PREPARATION AND EVALUATION OF ACEBUTOLOL MUCOADHESIVE FILMS

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ABSTRACT:

Mucoadhesive drug delivery offers a safe and easy method of drug utilization, because drug absorption can be promptly terminated in case of toxicity by removing the dosage form. A mucoadhesive film for systemic administration of Acebutolol has been developed using HPMC K4M, HPMC E5, HPMC E15, Carbopol and Eudragit and ethanol by solvent casting method. The prepared films characterized by means of film thickness, swelling capacity, Disintegration, drug release, weight variation, folding endurance, etc. The in vitro disintegration time and dissolution time of the optimized formulation (F12) was found to be 9 seconds and 99.23 % within 8 mins respectively. FTIR studies showed no drug polymer interaction takes place. These results revealed that mucoadhesive films of Acebutolol could be formulated for immediate drug release to ensure symptomatic relief which leads to improved patient compliance in the management of hypertension.

Key words: *Acebutolol, Solvent casting, HPMC E15, FTIR, Mucoadhesive, Carbopol.*

INTRODUCTION:

Over the last two decades mucoadhesion becomes of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (with in gastro intestinal tract) or systemic delivery, by retaining a formulation in intimate contact with absorption site (in the buccal cavity). Mucoadhesion may be defined as a state in which two materials, one of which mucus or a mucous membrane, is held together for extended period of time (Smart JD 2005) These mucoadhesive drug delivery systems improve the bioavailability of the drugs by bypassing the first pass effects and avoiding the pre systemic elimination of the drug within the GI tract (Shojaei AH et al., 2001) Out of the various sites available for mucoadhesive drug delivery, buccal mucosa is the most suited one for local as well as systemic delivery of drugs. It's anatomical and physiological features like presence of smooth muscles with high vascular perfusion, avoidance of hepatic first pass metabolism and hence can potentially improve bioavailability are the unique features which make it as an ideal route for mucoadhesive drug delivery. Moreover, these dosage forms are economic and patient-friendly. Mucoadhesive films are retentive dosage forms and release drug directly into a biological substrate. Furthermore, films have improved patient compliance due to their small size and reduced thickness, compared for example to lozenges and tablets (Mona S et al., 2008). Common oral viral infections cause primary herpetic gingivostomatitis, or oral herpes. In some hosts, it becomes latent and may periodically recur as a common cold sore. (McCullough MJ et al., 2005)Specific oral bacterial species have been implicated in oral diseases such as caries and periodontitis and in several systemic diseases, such as bacterial endocarditis, aspiration pneumonia, osteomyelitis in

children, preterm low birth weight, and cardiovascular disease.

In the present investigation, the drug Acebutolol has been selected for the formulation mucoadhesive films. Acebutolol is one of the commonly prescribed angiotensin drugs. It has low bioavailability (40-60%) due to hepatic first pass metabolism (Kusuma D et al., 2017). Hence to improve its therapeutic efficacy and bioavailability the drug may be administered by buccal route through buccal films. Mucoadhesive delivery of Acebutolol may circumvent hepatic first pass metabolism and improve bioavailability. Hence the present work deals with the formulation and characterization of mucoadhesive buccal film of Acebutolol using mucoadhesive polymer.

MATERIALS AND METHODS:

Acebutolol procured from goldfish pvt. Ltd, HPMC K4M, HPMC E15, HPMC E5, Eudragit procured from S.D. Fine chem. Ltd., Mumbai. Carbopol, PEG 200 procured from LOBA Chemie Pvt. Ltd. Mumbai. Aspartame, Citric acid procured from Thermo Fisher Scientific India Pvt. Ltd. Mumbai. Straw berry procured from MSN Labs Ltd., Hyderabad.

Methods:

Preparation:

The mucoadhesive films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different polymers. The polymeric solutions are levigation which served the purpose of plasticizer as well as penetration enhancer. The solution was mixed occasionally to get semisolid consistency. Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles. The dried films were separated and the backing membrane used was aluminium foil. Then the formulations were stored in desiccators until further use (Marina K et al., 2010).The formulation of mucoadhesive of films in shown in Table 1, 2, and 3.

Evaluation parameters:

Thickness and weight variation

The thickness of the film at three different points was determined using thickness gauge and the films were then weighed individually using digital balance to determine the weight of each film taken out from the casted film. The films were subjected to weight variation by individually weighing ten randomly selected films. Such determinations were carried out for each formulation (Bharti SN 2007).

Folding endurance

Strip of prepared film (4 × 4cm) was folded repeatedly at the same place till it broke. The number of times the film could be folded at the place without breaking or cracking is equal to the value of folding endurance (Mario J et al., 2010).

Tensile strength (Kg/cm^2) (Sahini J et al., 2008) the instrument used to measure the tensile strength designed in our laboratory especially for this project work. The instrument is a modification of chemical balance used in normal laboratory. One pan of the balance was replaced with one metallic plate having a hook for attaching the film. The equilibrium of the balance was adjusted by adding weight to the pan of balance. The instrument was modified in such a way that the film can be fixed up

between two hooks of horizontal beams to hold the test film. A film of 2.5 cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan.

$$T = \frac{M \times g}{B \times t} \text{ Dynes/cm}^2$$

Surface pH

To determine surface pH, 4^2 films of each formulation were allowed to swell for two hours on the surface of an agar plate. Surface pH was measured by using pH paper placed on the surface of the swollen film as per reported method. A mean of three readings was recorded (Nappinnai 2008).

Swelling index (Bala Subramanian J et al., 2012**)** mucoadhesive film of 4×4cm area from each formulation was taken. Initial weight of the film was taken by using single pan balance (w1gm) and it was placed in a petri dish containing 50 ml of water. After definite interval film was removed and blotted with filter paper and weighed again (w2gm).The swelling index was calculated from the formula,

$$\frac{W2 - W1}{W1} \times 100$$

Where, w_2 =wet weight of the film, W_1=dry weight of the film

Drug content uniformity

A film of 4×4cm area equal diameter were taken in separate buffer was added and continuously stirred. The solutions were filtered, suitably diluted and analyzed in a UV Spectrometer. The average of drug content of three films was taken as final reading (Noha AN et al., 2003).

***In vitro* disintegration studies**

Disintegration test was performed to ensure the disintegration of the mucoadhesive film in buffer. One film from each formulation was introduced into one tube of disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in a beaker containing buffer and the apparatus was operated until the film disintegrated (Devries ME et al., 1991).

Percent Elongation

This mechanical property was evaluated using the Instron universal testing instrument (Model F. 4026, Instron Ltd., Japan) with a 5 kg load cell. The percentage increase in the length of a film (L_2), when it is pulled under standard conditions of stress just before the point of break is known as percent elongation. The initial length of a film is L_1, the increase in length is (L_2-L_1). It is measured in terms of percentage. Percent elongation and tensile strength was carried for only 4 best formulations (Kusum Devi V et al., 2003).

$$\text{Percent elongation} = \frac{(L_2 - L_1)}{L_1 \text{ X Cross sectional area}} \text{ X } 100$$

***In vitro* dissolution studies**

The in-vitro dissolution studies were conducted using buffer (300 mL). The dissolution studies were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) at 37 ± 0.5 °C and at 50 rpm using specified dissolution media. Each film with dimension (4 cm^2 of each) was placed on a stainless-steel wire mesh with sieve opening 700µm. The film sample placed on the sieve was submerged into dissolution media. Samples were

withdrawn at regular time intervals and filtered through 0.45µm Whatman filter paper and were analyzed spectrophotometrically. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment. The dissolution testing studies were performed in triplicate for all the batches (Satish babu BK and Srinivasan BP, 2008).

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons. (Khanna R et al., 1997).

SEM studies:

The surface characteristics of film were determined by scanning electron microscopy (SEM) (HITACHI, S-3700N). Photographs were taken and recorded at suitable magnification (Parmar VJ et al., 2010).

Stability studies

The stability study of the optimized mucoadhesive films was carried out under different conditions according to ICH guidelines. The film was packed in the aluminium foil and stored in a stability chamber for stability studies. Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The patches were characterized for the drug content and other parameters during the stability study period (Avachat AM et al., 2013).

RESULTS AND DISCUSSION:

Preparation of mucoadhesive films of Acebutolol:

Mucoadhesive films of Acebutolol were prepared by solvent casting technique is shown figure 1 with the use of mucoadhesive polymers such as Carbopol, Eudragit . The prepared films were evaluated for different physicochemical tests such as weight variation, thickness, content uniformity, swelling index, surface pH, *in vitro* disintegration time, and *in vitro* drug release studies.

Evaluation of mucoadhesive films:

Thickness of all mucoadhesive films was measured with Digital Vernier calliper (Mitutoyo) (Table 4). The optimized film has thickness of 0.221±0.03mm. A result of thickness measurement showed that as the concentration of polymer increases, thickness of mucoadhesive film also increases. A result showed that as the concentration of polymer increases weight of film also increases. The weight variation of the optimized formulation was in the range of 21±0.60mm, which was acceptable.

The swelling of the films were observed in pH 6.8 phosphate buffer solution. F12.Swelling was more pronounced in films F12 which containing HPMC and Carbopol it is shown in Table 4.

The disintegrating time of all the formulations was ranges from 8 to 16 sec. The disintegration time of optimized

formulation (F12) was found to be 8 sec, which was very less and desirable for quick onset of action it is shown in figure 2.

Drug content in the mucoadhesive films was evaluated and the values were found to be between 91.45±0.45 to 99.23±0.55%. Surface pH of all mucoadhesive films prepared by using different polymers was found to be in the range of 6.14 to 6.94 pH .Results revealed that optimized formulation (F12) showed better tensile strength (11.7 g/cm^2) and moderate % elongation (9.8). folding Endurance of mucoadhesive film increases. The optimized film (F12) has folding endurance value of 119±4, which was desirable. Moisture content of mucoadhesive films ranges from 4.08 to 4.89% these are shown in Table 5.

The cumulative % drug release for the formulations F1 to F15 are tabulated in Table 7, 8, 9 and Figure 3,4,5. The optimized formulation (F12) shows highest Percent of drug release 99.89±5.25 by the end of 9 min.

The optimized formulation of Acebutolol mucoadhesive film (F12) was best explained by first order, it is shown in Table 10 as the plots showed the highest linearity (r2 = 0.994), followed by, Higuchi (r2 = 0.974), Korsmeyer Peppas (r2=0.969) and then zero order (r2 = 0.928). The corresponding plot for the Korsmeyer-Peppas equation of the optimized formulation F 12 indicated good linearity. The release exponent 'n' was found to be for F12 is 0.71, which appears to indicate Fickian diffusion and may indicate that the drug release was controlled by first order release are shown in figures 6-9 .

FTIR and SEM:

On performing FTIR and SEM studies it was concluded that there is no interaction between drug, excipients and optimized formulation.

Stability studies:

Optimized formulation was selected for stability studies on the basis of high cumulative % drug release. Disintegrating time, drug content and In vitro drug release studies were performed for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation F12 is stable and retained their original properties with minor differences which depicted in the table 11.

CONCLUSION:

The present study indicates a good potential of erodible mucoadhesive films containing Acebutolol for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. The results of the study show that therapeutic level of Acebutolol can be delivered by buccal cavity. It may concluded that the formulation F12 shows good swelling, good flexibility, a convenient residency time and promising sustained drug release, thus seems to be a potential candidate for development of mucoadhesive film for effective therapeutic use. The mechanism of drug release was diffusion followed by first order kinetics. FTIR studies showed no drug polymer interaction takes place. These results revealed that mucoadhesive films of Acebutolol could be formulated for immediate drug release to ensure symptomatic relief which leads to improved patient compliance in the management of hypertension.

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Figure 1: Preparation of Acebutolol mucoadhesive films

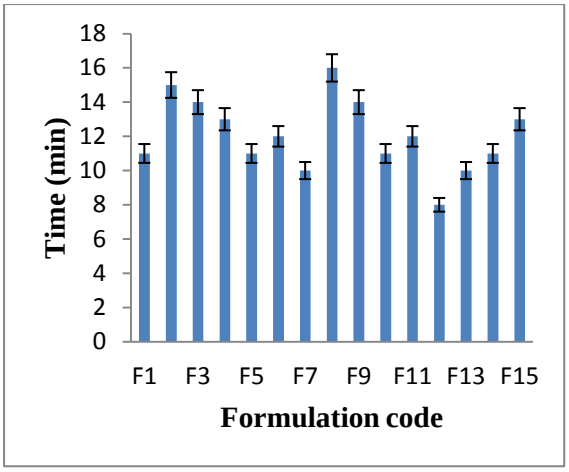

Figure 2: *In vitro* disintegrating time of all Formulations F1-F15

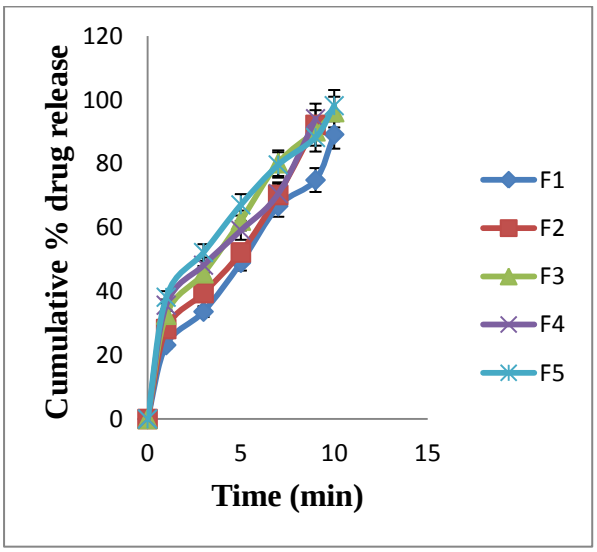

Figure 3 : Cumulative % Drug Release of formulation F1-F5

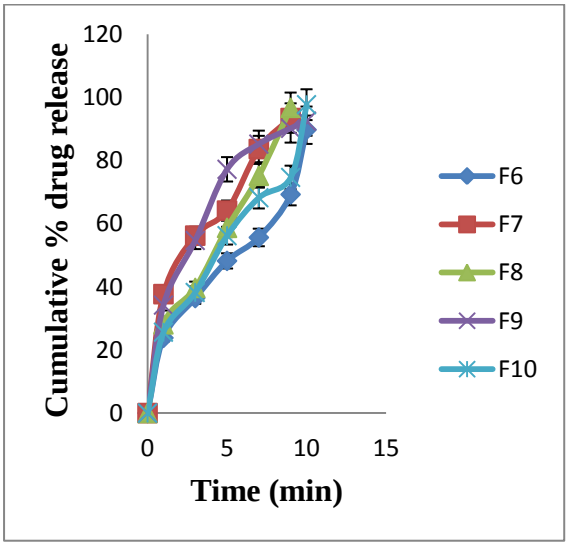

Figure 4 : Cumulative % Drug Release of formulation F6-F10

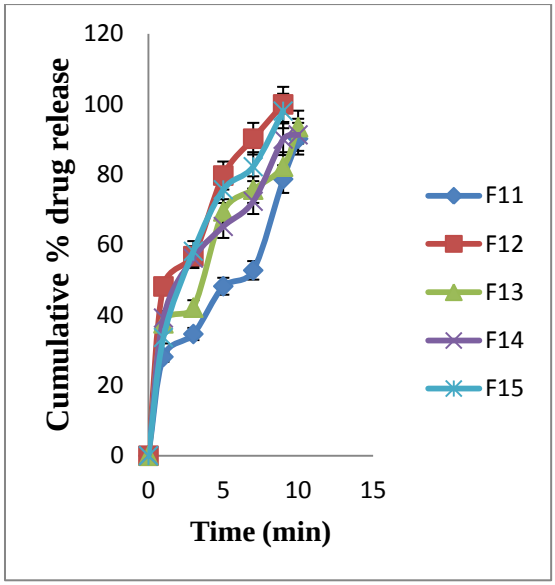

Figure 5 : Cumulative % Drug Release of formulation F11-F15

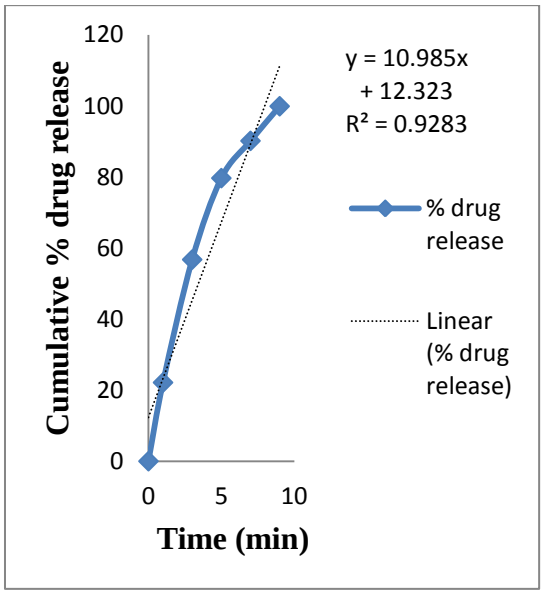

Figure 6 : Zero order kinetic plot of optimized formulation (F12)

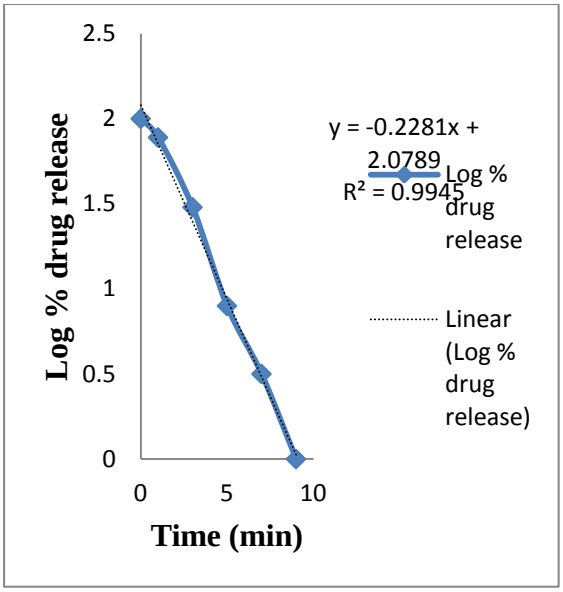

Figure 7: First order kinetic plot of optimized formulation (F12)

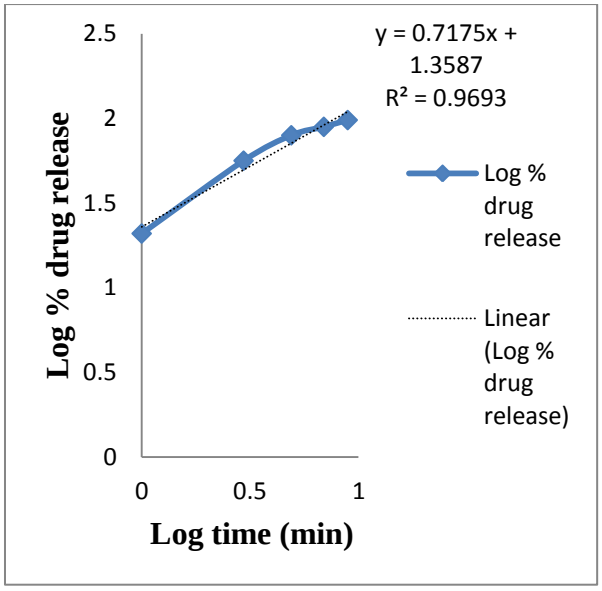

Figure 9 : Korsmeyer–Peppas kinetic plot of optimized formulation (F12)

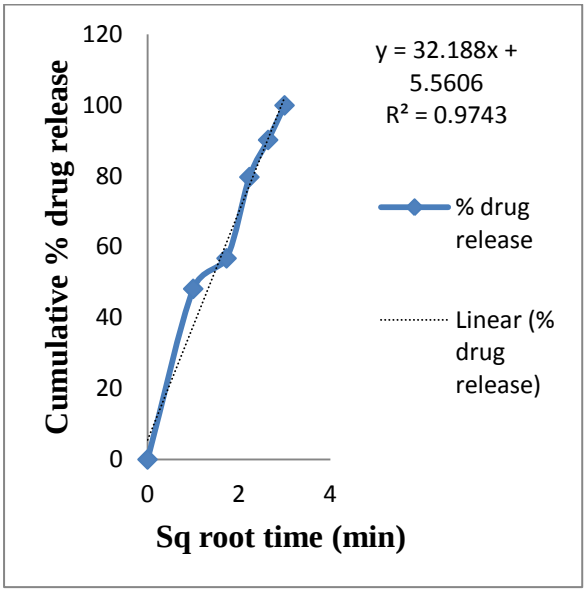

Figure 8: Higuchi kinetic plot of optimized formulation (F12)

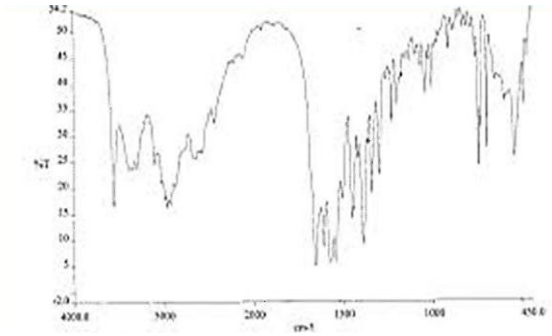

Figure 10 : FTIR Spectroscopy of Acebutolol Pure Drug

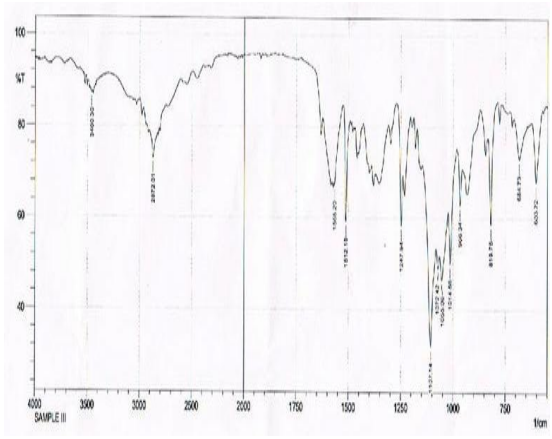

Figure 11 : FTIR Spectroscopy Of Acebutolol optimized mucoadhesive films(F12)

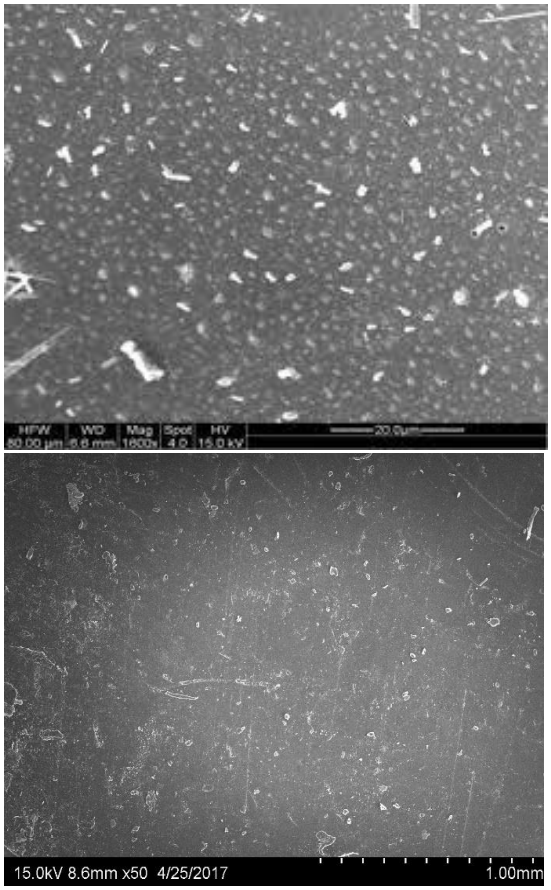

Figure 12: Scanning electron micrograph of Acebutolol optimized mucoadhesive films

Table 1: Formulation of mucoadhesive films by using HPMC K4M

INGREDIENTS	F1	F2	F3	F4	F5
Acebutolol	200	200	200	200	200
HPMC K4M	100	100	100	100	100
Carbopol	-	50	-	50	-
Eudragit	50	-	50	-	50
PEG 200	20	20	20	20	20
Aspartame	5	5	5	5	5
Citric acid	25	25	25	25	25
Strawberry	Q.S	Q.S	Q.S	Q.S	Q.S
Water	Q.S	Q.S	Q.S	Q.S	Q.S

Table 2: Formulation of Acebutolol by using HPMC E15

INGREDIENTS	F6	F7	F8	F9	F10
Acebutolol	200	200	200	200	200
HPMC E 15	100	100	100	100	100
Carbopol	50	-	50	-	50
Eudragit	-	50	-	50	-
PEG 200	20	20	20	20	20
Aspartame	5	5	5	5	5
Citric acid	25	25	25	25	25
Strawberry	Q.S	Q.S	Q.S	Q.S	Q.S
Water	Q.S	Q.S	Q.S	Q.S	Q.S

Table 3: Formulation of Acebutolol by using HPMC E5

INGREDIENTS	F11	F12	F13	F14	F15
Acebutolol	200	200	200	200	200
HPMC E 5	100	100	100	100	100
Carbopol	-	50	-	50	-
Eudragit	50	-	50	-	50
PEG 200	20	20	20	20	20
Aspartame	5	5	5	5	5
Citric acid	25	25	25	25	25
Strawberry	Q.S	Q.S	Q.S	Q.S	Q.S
Water	Q.S	Q.S	Q.S	Q.S	Q.S

Table 4: Evaluation parameters of Acebutolol Mucoadhesive films

Formulation Code	Weight (mg)	Thickness (mm)	Disintegration time (sec)	Swelling index (%)
F1	24± 0.65	0.224 ±0.05	11±0.22	27±0.30
F2	27± 0.68	0.223 ±0.05	15±0.26	29±0.30
F3	25± 0.65	0.225 ±0.06	14±0.24	40±0.45
F4	26± 0.67	0.226 ±0.06	13±0.24	41±0.45
F5	23± 0.64	0.224 ±0.05	11±0.22	36±0.38
F6	24± 0.65	0.223 ±0.05	12±0.22	38±0.40
F7	25± 0.65	0.226 ±0.06	10±0.22	27±0.18
F8	22± 0.63	0.224 ±0.05	16±0.25	20±0.21
F9	27± 0.68	0.223 ±0.05	14±0.24	22±0.24
F10	24± 0.65	0.225 ±0.06	11±0.22	24±0.26
F11	26± 0.67	0.223 ±0.05	12±0.22	28±0.30
F12	21± 0.60	0.221 ±0.03	8±0.21	48±0.35
F13	23± 0.64	0.224 ±0.05	10±0.22	29±0.30
F14	24± 0.65	0.225 ±0.06	11±0.22	27±0.29
F15	22± 0.63	0.226 ±0.06	13±0.24	24±0.26

Table 5: Evaluation parameters of Acebutolol Mucoadhesive films

Formulation Code	Drug Content (%)	Moisture content (%)	Folding Endurance (count)	Surface pH
F1	92.02± 0.45	4.87± 0.48	97±1	6.23 ±0.3
F2	91.45± 0.45	4.70± 0.32	95±2	6.14 ±0.2
F3	94.63± 0.48	4.72± 0.33	92±3	6.20 ±0.3
F4	95.24± 0.48	4.64± 0.30	91±1	6.32 ±0.4
F5	97.17± 0.52	4.34± 0.33	101±2	6.30 ±0.4
F6	93.89± 0.46	4.75± 0.34	105±5	6.45 ±0.5
F7	96.36± 0.47	4.66± 0.31	96±1	6.56 ±0.6
F8	94.78± 0.48	4.54± 0.28	98±2	6.74 ±0.8
F9	93.45± 0.46	4.38± 0.19	110±3	6.84 ±0.9

F10	92.28± 0.45	4.66± 0.31	114±1	6.79 ±0.8
F11	91.79± 0.45	4.89± 0.48	106±2	6.67 ±0.7
F12	**99.23**± 0.55	**4.08**± 0.11	**119**±4	**6.94** ±0.9
F13	94.66± 0.48	4.66± 0.31	101±2	6.54 ±0.6
F14	95.20± 0.48	4.52± 0.24	108±1	6.79 ±0.8
F15	98.37± 0.52	4.68± 0.32	99±3	6.37 ±0.4

Table 6 : Tensile Strength and Percent Elongation

FORMULATION CODE	TENSILE STRENGTH (g /cm^2)	PERCENT ELONGATION (%)
F12	11.7	9.8

Table 7 : *In vitro* drug release Studies of Formulation F1 to F5

Time(min)	F1	F2	F3	F4	F5
0	0±0	0±0	0±0	0±0	0±0
1	23.17±2.05	28.19±2.15	32.67±2.16	35.66±2.20	38.16±2.30
3	33.64±2.16	39.46±2.20	45.67±2.86	48.19±2.89	52.18±2.98
5	48.96±2.89	52.19±2.98	62.19±3.42	59.11±3.20	67.11±3.46
7	66.71±3.45	70.20±4.08	80.16±4.38	70.62±4.08	79.61±4.37
9	74.88±4.10	92.16±5.04	90.16±5.02	94.11±5.10	88.21±4.90
10	89.17±4.98		96.18±5.12		98.19±4.19

Table 8 : *In vitro* drug release Studies of Formulation F6 to F10

Time (min)	F6	F7	F8	F9	F10
0	0±0	0±0	0±0	0±0	0±0
1	23.81±2.09	37.66±2.30	28.11±2.10	34.19±2.24	25.61±2.10
3	36.42±2.15	56.19±3.06	39.64±2.31	54.66±3.04	38.19±2.31
5	48.19±2.89	64.11±3.42	58.66±3.19	77.19±4.18	56.18±3.06
7	55.61±3.05	83.61±4.50	75.14±4.12	85.18±4.89	68.20±3.51
9	69.24±3.52	93.42±5.04	96.66±5.11	90.16±5.02	74.62±4.11
10	89.72±4.98			92.45±5.04	97.66±5.15

Table 9: *In vitro* drug release Studies of Formulation F7 to F15

Time(min)	F11	F12	F13	F14	F15
0	0±0	0±0	0±0	0±0	0±0

1	28.11 ±2.10	48.13±2.90	37.64±2.30	39.16 ±2.32	33.61 ±2.27
3	34.61 ±2.28	56.74±3.06	42.11±2.82	56.17 ±3.06	58.12 ±3.08
5	48.19 ±2.90	79.66±4.21	69.46±3.53	65.18 ±3.42	75.64 ±4.11
7	52.71 ±3.02	90.14±5.02	75.66±4.11	72.34 ±4.08	82.19 ±4.49
9	78.66 ±4.20	99.89±5.25	82.19±4.49	89.99 ±4.98	98.02 ±5.08
10	90.14 ±5.02		93.44±5.04	91.24 ±5.03	

Retest Time For Optimized formulation (F12)	**Disintegrating Time (sec)**	**Drug Content**	**In vitro drug release profile (%)**
0 days	8	99.23	99.89
30 days	8	99.02	99.26
60 days	9	98.89	98.74
90 days	10	98.10	98.36
120 days	10	97.24	98.12
180 days	11	97.03	97.79

Table 10: Release order kinetics for optimized release

Formula Code	**Zero Order**		**First Order**		**Higuchi**		**Korsmeyer-Peppas**	
	R^2	**K**	**R^2**	**K**	**R^2**	**K**	**R^2**	**N**
F12	0.928	10.98	0.994	0.228	0.974	32.18	0.969	0.717

Table 11: Physicochemical characteristics of optimized formulation stored at 40 ±2ºC /75 ±5%RH