	Cumulative amount of Esomeprazole permeated (mg)
0	0
0.5	0.92±0.01
1	2.05±0.06
2	3.46±0.04
3	5.17±0.03
4	7.29±0.04
5	10±0.04
6	13.27±0.03
FLUX	0.43 mg/hr/cm2

EVALUATION

EVALUATION OF PHYSICAL PROPERTIES OF PREPARED MIXTURE.

Table 12: Physical properties of prepared mixture

Formulation code	Angle of repose	Compresability index (%)	Hausner ratio
F1	24.92±0.09	13.05±0.03	1.15±0.02
F2	26.08±0.01	12.85±0.05	1.12±0.05
F3	23.54±0.03	13.72±0.08	1.14±0.02
F4	24.25±0.02	14.52±0.06	1.17±0.02
F5	26.38±0.03	11.85±0.02	1.15±0.03
F6	25.18±0.09	13.23±0.01	1.16±0.05
F7	24.92±0.08	12.42±0.07	1.12±0.07
F8	23.54±0.05	11.75±0.04	1.17±0.03
F9t	23.78±0.07	11.65±0.04	1.16±0.04
F10	24.79±0.05	11.45±0.05	1.15±0.02
F11	25.65±0.06	14.30±0.03	1.18±0.03
F12	27.75±0.08	13.22±0.01	1.19±0.05

Each value represents the mean ±SD (*n* =3).

PHYSICOCHEMICAL CHARACTERIZATION OF BUCCAL TABLETS

Table 13: Physico-chemical parameters of Esomeprazole tablets.

Formulation Code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	100.74 ± 0.61	2.55 ± 0.03	3.2±0.14	0.16	99.15 ± 0.44
F2	100.04 ± 0.80	2.55 ± 0.02	3.3±0.29	0.25	99.53 ± 0.75
F3	100.38 ± 0.71	2.54 ± 0.03	3.2±0.49	0.41	99.18 ± 0.92
F4	99.95±1.02	2.53±0.03	3.3±0.35	0.26	99.45±0.85
F5	100.45 ± 0.64	2.55 ± 0.02	3.4±0.17	0.34	98.77 ± 1.00
F6	99.91 ± 1.01	2.51 ± 0.02	3.5±0.28	0.21	98.96 ± 0.44
F7	99.98 ± 0.82	2.52 ± 0.01	3.9±0.24	0.23	98.81 ± 0.92
F8	100.34±0.59	2.54±0.004	3.7±0.25	0.15	99.75±0.95
F9	100.38 ± 0.80	2.55 ± 0.02	3.8±0.17	0.29	99.77 ± 0.72
F10	100.04 ± 0.71	2.54 ± 0.03	3.5±0.49	0.34	99.81 ± 0.44
F11	99.94 ±0.75	2.55 ± 0.02	4.0±0.19	0.38	99.15 ± 0.75
F12	99.99±0.74	2.58±0.04	4.3±0.15	0.48	99.19±0.85

Each value represents the mean ±SD (*n* =3).

***In vitro* drug release studies**

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Esomeprazole from different formulations varies with characteristics and composition of matrix forming polymers as shown in graphs.

Table 14: *In vitro* cumulative percentage drug release profile of Esomeprazole formulations with guar gum +HPMC K 15 M

Time (hrs)	Cumulative percentage drug release		
	F1	F2	F3
	Mean ± SD	Mean ± SD	Mean ± SD
0	0	0	0
1	53±0.03	48±0.06	44±0.02
2	64±0.04	63±0.03	56±0.04
3	76±0.06	72±0.05	62±0.06
4	99±0.01	89±0.04	79±0.04
5		97±0.03	86±0.03
6			98±0.03

Each value represents the mean ± SD (n=3).

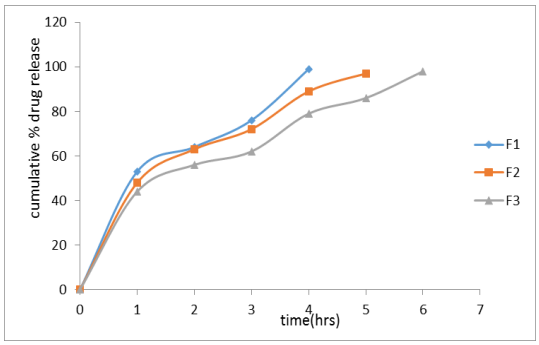


Fig 11: *In-vitro* cumulative % drug release of Esomeprazole with guargum + HPMC K 15 M

The release profile of formulations made of GUAR GUM & HPMC K 15 M (F1-F3) were given in *fig11*. more than 90% (t90%) of the drug released in 4 hrs for F1, 5 hrs for F2, & 6hrs for F3 formulation.F1 and F2 were unable to sustain the drug release for desired period of time. Drug: polymer ratio for F3 is 1:1.5, this F3 formulation was considered as an optimized formulation among all these formulations because it released maximum amount of drug and showed good swelling index properties.

Table 15: *In-vitro* cumulative percentage drug release profile of Esomeprazole formulations with guar gum + HPMC K 100 M.

Time (hrs)	Cumulative percentage drug release		
	F4	F5	F6
0	0	0	0
1	49±0.02	37±0.06	37±0.01
2	57±0.06	48±0.04	46±0.03
3	74±0.04	59±0.03	61±0.03
4	87±0.03	64±0.08	74±0.04
5	98±0.02	86±0.06	78±0.06
6		98±0.02	87±0.03

Each value represents the mean ± SD (n=3).

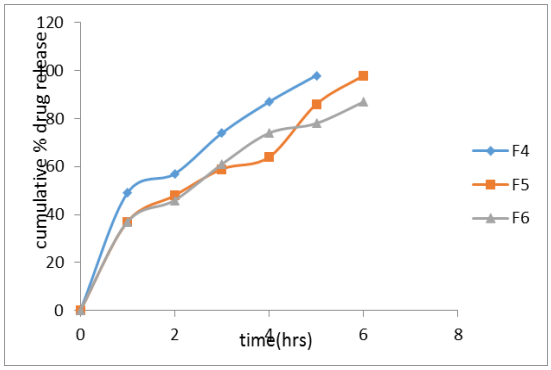


Fig 12: *In-vitro* cumulative % drug release of Esomeprazole buccal tablets with GUAR GUM + HPMC K 100 M.

The release profile of formulations made of GUAR GUM & HPMC K 100M (F4-F6) were given in *fig* .more than 90% (t90%) of the drug released in 4 hrs for F4, 6

hrs for F5, & less than 90% in 6hrs for formulation F6. .F4 was unable to sustain the drug release for desired period of time. Drug: polymer ratio for F5 is 1:1, this F5 formulation was considered as an optimized formulation among all these formulations because it released maximum amount of drug in desired period of 6hrs and showed good swelling index properties. with increase in polymer ratio the invitro drur release was decreased such a case is seen in F6 formulation.

Table 16: *In-vitro* cumulative percentage drug release profile of Esomeprazole formulations with CARBOPOL 934 + HPMC K 15 M.

Time (hrs)	Cumulative percentage drug release		
	F7	F8	F9
	Mean ± SD	Mean ± SD	Mean ± SD
0	0	0	0
1	48±0.02	47±0.03	44±0.02
2	59±0.01	59±0.04	56±0.03
3	77±0.06	72±0.06	68±0.02
4	95±0.04	89±0..03	85±0.05
5	98±0.03	91±0.06	93±0.06
6		98±0.01	95±0.02

Each value represents the mean ± SD (n=3).

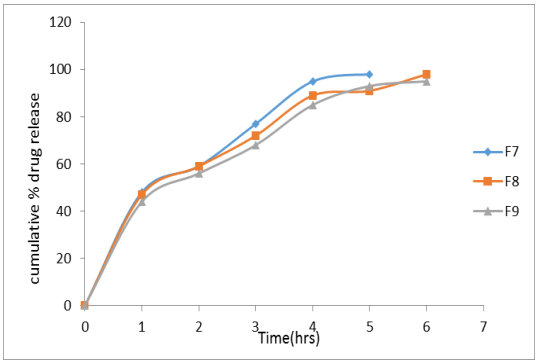


Fig 13: *In-vitro* cumulative % drug release of Esomeprazole buccal tablets with CARBOPOL 934 P + HPMC K 15M.

The release profile of formulations made of CARBOPOL 934P & HPMC K 15M (F7-F9) were given in *fig15* .more than 90% (t90%) of the drug released in 5 hrs for F7, 6 hrs for F8 & F9.F7 was unable to sustain the drug release for desired period of time. Drug:polymer ratio for F8 is 1:1, this F8 formulation was considered as an optimized formulation among all these formulations because it released maximum amount of drug in desired period of 6hrs and showed good swelling index properties. with increase in polymer ratio the invitro drur release was decreased such a case is seen in F9 formulation

Table 17: *In-vitro* cumulative percentage drug release profile of Esomeprazole formulations with the combinations of CARBOPOL 934 +HPMC K 100M

Time (hrs)	Cumulative percentage drug release		
	F10	F11	F12
	Mean ± SD	Mean ± SD	Mean ± SD
1	46±0.01	41±0.05	36±0.03
2	54±0.02	53±0.03	47±0.02
3	73±0.03	68±0.04	59±0.04
4	84±0.02	82±0.02	68±0.09
5	91±0.04	89±0.04	79±0.04
6	98±0.01	94±0.03	85±0.05

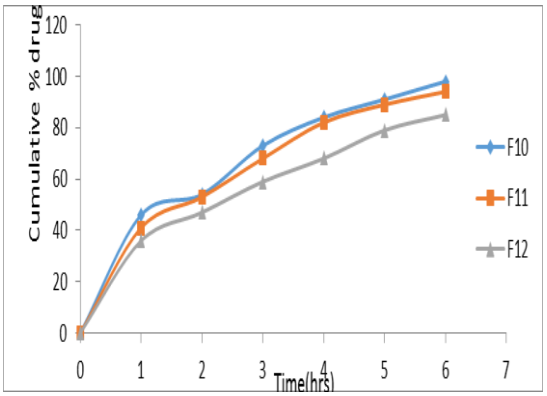


Fig 14: *In-vitro* cumulative % drug release of Esomeprazole buccal tablets with combinations of CARBOLPL 934P and HPMC K 100 M.

***Ex-vivo* bioadhesive strength measurement**

In all the formulations, as the polymer concentration increased, the mucoadhesion was increased. The bioadhesive strength was strong in the formulations containing carbopol 934 than in formulaion containing guar gum.

Table 18: *Ex-vivo* residence time, Moisture absorption, Surface pH, Bioadhesive strength values of selected formulations

Formulation code	*Ex-vivo* residence time	Moisture absorbance	Surface pH	Bioadhesive strength	
				Peakdetachment force(N)	Work of adhesion(mJ)
F3	7 Hrs 35 min	35.28 ± 0.25	6.8±0.16	2.3±0.52	9.42±6.28
F5	7 Hrs 55 min	42.28 ± 0.25	6.7±0.53	3.2±0.52	12.42±6.28
F8	8 Hrs 15 min	54.28 ± 0.25	6.9±0.45	5.3±0.52	25.42±6.28
F10	8 Hrs 25 min	57.08 ± 0.30	6.8±0.152	7.2±0.52	45.42±6.28

Each value represents the mean ± SD (n=3).

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