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PREPARATION AND EVALUATION OF BUCCAL FILMS OF CARVEDILOL

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Abstract:

An impermeable backing layer was made of ethyl cellulose, and buccal films containing carvedilol were made using the polymers carbopol-P 934 (CP), sodium carboxymethyl cellulose (SCMC), hydroxypropyl methyl cellulose-100K cps (HPMC), and polyvinyl pyrrolidone K 30 (PVP). Through the use of Fourier transform infrared spectroscopy (FTIR), the compatibility of the medication and the polymer was examined. The generated carvedilol films were assessed for surface pH, swelling percentage, thickness, weight variation, hardness, friability, and active ingredient concentration.

Keywords: *Carvedilol, Carbopol-P 934, buccal, films.*

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INTRODUCTION:

Hypertension is a highly prevalent disorder all over the world requiring prolonged treatment. Usually, therapy is for lifetime. Conventional oral therapies, such as tablets are convenient but for certain drugs that encounter bioavailability problems due to one or the other reasons, a convenient alternative route is much needed [1]. Carvedilol is one such drug that suffers from the problem of bioavailability mainly due to first-pass metabolism. It is an alpha and beta blocker used to treat high blood pressure and heart failure. Though it is rapidly absorbed after an oral administration, the bioavailability of carvedilol is 25%–35% as it undergoes stereo-selective first-pass metabolism and will be eliminated from body through urine (16%) and feces (60%). Carvedilol is a weak base with pK_a value 7.7–7.9 and log PC (partition coefficient) value of 3.967 which indicates sufficient lipophilicity to pass through any biological membrane including buccal membranes [2].

Buccal drug delivery systems offer a promising route for drug delivery not only to the buccal mucosa for the treatment of oral conditions but also for systemic delivery by absorption through the mucosa to the systemic circulation at a predetermined and controlled rate [3]. Absorption of therapeutic agents from the oral mucosa overcomes premature drug degradation due to enzyme activity and pH of the gastrointestinal tract, avoids active drug loss due to first-pass hepatic metabolism and thus improves systemic bioavailability. In addition, the buccal mucosa permits a prolonged retention of a dosage form especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the sublingual route [4].

MATERIALS AND METHODS:

Materials:

Carvedilol was a gift sample from Micro labs, Bangalore, India. Polyvinyl pyrrolidone (PVP)-K 90, hydroxy propyl methyl cellulose (HPMC), and carbopol 934P were purchased from CDH, New Delhi, India; methanol and PEG 400 were purchased from Rankem, New Delhi, India.

Methods:

Fabrication of carvedilol buccal films:

Ethanol at a 70% (v/v) concentration was used to dissolve the necessary amount of polymers. After levigation with 30% w/w propylene glycol, which acted as a plasticizer and penetration enhancer, 20 mg of Carvedilol was added to the polymeric solutions. The solution was agitated at regular intervals until it reached a semisolid state. Next, a bath sonicator was used to agitate the fluid and break up the bubbles [5]. Overnight, at room temperature, a 3.6 cm 'O' ring was used to cast an item onto a glass surface, and the solvent was allowed to evaporate while being confined by covering the ring with a funnel. Aluminum foil was employed as the backing membrane once the dry films were removed. The finished products were stored in desiccators for an unlimited amount of time.

Table 1: COMPOSITION OF CARVEDILOL BUCCAL FILMS

Formulation code	Polymers in mg			Solvents in ml	
	HPMC	CP	PVP	Ethanol (70 % v/v)	PG
F1	200	0	-	9.0	1.0
F2	190	10.0	-	9.0	1.0
F3	180	20.0	-	9.0	1.0
F4	170	30.0	-	9.0	1.0
F5	160	40.0	-	9.0	1.0
F6	150	50.0	-	9.0	1.0
F7	190	-	10.0	9.0	1.0
F8	180	-	20.0	9.0	1.0
F9	170	-	30.0	9.0	1.0
F10	160	-	40.0	9.0	1.0
F11	150	-	50.0	9.0	1.0

Carvedilol: 10 mg

Compatibility studies by ftir:
FTIR (Fourier transform infrared spectroscopy) was used to investigate the drug-polymer interaction. There must be conclusive proof that pharmaceuticals within these containers do not interact with the polymers.

Physico - chemical evaluation:
Surface ph:
The buccal films was dissolved in a warmed isotonic phosphate buffer (pH 6.8) with stirring, and the resultant solution was spread onto a Petri dish to set at room temperature. pH paper was used to determine the pH of the affected area [6].

Percentage moisture absorption (pma):
To determine how well the buccal films withstood high levels of humidity, they were subjected to the % moisture absorption test31. Using the following techniques, we were able to quantify the films' moisture absorption capabilities in this research. We carefully measured and weighed three films with a diameter of one centimeter before putting them into desiccators with a saturated solution of aluminum chloride and keeping them at a relative humidity of 79.5 percent [7]. The films were removed after 3 days and weighed to see how much moisture they had absorbed.

$$\text{Percentage Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{X100}$$

Percentage moisture loss (pml):
When the films were dry, we also tested how long they would last [8]. Three 1-centimeter-diameter films were weighed and stored in desiccators with fused anhydrous calcium chloride. The films were collected after 72 hours and weighed.

$$\text{Percentage Moisture Loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X100}$$

Swelling percentage (%s):
To store the drug, 50 ml of phosphate buffer at a pH of 6.8 was added to a clean petridish containing the film [9].

$$\% S = \frac{X_t - X_0}{X_0} X100$$

For 60 minutes, we measured the patch's weight every 15 minutes.
Where,
X_t - the mass of swollen film after time t,
X_0 -mass of film at zero time.

Water vapour transmission rate[59] (wvt):
For this study, we employed transmission cells stored in uniformly-sized vials. After washing and drying in an oven, these cells were analyzed. The cell was filled with calcium chloride to a density of about 1 gram, and polymeric sheets, each measuring 1 square centimeter, were glued to the outer border [10]. Once the cells' original weight was determined, they were stored in desiccators with a potassium chloride solution. The relative humidity values within the desiccators varied between 80% and 90%. After 18, 36, 54, and 72 hours, the cells were collected and weighed.

V T = WL/S

Where W is the amount of water vapor transferred in milligrams, L is the film thickness in millimeters, and S is the film's exposed surface area in square centimeters.

Thickness:
Each film's thickness was measured in six separate spots using a digital vernier calliper, and an average was then determined [11].

Weight of films:
Three films were weighed, and the weight difference was computed.

Folding endurance:
The film's ability to withstand being folded was determined by physically folding a small sample of the film up to 300 times, at which point the sample was declared to have broken. The folding endurance

rating was determined by counting the number of times the film could be folded in the same spot before tearing [12]. This procedure was used to three separate films.

Drug content estimation:
The film was sliced into thirds, and each third was placed in 100 cc of phosphate buffer with a pH of 6.8 for 24 hours while being swirled constantly. Before being measured at 272 nm by a UV Spectro photometer, solutions were filtered and diluted to the necessary concentration. Three films' total drug use was added up and then averaged [13].

***In-vitro* drug release studies:**
An open-ended tube acted as the donor, and a 250 ml beaker as the receiver for the modified dissolving device. Using a thermo-regulated hot plate, the temperature of the dissolving solution, which was 100 millilitres of phosphate buffer (pH 7.5), was kept at 37± 1°C. The assembly's donor chamber, which is separated from the external medium by a semipermeable barrier, was filled with film. From each batch, one millilitre sample was extracted at regular intervals [14]. To maintain a constant volume after each sample was collected, the phosphate buffer used for dissolution was gradually changed. Spectrophotometry at 272 nm was used to analyse the solutions obtained after each sample was diluted by a factor of 10.

Measurement of buccoadhesive strength:
The in-vitro buccoadhesive strength was measured using a modified balancing technique. The buccal mucosa was taken as the cellophane membrane. The glass slide to receive the buccal mucosa by taping it to the bottom of a smaller beaker and inverting the whole assembly into a larger, 500 ml beaker. When the IPB was left on the open surface, the patch expanded and moistened in 30 seconds. The platform was steadily elevated when the film's surface made contact with mucosa. The right pan of the balance was kept at a constant weight to ensure that both pans were at the same level before analysis [15]. To lower the pan and patch over the mucosa on the right side, 5 g of weight had to be removed from the pan. The five minutes of contact time were spent using the scale in the same location. We increased the right hand pan's weight as soon as we saw film detaching from the mucosal surface. The adhesive power of the buccal film was determined by measuring the force required to separate the two surfaces (in grams). Using the bioadhesive strength, we were able to determine the following.

$$\text{Force of adhesion (N)} = (\text{Bioadhesive strength (g)} \times 9.8)/100$$

$$\text{Bond strength (N m–2)} = \text{Force of adhesion / surface area}$$

RESULTS AND DISCUSSION:

Drug –polymer compatibility studies by FTIR:
The peaks at wave numbers 3504, 3399, 3375 (N-H Asymmetric stretching), 3238, 3104 (Associated N-H stretching), 2938 (CH2 Asymmetric stretching), 1638 (C=C Stretching), 1433 (CH2 Bending), 1326, 1284 (C=S Stretching), 1251 (C-N Stretching), 1146, 1119 (SO2 Asymmetric stretching), 980 (Ring Stretching), 778, 698, and 607 (C-S Stretching) were found in the IR spectral analysis of carvedilol. These wave numbers, respectively, confirmed the drug's purity with standards.

Major peaks for Carvedilol in a physical mixture with hydroxypropyl methyl cellulose, 3399.89 for N-H asymmetric stretching, 3375.11 for Associated N-H stretching, 2937.22 for CH2 asymmetric stretching, 1638.48 for C=C stretching, 1449.09 for CH2 bending, and 1325 for hydroxypropyl methyl cellulose, carbopol, and polyvinylpyrrolidone. There was no evidence of a chemical reaction between Carvedilol and the other excipients; nevertheless, physical combinations indicated additional peaks absorbed, perhaps due to the presence of polymers.

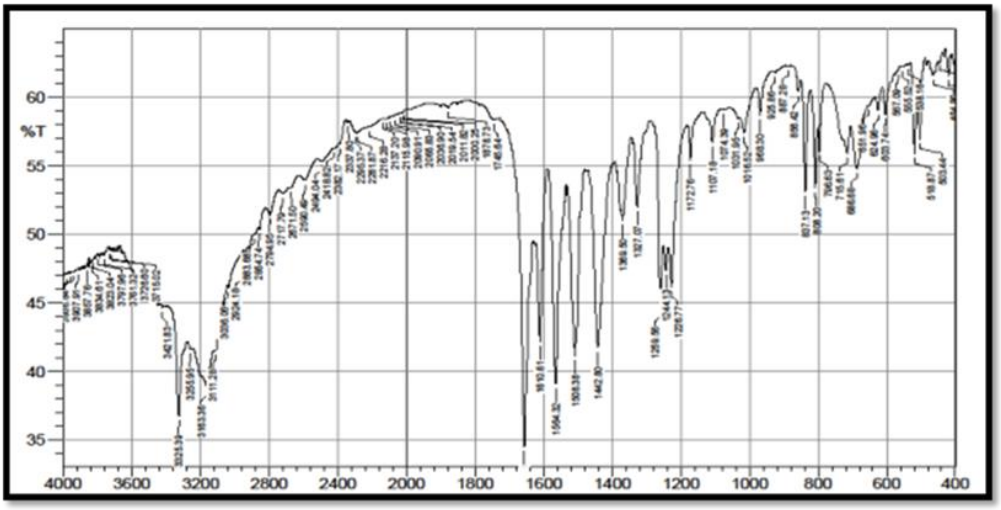

Fig.1. FTIR SPECTRA OF CARVEDILOL

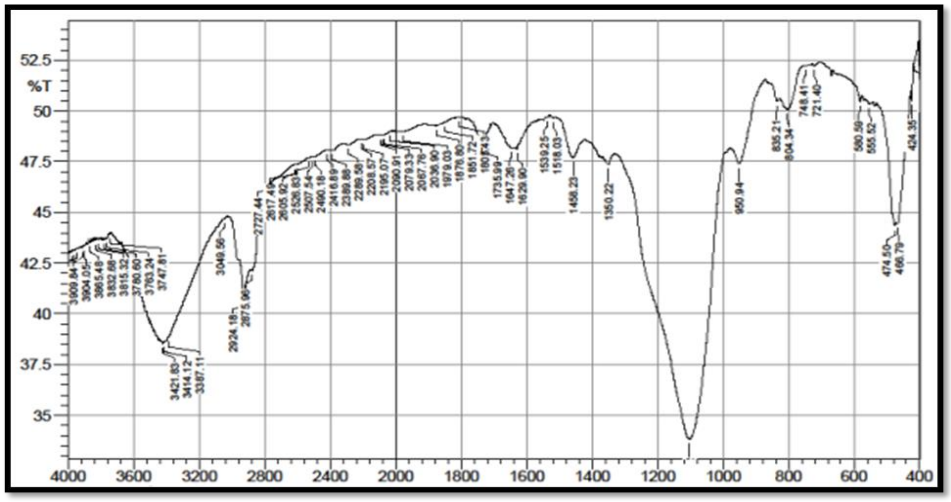

FIG.2. FTIR SPECTRA OF OPTIMIZED FORMULATION

Surface pH:
The surface pH of the formulations was measured, and the results were found to be in the range of 6.520.03 and 6.810.01. All of the formulations fall within the pH range of saliva (6.5-6.8), a finding supported by statistical research, which makes them less irritating and more likely to be accepted by patients.

Percentage Moisture Absorption and Percentage Moisture Loss:
The maximum moisture absorption rate was found in Formulation F6 (150 mg, HPMC, 50 mg CP). The anomaly may be explained by the high concentrations of both CP and HPMC.

The most moisture loss occurs in Formulation F11 (150 mg, HPMC, 50 mg PVP), due to the greater PVP content, whereas the lowest occurs in Formulation F6 (150 mg, HPMC, 50 mg CP), due to the lower CP concentration.

Swelling percentage:
When a polymer tissue is over-hydrated, adhesion suddenly weakens towards the surface, where it had previously grown to the point of disentanglement. F6 has a greater swelling percent. This is due to the higher concentration of carbopol in this formulation.

Water Vapour Transmission:
The proportion of water vapor transmitted by various films is shown in Table 3. All of the films passed the water vapor permeation tests. The film formulation F11 (150 mg HPMC and 50 mg PVP) showed the highest water vapor transmission (12.440.48). It's possible that this is due to an excess of PVP.

The F6 formulation (150 mg HPMC and 50 mg CP) produced the film with the lowest water vapor transmission (5.390.32). Possible explanation: an abundance of carbopols.

Thickness and Weight of films:

The film thicknesses ranged from 0.200.01 mm to 0.620.01 mm, as measured using a digital vernier caliper. The weight of the films was measured, and it ranged from 210.121.06 mg to 163.180.9 mg.

Folding endurance:

It was determined that more than 300 folds could be applied to all formulations. This means the system can handle the pressures caused by talking and eating without breaking. The results of the folding endurance tests demonstrated that the films retained their shape when applied to the buccal mucosa.

Drug content estimation:

The results of the analysis of content uniformity showed that the drug was distributed uniformly, with minimal difference across batches. It's possible to go back between 18.1% and 19.9%.

Table 2: Physicochemical Evaluation Of Buccal Films Of Carvedilol

Formulation Code	Surface pH	PMA	PM	Swelling Index	WTR	Thickness (mm)	Weight of films in mg	Drug Content in mg
F1	6.73	5.21	5.97	69.4	10.58	0.24	180.93	19.7
F2	6.79	7.32	5.14	99.6	7.64	0.62	163.18	18.9
F3	6.78	7.86	6.44	67.5	10.87	0.22	181.17	19.7
F4	6.8	6.18	7.13	69.7	11.48	0.21	172.35	18.6
F5	6.77	5.34	9.12	71.6	11.58	0.23	172.31	19.1
F6	6.8	4.12	10.06	78.5	12.3	0.25	174.37	18.2
F7	6.8	3.56	11.21	82.6	12.44	0.31	174.94	19
F8	6.71	13.02	4.84	86.9	5.69	0.48	172.2	18.6
F9	6.67	11.26	5.72	77.4	5.91	0.43	170.37	18.9
F10	6.63	9.89	6.14	72.53	6.32	0.36	171.07	19.9
F11	6.61	7.02	7.45	69.56	6.94	0.32	182.43	19.3

The most stable patches (F 14) did not display any observable changes in color or shape or any signs of physical instability.

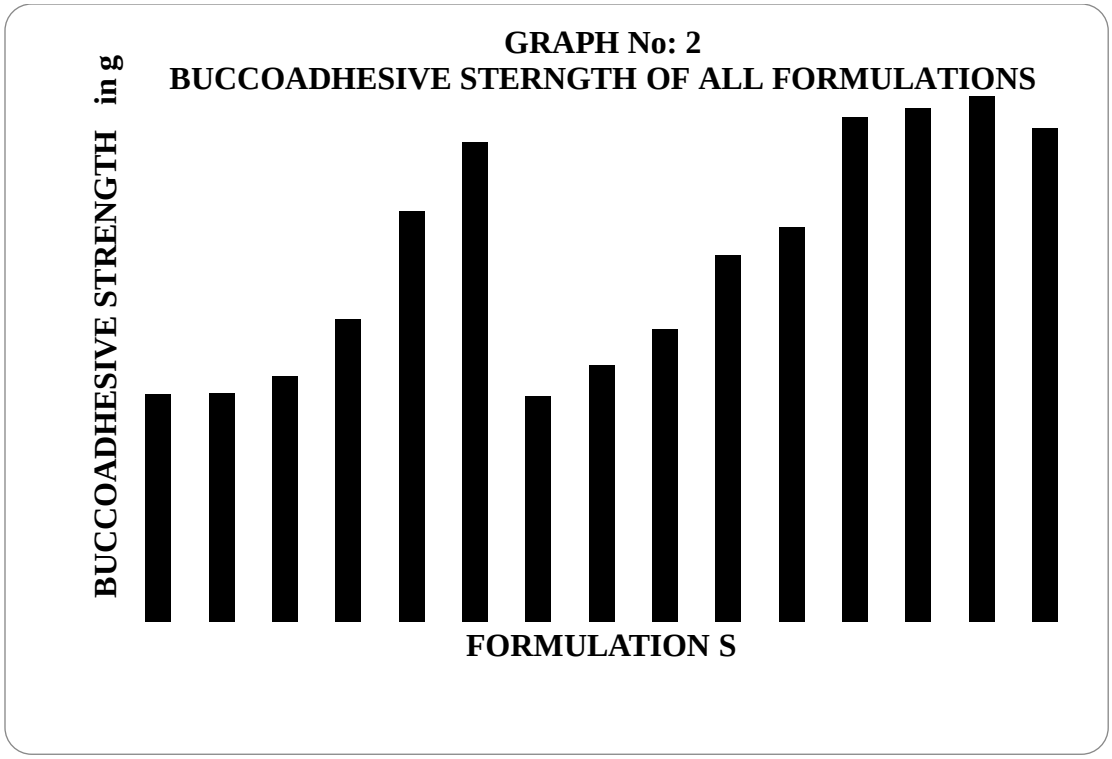

Figure 3: Buccoadhesive strength of all formulations

***In-vitro* drug release studies**

Carvedilol release rates varied greatly amongst various formulations. Tables 6–20 and Figures 3-47 provide the outcomes and data from in vitro investigations, respectively. Figures 49–57 contrast Higuchi and peppas in vitro drug release models.

Preparations F1, F2, and F3 exhibited acceptable Carvedilol release for up to 10 hours.

Formulations F4, F5, and F6 comprising carbopol and HPMC showed acceptable Carvedilol release for up to 11 hours.

Formulas F3, F4, and F5 displayed Super Case II Transport Type, as shown by their diffusion exponent (n) values of 1.13872, 1.118578, and 1.157541, respectively, from peppas plots, whereas Formulas F1 and F2 had Non fickian exponents.

The release rate was 95.2% for formulation F7, 94% for F8, 94% for F9, 94% for F10, 94% for F11, and 91% for F12. Higuchi's diagram and the in vitro drug release data both corroborated the conclusion that the drug release followed zero-order kinetics. The slope values of Peppa's plots (0.712362, 1.062854, 1.098589, 1.073329, and 1.1027 for Formulation F7, and Super Case II Transport Type for Formulations F8, F9, F10, and F11) indicate that drug release occurred through a non-fickian diffusion process.

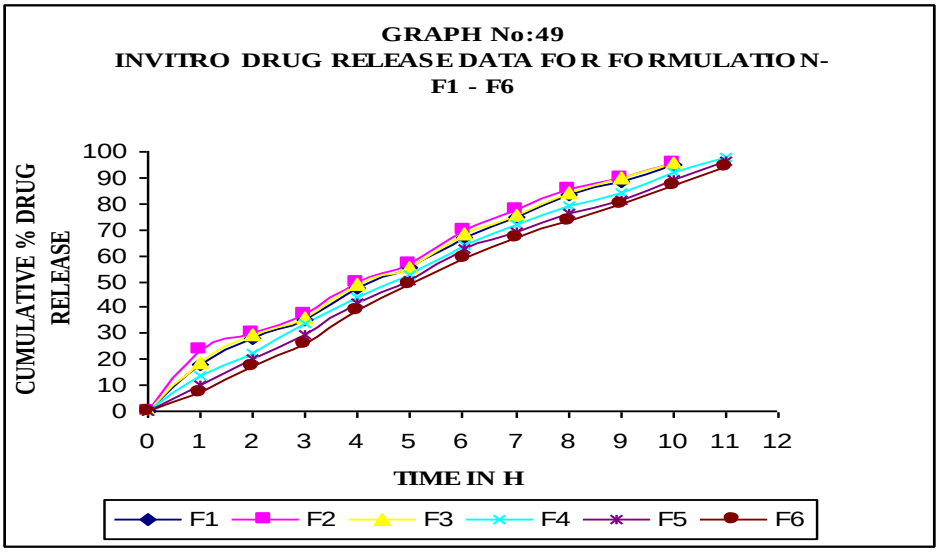

Figure 4: In-vitro release data of F1-F6

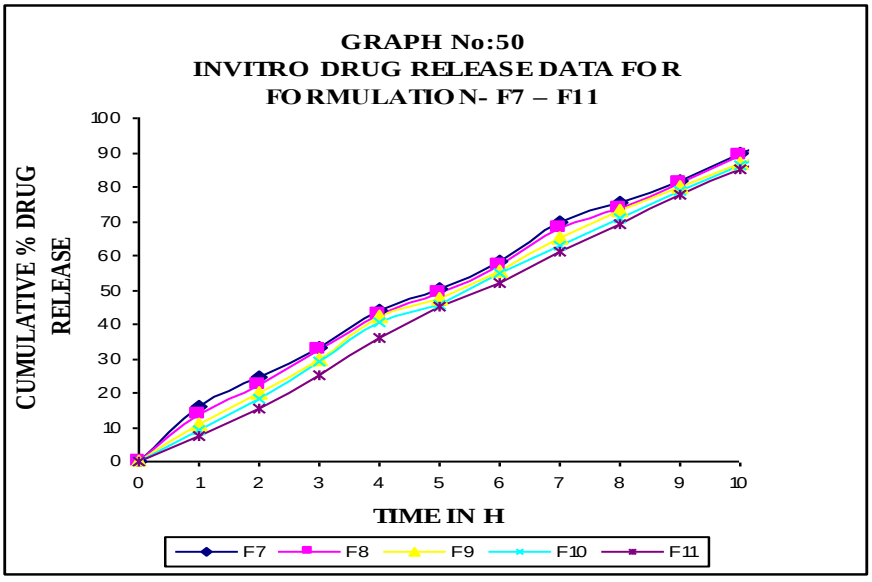

Figure 5: In-vitro release data of F7-F11

SUMMARY AND CONCLUSION:

Ethyl cellulose was used as an impermeable backing layer, and the polymers Hydroxypropyl methyl cellulose - 100K cps (HPMC), sodium carboxy methyl cellulose (SCMC), Poly vinyl pyrrolidone K 30 (PVP), and Carbopol-P 934 (CP) were used to create buccoadhesive bilayer tablets of Carvedilol via the direct compression method. To check for drug-polymer compatibility, FTIR examination was conducted. Surface pH, swelling percentage, thickness, weight variation, hardness, friability, and drug content were evaluated for the produced carvedilol buccal films, Even though all of the formulations developed were effective, compound 5 stood out from the others. This high degree of agreement between in vitro and in vivo profiles suggests that the formulation was successful in producing the same release pattern through the biological membrane as was seen in vitro.

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